

RESEARCH ARTICLE

Cellular senescence limits translational readthrough

Neylen del Toro^{1,*}, Frédéric Lessard^{1,*}, Jacob Bouchard¹, Nasrin Mobasheri¹, Jordan Guillon², Sebastian Igelmann^{1,2}, Sarah Tardif¹, Tony Buffard¹, Véronique Bourdeau¹, Léa Brakier-Gingras¹ and Gerardo Ferbeyre^{1,2,‡}

ABSTRACT

The origin and evolution of cancer cells is considered to be mainly fueled by DNA mutations. Although translation errors could also expand the cellular proteome, their role in cancer biology remains poorly understood. Tumor suppressors called caretakers block cancer initiation and progression by preventing DNA mutations and/ or stimulating DNA repair. If translational errors contribute to tumorigenesis, then caretaker genes should prevent such errors in normal cells in response to oncogenic stimuli. Here, we show that the process of cellular senescence induced by oncogenes, tumor suppressors or chemotherapeutic drugs is associated with a reduction in translational readthrough (TR) measured using reporters containing termination codons withing the context of both normal translation termination or programmed TR. Senescence reduced both basal TR and TR stimulated by aminoglycosides. Mechanistically, the reduction of TR during senescence is controlled by the RB tumor suppressor pathway. Cells that escape from cellular senescence either induced by oncogenes or chemotherapy have an increased TR. Also, breast cancer cells that escape from therapyinduced senescence express high levels of AGO1x, a TR isoform of AGO1 linked to breast cancer progression. We propose that senescence and the RB pathway reduce TR limiting proteome diversity and the expression of TR proteins required for cancer cell proliferation.

KEY WORDS: Senescence, Translational readthrough, Translation termination, Retinoblastoma (RB) tumor suppressor

INTRODUCTION

Cellular senescence is a tumor suppressor mechanism that prevents proliferation in cells bearing oncogenic stimuli (Collado and Serrano, 2010). Senescent cells can efficiently halt tumor progression by remaining out of the cell cycle permanently as benign lesions (Collado and Serrano, 2010; Vernier and Ferbeyre, 2014). Ideally, they also activate their elimination through immune mediated clearance (Kang et al., 2011; Xue et al., 2007). However, if not cleared, some senescent cells can occasionally escape from their dormancy and progress into malignant tumors

¹Département de Biochimie et Médecine Moléculaire, Université de Montréal C.P. 6128, Succ. Centre-Ville, Montréal, Québec, H3C 3J7, Canada. ²CRCHUM-Université de Montréal, 900 Saint-Denis, bureau R10.432, Montréal, Québec, H2X 0A9, Canada,

*co-first authors

*Author for correspondence (g.ferbeyre@umontreal.ca)

D G.F., 0000-0002-2146-618X

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heterogeneity in the senescence response depending on the inducer, tissue type and genetic background (Hernandez-Segura et al., 2017). Nevertheless, most senescent cells activate the p53 and retinoblastoma (RB) tumor suppressor pathways that block cell cycle progression (Collado and Serrano, 2010; Vernier et al., 2011; Vernier and Ferbeyre, 2014). In epithelial cells, reactive oxygen species, defective DNA repair and DNA damage were linked to senescence bypass and malignant progression (Gosselin et al., 2009; Nassour et al., 2016). It is commonly accepted that DNA damage and mutations fuel tumor initiation and progression (Harfe and Jinks-Robertson, 2000; Kandoth et al., 2013) by generating both oncogenic drivers and genetic diversity (Bielas et al., 2006). However, little is known about the contribution of translational errors in tumorigenesis.

(Milanovic et al., 2018; Romanov et al., 2001). There is a great

In normal cells, translational errors in the form of aminoacid misincorporation are estimated to occur at a reduced frequency and unlikely to significantly affect the proteome (Drummond and Wilke, 2009). In microorganisms, mistranslation contributes to adaptive evolution by purging deleterious mutations and inducing stress adaptation (Bratulic et al., 2017; Ribas de Pouplana et al., 2014; True et al., 2004). Moreover, translational recoding is often used by viruses to increase the coding potential of their small genomes (Bidou et al., 2010). For example, retroviruses use frameshifting to control the synthesis of viral replication proteins (Charbonneau et al., 2012). Overall, translational readthrough (TR), originally discovered in viruses and now extended to metazoans, can add a new C-terminal signal to proteins that may change their function and localization (Jungreis et al., 2011; Schueren et al., 2014; Schueren and Thoms, 2016; Singh et al., 2019). The extensions usually contain potential signals to target proteins to the nucleus, peroxisomes or the membrane (Schueren et al., 2014; Schueren and Thoms, 2016; Singh et al., 2019). Taken together, the available evidence suggests that tumor cells could use such recoding mechanisms to generate new protein variants and evolve. Therefore, tumor suppressor pathways could counteract TR as part of their mechanism of action.

TR results from the recognition of stop codons (UAA, UAG and UGA) by near cognate tRNAs instead of the release factors (RFs) that can also recognize the termination codons to end translation (Tate et al., 2018). The efficiency of translation termination depends on the identity of the stop codon (Firth et al., 2011; Grentzmann et al., 1998; Loughran et al., 2014) and is modulated by metabolic stress in bacteria (Zhang et al., 2020) or oxidative stress in yeast (Gerashchenko et al., 2012). However, little is known about the processes controlling TR in mammalian cells.

Here, we report that TR is significantly reduced during oncogeneinduced senescence (OIS) or therapy-induced senescence (TIS), which are anticancer responses controlled by the tumor suppressors RB, p53 and PML. Using defined genetic tools, we also show that senescence-associated readthrough suppression is mostly mediated by the RB tumor suppressor pathway. In addition, we show that cells

that escape from senescence increase the expression of AGO1x, an endogenous TR isoform of AGO1 that suppress the interferon pathway stimulating cell proliferation in breast cancer cells (Ghosh et al., 2020). Hence, like DNA mutations, TR can both increase the expression of specific cancer drivers and generate proteome diversity fueling cancer cell evolution.

MATERIALS AND METHODS

Cell culture and materials

IMR-90 human diploid fibroblasts were obtained from Coriell Institute for Medical Research (New Jersey, NY). Prostate Cancer cells (PC-3) and MDA.MB.231 breast cancer cells were obtained from ATCC. A certificate of authentication was obtained from Coriell for IMR-90 cells and from ATCC for PC-3 and MDA.MB.231 cells. All cells were mycoplasma free after testing that was performed once a month for all cell lines by immunofluorescence. IMR-90 containing human telomerase reverse transcriptase (hTERT) were generated in our laboratory by transducing cells with the FG12-hTERT lentiviral vector (Voghel et al., 2010). Phoenix ampho packaging cells used for retroviral infections were given by S.W. Lowe (Memorial Sloan Kettering Cancer Center, New York, NY). IMR-90 and MDA.MB.231 were cultured in Dulbecco's modified Eagle medium (DMEM; Wisent) supplemented with 10% fetal bovine serum (FBS; Wisent), 1% penicillin G/streptomycin sulfate (Wisent) and 2 mmol/l L-glutamine (Wisent). PC-3 were cultured in Roswell Park Memorial Institute Medium (RPMI 1640; Wisent) supplemented with 10% fetal bovine serum (FBS; Wisent), 1% penicillin G/streptomycin sulfate (Wisent) and 2 mmol/l L-glutamine (Wisent).

The translation elongation inhibitor cycloheximide and the aminoglycoside gentamicin sulfate were purchased from Sigma-Aldrich (Oakville, ON). The CDK4/6 inhibitor palbociclib (PD-0332991) was purchased from Chemietek. Camptothecin and 4-hydroxy-tamoxifen were purchased from Sigma-Aldrich (Oakville, ON). A phthalamide derivative named CDX5-1 was donated by M. Roberge (University of British Columbia, Vancouver, BC, Canada).

Plasmids and cloning

Retroviral vectors pBabe/pBabe-ER, pBabe-H-RasV12, pWZL/pWZL-H-RasV12 were described in (Ferbeyre et al., 2000), pBabe-PML-IV-ER in (Vernier et al., 2011), pLXSN, pLXSN-E6, pLXSN-E7, pLXSN-E6/E7 and pLXSN-E7 Δ 21-24 in (Mallette et al., 2004), pBABE-RPL22(WT)-Myc in (Del Toro et al., 2019), pBABE-RPS14(WT)-Myc in (Lessard et al., 2018). pBABE-CDK4(WT) was a gift from Scott W. Lowe (Memorial Sloan-Kettering Cancer Center, New-York, NY, USA). The genes coding for Renilla luciferase (Rluc) and Firefly luciferase (Fluc) were linked by an intercistronic region in order to obtain a 96 kDa bifunctional protein (Gendron et al., 2005). These reporters were PCR-amplified and subcloned in NotI/NsiI restriction sites to obtain pMSCV-Rluc-Fluc variants. A UGA stop codon, created by site-directed mutagenesis using PfuUltra II fusion HS DNA polymerase (Agilent, Canada), was inserted in the intercistronic sequence. Primers for PCR are provided in Table S1. The readthrough region from Moloney Murine Leukemia Virus (MMuLV) as well as sequences flanking the stop codon from the readthrough sequence of Aquaporin 4 (AQP4, NM_001650.4) (Loughran et al., 2014) were chemically synthesized (Biocorp, Canada) and subcloned in XhoI/ApaI restriction sites between Rluc and Fluc genes. The readthrough region sequences are provided in Table S2. The non-readthrough control was performed by mutating the stop codon TGA to CGA.

Identification of readthrough candidates in mammalian cells using bioinformatic analysis

In order to look for endogenous readthrough candidates, we looked in silico for peptides encoded after termination codons detected in proteomics experiments. We first built a database of peptide sequences located between the first arginine/lysine after the canonical stop codon and the next stop codon, always in the same reading frame using sequences deposited in RefSeq hg38.2. We discarded sequences shorter than five aminoacids. Candidate readthrough peptides were then matched to the data set of

peptides identified by trypsin digestion of human proteins and mass spectrometry published in (Rosenberger et al., 2014). We found 278 candidates for endogenous readthrough above the false discovery rate (FDR) threshold (Table S3). Following a readthrough propensity predictor algorithm (Schueren et al., 2014), four candidates showing the highest readthrough propensity values were chosen. This algorithm assigns regression coefficients to the stop codon and all possible nucleotides in the stop codon context based on experimental data. The stop codon context comprises the nucleotide sequences from -6 to +9 positions surrounding the stop codon. The new readthrough candidates are: Vasodilator-stimulated phosphoprotein (VASP, NM_003370.3), Aspartate beta hydroxylase (ASPH, NM_004318.3), Hepsin (HPN, NM_182983.2) and Fibrillarin (FBL, NM_001436.3). Oligonucleotides containing 30 up-stream and 30 down-stream nucleotides flanking the stop codon, as well as the stop codon of those readthrough candidates were chemically synthesized (Biocorp, Canada) and subcloned in XhoI/ApaI restriction sites between Rluc and Fluc genes of our pMSCV-Rluc-Fluc reporter construct. The sequences of all new readthrough candidates' regions are provided in Table S2.

Polysome fractionation

The protocol was performed as previously described (Gandin et al., 2014). Briefly, 60% (w/v) sucrose stock solution was used to make sucrose gradients (5 to 50%) in a buffer containing 200 mM Tris-HCl (pH 7.6), 1 M KCl, 50 mM MgCl₂, 100 μg/ml cycloheximide, 1X cOmplete EDTA-free protease inhibitor cocktail (Roche) and 200 units/ml of RNase inhibitor (abm-Applied Biological Materials, BC). After 12 days post infection, proliferating and senescent fibroblasts at 80-90% confluence were treated with cycloheximide at a final concentration of 100 μg/ml for 5 min at 37°C. Cells were washed with ice-cold 1X PBS, 100 µg/ml cycloheximide, scratched and lysed in a hypotonic buffer (5 mM Tris-HCl pH 7.5, 2.5 mM MgCl₂, 1.5 mM KCl, 1X cOmplete EDTA-free protease inhibitor cocktail, 100 μg/ml cycloheximide, 1 mM DTT, 100 units of RNAse inhibitor, followed by addition of 25 µl of 10% Triton X-100 (final concentration of 0.5%) and 25 µl of 10% sodium deoxycholate (final concentration of 0.5%). Cells were vortexed and then centrifuged at low speed $(140 \times g)$ for 15 min at 4°C. Sample supernatants were adjusted so that they contain the same OD (10–20 OD at 260 nm). The lysate was loaded onto the ultracentrifuge tubes containing sucrose gradients, then centrifuged at 22,223×g (36,000 rpm) for 2 h at 4°C using SW41Ti rotor Beckman Coulter (Optima L80 XP ultracentrifuge). After ultracentrifugation, the samples were placed in the UV detector (Brandel #IV-22-117140) and fraction collector (Retriever 500, Teledyne Isco). Each fraction was collected and monitored from the top to the bottom of the ultracentrifuge tube.

Dual-luciferase assays

IMR-90 transduced cells were washed with 1X PBS, scratched and lysed in 1X Passive lysis buffer supplied in the Dual Luciferase Stop & Glo Reporter Assay System (Promega). A 20 μ l cell lysate sample was used for luminescence measurements with Lumin Triathler-Hidex. After adding 50 μ l of the Fluc reagent (Substrate+Buffer) to the samples, luminescence was measured for 10 s. Addition of 50 μ l of the Rluc reagent-Fluc quenching (Stop & Glo Perceded another 10 s measurement. The efficiencies of readthrough (% Readthrough) were determined by averaging the relative Fluc activities (Fluc/Rluc ratio) from luciferase reporters UGA or AQP4, divided by the relative luciferase activities of their non-readthrough controls.

We also compared the readthrough fold-changes, relative Fluc activities (Fluc/Rluc) of each condition were normalized to the relative Fluc activities from non-senescent cells:

$$\label{eq:Normalized_Fluc_Rluc} \text{Normalized Fluc/Rluc} = \left(\frac{Fluc/Rluc \left(x \ condition\right)}{Fluc/Rluc (non - senescent \ cells)} \right).$$

To measure readthrough after therapy-induced senescence, PC3 and MDA.MB.231 cells were retrovirally transduced with luciferase reporter AQP4 or UGA. Transduced cells were treated 24 h using 100 nM of camptothecin or vehicle (DMSO), to induce senescence. Following the treatment, cells were washed with 1X PBS and fresh medium was added.

Luciferase activities were measured at day 7 post treatment. All assays were performed in technical triplicates. Normalized relative Fluc fold changes and Fluc/Rluc ratios are provided in Table S4 as well as all biological replicates.

Immunoblotting and Immunofluorescence

To prepare total cell extracts, cells were washed with 1X PBS containing 1X protease- and phosphatase-inhibitor cocktails (Roche), scratched and collected by centrifugation at low speed (140×g) for 5 min, lysed in 200 µl of SDS sample buffer (62.5 mM Tris-HCl, pH 6.8, 10% glycerol, 2% SDS and 5% 2-mercaptoethanol), and boiled for 5 min. Fifteen µg of total cell proteins were separated on SDS-PAGE and transferred to nitrocellulose membranes (Millipore). The primary antibodies used were anti-Renilla Luciferase rabbit polyclonal (1:3000, Code No. PM047, MBL), anti-H-Ras mouse monoclonal (1:250, clone F235, sc-29, Santa Cruz Biotechnology, CA, USA), anti-phospho-H3^{S10} rabbit polyclonal (1:1000, #06–570, Millipore, Billerica, MA, USA), anti-phospho-RBS795 rabbit polyclonal (1:500, #9301, lot: 13, Cell Signaling), anti-RB mouse monoclonal (1:1000, clone 4H1, #9309, Cell Signaling Technology), anti-MCM6 rabbit polyclonal (1:1000, A300-194A, Bethyl Laboratories), anti-p53 mouse monoclonal (1:1000, clone DO-1, sc-126, Santa Cruz Biotechnology), antip21 (1:500, 556431, BD Pharmingen), anti-RNR (1:500, sc-398294, Santa Cruz Biotechnology), anti-phospho-γH2A.XS139 mouse monoclonal (1:500, JBW-301, lot: 2552645, Millipore, Billerica, MA), anti-c-Myc rabbit polyclonal (1:1000, clone A-14, sc-789, Santa Cruz Biotechnology) and anti-α-tubulin mouse monoclonal (B-5-1-2, 1:20000, Sigma-Aldrich). Signals were revealed after incubation with goat anti-mouse IgG (1:3000, #170-6516, Bio-Rad, Mississauga, ON, Canada) or goat anti-rabbit IgG (1:3000, #170-6515, Bio-Rad) secondary antibodies, and by using enhanced chemiluminescence (ECL, Amersham) or Lumi-LightPLUS (Roche).

Immunofluorescence were done as described (Igelmann et al., 2021) with the following modifications for the AGO1x staining. For blocking 10% goat serum (#16210072, Life Technologies), and 1% BSA (BioShop Canada) in PBS for 30 min. Primary antibodies were AGO1x (1:50, #RBP 1510, Lucerna-Chem.) and KI67 (1:200, Cat# RM9106, ThermoFisher Scientific). Cells were analyzed using upright microscope Zen Imager with 20X air objective. Images were processed using Image J and quantification was done using region of interest (ROI) mean intensity staining. To determine ROI, DAPI staining was used.

Cell proliferation assay and senescence-associated $\beta\text{-}\textsc{galactosidase}$ assay

Relative density of cells was assessed from estimations of cell number according to crystal violet retention assay (Vernier et al., 2011). The senescence-associated β -galactosidase (SA- β -Gal) activity was measured at day 7, 12 or 35 post-infection as previously described (Vernier et al., 2011). All assays were performed in technical triplicates.

RT-aPCR

Senescent and non-senescent IMR-90 s were collected at 12- or 35-days post-infection, with either pBabe-H-RasV12 or pBabe control vector in TRIzol reagent (Invitrogen) and total RNA was extracted following manufacturer's instructions. Two μg of total RNA were then used for the RT-qPCR reactions as described in (Igelmann et al., 2021). Primers for qPCR were designed using the Universal Probe Library Assay Design Center (https://www.roche-applied-science.com/sis/rtpcr/upl/index/jsp) and are provided in Table S5. Analysis for indicated genes were done using the $\Delta\Delta CT$ method. HMBS and TBP were used as reference genes (Vernier et al., 2011). All assays were performed in technical triplicates.

Statistics and reproducibility

Statistical analysis (one-way ANOVA with post-hoc Tukey's honestly significant difference (HSD) test) was done using the one-way ANOVA test calculator at: http://astatsa.com/OneWay_Anova_with_TukeyHSD/. Two-tailed Student's *t*-tests were performed using GraphPad Prism version 6.0c software. A *P*<0.05 was considered statistically significant. Each

experiment was repeated at least three times, except for those in Fig 2C,D, Fig 3B,C (UGA); Fig S1C–E and Fig S2D, which were done twice. SA- β -Gal assays were quantified from many fields within one experiment to represent the entire petri dish and confirmed as described in Figs 5F, 6A, 7A and Fig. S1A.

RESULTS

Translation termination is improved in oncogene-induced senescence

To investigate the effect of cellular senescence on TR efficiency, we first used a model of oncogene-induced senescence (OIS) in human primary cells. Primary fibroblasts were retrovirally transduced with H-RasV12 oncogene (senescence inducer) or the control empty vector. They were also transduced with luciferase reporter plasmids containing either: (1) a TGA within an artificial intercistronic region (UGA readthrough); (2) the stop codon context from AQP4, a well-known mammalian readthrough candidate (Loughran et al., 2014); or (3) the non-readthrough controls (TGA mutated to CGA) between Rluc and Fluc fusion protein gene (Fig. 1A). Immunoblotting shows a band at 35 kDa corresponding to Renilla luciferase, as well as a weak band at 100 kDa indicating the fusion protein Renilla-Firefly luciferase produced after a ribosomal readthrough in cells transduced with the AQP4 readthrough reporter (Fig. 1B, right). For UGA reporter, the fusion protein is not detectable. On the other hand, in cells transduced with the nonreadthrough control only the fusion protein can be detected (Fig. 1B, left). At early stages of H-RasV12 oncogene expression, cells present a cancer-like behavior characterized by a hyperproliferation phase. However, around 6 days after introduction of oncogenic ras, cells stop proliferation and enter a well-characterized and stable cell cycle arrest (Serrano et al., 1997). We confirmed this senescent cell cycle arrest at day 12 post infection, using an assay for the senescence-associated B-galactosidase activity that allowed visualizing characteristically large and flat cells that stained positive for this biomarker (Fig. S1A). RT-qPCRs were carried out to evaluate the decrease of Ki67 expression, indicating the proliferation arrest, and the activation of p53 targets (CDKN1A/ p21, GADD45A) and RB pathway (CDKN2A/p16INK4a, MCM6) in senescent cells (Fig. S1B). Global translation was not affected in senescent cells since their polysome profiles were similar to control growing cells (Fig. 1C). This is consistent with previous reports and with the fact that senescent cells are actively secreting multiple proinflammatory mediators (Young et al., 2009). In addition, the nonreadthrough (CGA) controls presented similar relative Fluc activities both in senescent and proliferating cells (Fig. S1C). Cap-dependent Rluc expression increased with time (Fig. 1D). Readthrough-dependent translation of the firefly luciferase reporter increased early after introduction of oncogenic ras in normal human fibroblasts when cells proliferate rapidly but it decreased when the cells underwent OIS as measured at days 12 or 20 after H-Rasintroduction (Fig. 1E). The relative efficiency of TR was calculated by dividing Fluc by Rluc values, then normalizing to the Fluc/Rluc ratio obtained in the same cells using the non-readthrough (CGA) control. The results clearly show that the senescent program reduced TR efficiency at UGA codons without any particular context and in the sequence flanking the AQP4 translation termination signal (Fig. 1F). Similar results can be seen after plotting the Fluc/Rluc ratio of senescent Ras-expressing cells relative to cells with empty vectors (Fig. 1G). In contrast, control cells did not change TR efficiency during the same time in culture (Fig. S1D). To discard the possibility that TR efficiency might be decreased due to a cell-cycle arrest independent from the senescent phenotype, proliferating cells

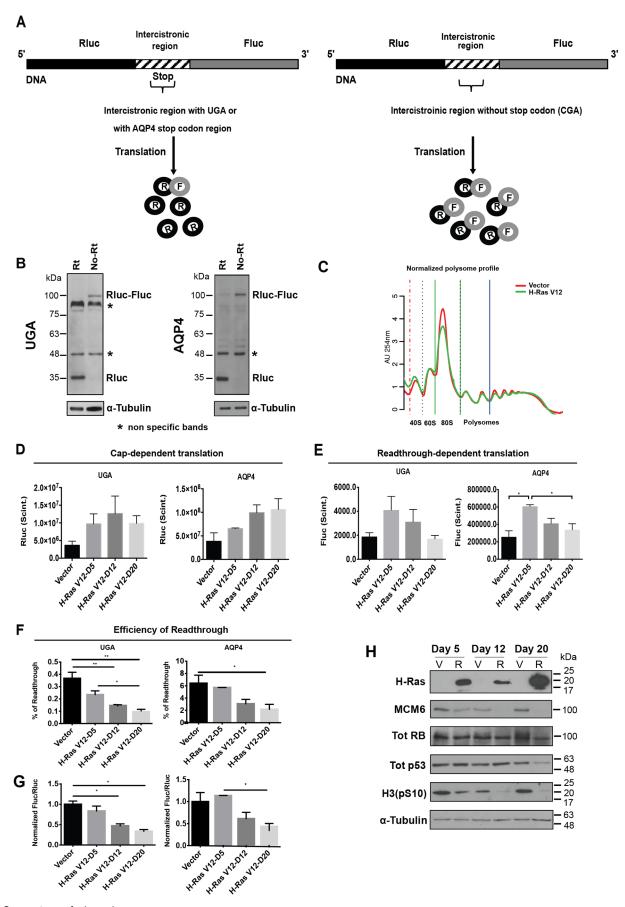


Fig. 1. See next page for legend.

Fig. 1. Readthrough is reduced in OIS. (A) Rluc (Renilla luciferase) in black is linked to Fluc (Firefly luciferase) in gray, by an intercistronic region in stripes. Rluc is the internal control of the gene, while Fluc is the readthrough sensor. A UGA codon within an artificial context or the AQP4 stop codon region is inserted in the intercistronic region (left). The expression of Fluc indicates the efficiency of readthrough. The intercistronic region from the non-readthrough control lacks the stop codon (TGA mutated by CGA) (right). (B) Immunoblots for Rluc in IMR-90 cells transduced with UGA and AQP4 reporters (Rt) or with the non-readthrough controls (No Rt), 12 days post infection. Alpha-Tubulin was used as a loading control. *, non-specific bands at 48 and 90 kDa; n=3. (C) Polysome profiles were performed 12 days post infection with an empty vector (Vector) or H-Ras V12 oncogene (H-RasV12) showing that global translation is similar in senescent and non-senescent IMR-90 cells, n=3. (D) Rluc plots indicate cap-dependent translation in IMR-90 cells with an empty vector (Vector) or with the oncogene H-Ras V12 (H-RasV12) at day 5 (D5, still proliferating), 12 (D12, senescent cells) or 20 (D20, senescent cells). Error bars indicate s.d of three independent experiments, n=3. (E) Fluc plots indicate the decrease of readthroughdependent-translation of cells as in D. Error bars indicate s.d. of three independent experiments, n=3. (F) The percent of readthrough was calculated in cells as in D by dividing the Fluc/Rluc ratio from UGA or AQP4 luciferase reporters by the Fluc/Rluc ratio from non-readthrough controls multiplied by 100, n=3. (G) Fluc/Rluc ratios with data as in F but normalized relative to empty vector-infected cells n=3. (H) Immunoblots of H-Ras, total RB (Tot RB), total p53 (Tot p53), MCM6, phosphorylated Histone H3 on serine 10 [H3(pS10)] and tubulin at days 5, 12 and 20 post infection with an empty vector (V) or H-RasV12 oncogene (R), n=3, representative blot is shown. For panels E, F and G, significance was tested with one-way ANOVA with post-hoc Tukey HSD tests. Error bars indicate SD of three independent experiments. Tukey HSD *P*-values indicate that *=*P*<0.05 and ***P*<0.01.

were starved for a week to induce quiescence. Starved normal cells compared to cells supplied with fetal bovine serum (FBS) showed no differences in the efficiency of TR. Besides, starved and FBS-supplied senescent cells showed similar TR values (Fig. S1E). These observations lead us to conclude that the decrease of TR efficiency is senescence-specific. Immunoblots showed the gradual reduction of phosphorylated RB, the absence of the E2F target MCM6 and the reduction of the mitotic marker H3(pS10) in H-Ras cells, confirming the establishment of senescence. P53 accumulates in senescent cells but decreases after 20 days post-infection in H-Ras cells (Fig. 1H).

The aminoglycoside gentamicin disrupts prokaryotic protein synthesis by binding to 16S ribosomal RNA, but also affects eukaryotic ribosome proofreading, inducing a conformational change in the ribosome-mRNA complex stimulating the efficiency of TR (Manuvakhova et al., 2000). We sought to investigate whether OIS can decrease TR stimulated by gentamicin. We added 900 µg/ml of gentamicin sulfate to OIS cells 24 h before luciferase assays. The non-readthrough controls were unaffected by gentamicin stimulation (Fig. S2A). Gentamicin increased TR efficiency and this effect was reduced in senescent cells both at UGA stop codons and the natural readthrough sequence of AQP4 (Fig. 2A; Fig. S2B,C). Of note, for the UGA reporter the TR efficiency was very small (0.1%) but increased more than 50-fold for the AQP4 reporter (6.9%). In both cases, the levels of TR were reduced by about a factor of 2 in senescent cells and we obtained similar results after gentamicin treatment (Fig. S2B,C). Strikingly, TR levels were the same in senescent and proliferating cells with the reporter containing the programmed readthrough region from Moloney Murine Leukemia Virus (MMuLV) (Fig. 2A). This region contains a UAG stop codon followed by a pseudo-knot structure (Houck-Loomis et al., 2011) and it allows up to 10% of ribosomes to suppress translation termination in order to synthesize the Gag-Pol polyprotein in cells infected with the virus (Yoshinaka

et al., 1985). Also, the aminoglycoside gentamicin did not affect MMuLV TR efficiency.

We also treated cells 72 h before cells lysis with $600 \,\mu g/ml$ of gentamicin and 25 μM of CDX5-1, a novel small molecule that potentiates TR efficiency when combined with aminoglycosides although it has by itself no effect (Baradaran-Heravi et al., 2016). We observed that while single gentamicin treatment increased UGA TR efficiency up to 6.6-fold in control cells, the combination increased it up to 16.5-fold. Surprisingly, the TR efficiency was still limited in senescent cells after the combination, which improved the efficiency only 1.7-fold over gentamicin treatment alone (Fig. S2D). Together, these results indicate that senescence engages a significant barrier for TR.

To investigate more broadly whether senescence affects natural readthrough signals, we made luciferase reporters using the stop codon context of several mRNAs, which we predicted *in silico* as candidates for readthrough (see Materials and Methods). We tested both their basal and gentamicin-stimulated TR. We found that the TR of VASP and HPN were significantly reduced during OIS while the TR of FBL showed a tendency to be reduced (Fig. S2E). ASPH TR was undetectable neither in proliferating nor in senescent fibroblasts. Nevertheless, after gentamicin stimulation, we could observe the TR decrease in senescent cells (Fig. S2F).

Translation termination is improved in PML-induced senescence

The tumor suppressor PML controls p53 and RB which are central for the establishment of OIS response (Vernier et al., 2011). Also, PML plays a role in antiviral responses (El Asmi et al., 2014; Regad et al., 2001) and, since many viruses use readthrough, we wanted to investigate whether PML modulates this process. Normal human fibroblasts IMR-90 cells were retrovirally transduced with a vector that allows expression of a conditionally inactive PML (pBabe-PML-IV-Estrogen Receptor) as well as with UGA, MMuLV and AQP4 luciferase reporters, in order to analyze TR efficiency in this model. Transduced cells were stimulated with 100 nM of the estrogen antagonist 4-hydroxy-tamoxifen (4-OHT), to induce PML-IV nuclear translocation and senescence (Acevedo et al., 2016). We found that induction of PML reduced basal or gentamicininduced TR at UGA stop codons (Fig. 2B). Intriguingly, the effect of PML on gentamicin-induced readthrough was much more important than the effect of OIS, suggesting that PML could be one important regulator of TR efficiency. TR was also reduced after PML induction with 4-OHT, with or without gentamicin, in AQP4 and MMuLV transduced cells (Fig. 2C,D). The decrease of TR efficiency in MMuLV reporter further suggest an antiviral role of PML-IV.

Circumventing senescence decreases the fidelity of translation termination

Although senescence in response to oncogenes includes a very stable cell cycle arrest, some cells escape from the process and progress towards malignant transformation. Cells that circumvent OIS display a gene expression profile typical of malignant cells and chromosomal aberrations (Deschenes-Simard et al., 2016). We sought to determine whether these cells also lose their tight control over TR. We obtained cell populations that bypassed OIS from long-term cultures (35 days) of IMR-90 cells expressing oncogenic *ras*. Cells that escaped senescence revert their morphology to that of normal growing cells (not shown) and expressed lower levels of oncogenic *ras* (Fig. 3A), indicating a mechanism that allow them to prevent pro-senescence *ras*/ERK signaling. This is consistent with our previous observation that decreasing ERK signaling accelerates

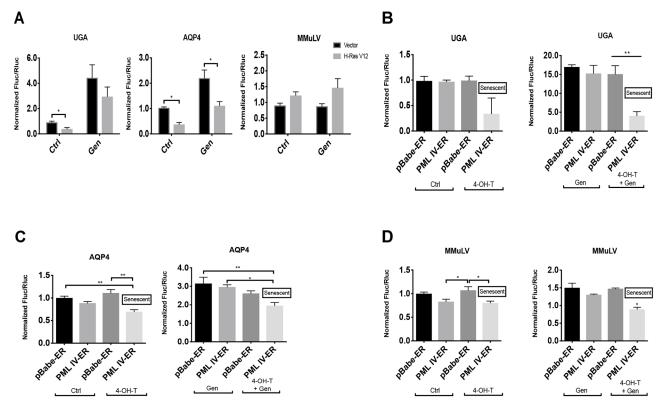


Fig. 2. Gentamicin-dependent translation errors are reduced in OIS and PML-induced senescence. (A) IMR-90 cells were transduced with either an empty vector (Vector) or H-RasV12 oncogene (H-RasV12), to induce OIS, and with a luciferase reporter containing either: a UGA within an artificial context, a stop codon within the natural context from AQP4 or a MMuLV programmed readthrough region for gag-pol proteins inserted in the intercistronic region of the reporter. Cells were treated with vehicle (Ctrl) or 900 μg/ml of gentamicin sulfate (Gen) for 24 h before measuring luciferase activities at day 12 post infection. Unpaired Student's *t*-test were performed. Error bars indicate SD of biological triplicates. *=P<0.05 is significantly different, using two-tailed Student's *t*-test, *n*=3. B-D. IMR-90 cells were transduced with pBabe-ER empty vector (pBabe-ER) or pBabe-PML-IV-ER (PML IV-ER), and with luciferase reporters UGA (B), AQP4 (C) or MMuLV (D). Cells were treated with vehicle (Ctrl) or 100 nM 4-hydroxy-tamoxifen (4-OHT), inducing or not PML-IV nuclear translocation to induce senescence. Moreover, cells were treated with vehicle or 900 μg/ml of gentamicin sulfate (Gen) for 24 h before measuring luciferase activities at day 12 post PML-IV induction. Normalized Fluc/Rluc ratios indicate the efficiency of readthrough. Normalizations are presented as means relative to empty vector-infected cells from three independent experiments with technical triplicates for each experiment, except for (C,D), which are representative of two independent experiments with similar results. B-D: One-way ANOVA with post-hoc Tukey HSD were performed. Error bars indicate SD of biological triplicates (B) or technical triplicates (C, D). Tukey HSD *P*-values indicate that *=*P*<0.05, **=*P*<0.01 are significantly different.

senescence bypass in H-Ras-expressing cells (Deschenes-Simard et al., 2013, 2016). Cells that bypassed senescence also had lower levels of the CDK inhibitor p16INK4a and higher levels of the proliferation marker KI67 (Fig. 3A). We next measured TR in these cells using the UGA stop codon or the natural signals for AQP4 (Loughran et al., 2014), VASP and HPN. In all cases, the cells that bypassed senescence displayed an increased TR even higher than control non-senescent cells (Fig. 3B).

E7 Oncoprotein increases TR

Since low translation fidelity and increased TR are associated to escape from senescence and malignant transformation (Marcel et al., 2013), we next investigated which tumor suppressor pathways activated in senescent cells could modulate TR. To investigate whether p53 and/or RB pathways are implicated in translation termination efficiency, we used E6 (inhibits p53) and E7 (inhibits RB) oncoproteins from HPV-16 virus. Transduction of E6 did not affect the TR levels in senescent cells. However, RAS-senescent cells infected with E7 oncoprotein or with both E6 and E7, showed a significant increase in TR at UGA stop codons and the natural readthrough signals from AQP4 and VASP (Fig. 4A–C). These results indicate that E7 targets, likely the pocket proteins family including RB, p107 and p130, mediate the readthrough decrease in

senescent cells. We also knocked down RB mRNAs' expression with shRNAs in H-Ras cells, but we failed to see the increase of TR levels (data not shown) that we observed in E7 expressing cells, suggesting that RB in coordination with p107 and p130 must influence the reduction in TR.

To further implicate the RB pathway in the control of TR in senescent cells, we used an in-frame deletion mutant of E7 whose interactions with RB, P107 and p130 are disrupted (E7 Δ 21–24) (Helt and Galloway, 2001). As expected, H-Ras cells transduced with wild-type E7 showed a twofold increase in TR compared to senescent cells but the mutant E7 $\Delta 21-24$ failed to do so (Fig. 4D). Besides, the proliferating cells transduced with E7 presented a tendency to increase TR, while the TR was not affected in proliferating cells transduced with the mutant E7 $\Delta 21-24$ (Fig. S3A). In addition, RT-qPCRs were carried out to evaluate the expression of E2Fs target genes in cells transduced with E7 or the E7 $\Delta 21-24$ mutant. As expected E7 but not E7 $\Delta 21-24$ increased E2F target genes expression (Fig. S3B). Next, we used a retroviral vector for CDK4 overexpression to block pocket proteins activity in senescent cells (Sherr et al., 2016) and, as expected, we observed an increase in TR (Fig. 4E). Relative cell growth and RT-qPCRs show that CDK4 overexpression does not affect proliferation arrest markers at day 12 post infection in senescent

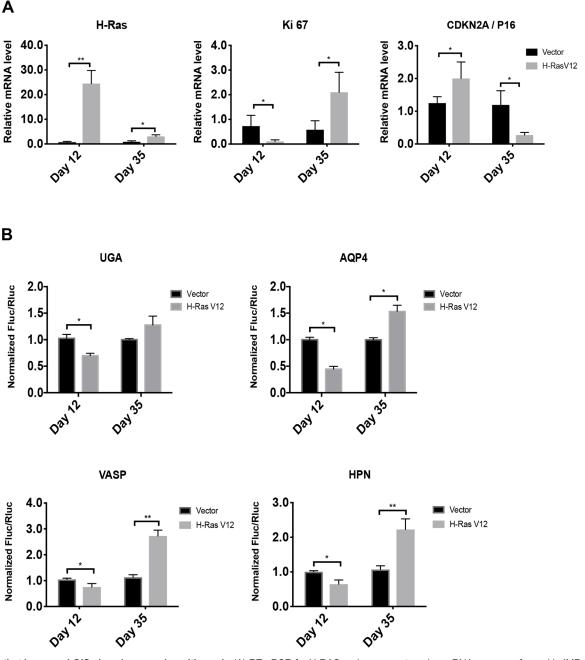


Fig. 3. Cells that bypassed-OIS show increased readthrough. (A) RT-qPCR for H-RAS and senescent marker mRNAs were performed in IMR-90 cells at day 12 and 35 post infection with an empty vector (Vector) or H-RasV12 oncogene (H-RasV12). Data are normalized over TBP and HMBS, and presented as means relative to vector infected cells, *n*=3. B. Luciferase activities in non-senescent and senescent cells measured at day 12 and 35 post-infection in cells having the indicated reporters. Normalizations are presented as means relative to vector-infected cells from three independent experiments with technical triplicates for each experiment, except for UGA reporter, which are representative of two independent experiments with similar results. Error bars indicate SD of biological triplicates (AQP4, HPN, VASP) or technical triplicates (UGA). *=P<0.05, **=P<0.01 are significantly different, using two-tailed Student's *t*-test.

IMR-90 cells (Fig. S3C,D). Taken together, these results indicate that the observed reduction in TR is not a simple consequence of the growth arrest of senescent cells and strongly suggest that the activation of the RB tumor suppressor pathway increases the fidelity of translation termination during OIS.

RB pathway activation reduces **TR**

Having demonstrated that RB pathway inhibition increased TR we next investigated whether activation of the RB pathway would inhibit TR. First, we used the CDK inhibitor palbociclib (Law et al.,

2015). Treatment of proliferating fibroblasts with palbociclib reduced TR of the AQP4 reporter and gentamicin-stimulated TR at the UGA stop codon (Fig. 5A,B). Interestingly, palbociclib also reduces TR in cells that spontaneously escaped from senescence (Fig. 5C). As expected, palbociclib also inhibits cell proliferation and strongly activates the RB pathway in proliferating and H-Ras-escaped IMR-90 cells (Fig. 5D; Fig. S4) restoring their senescent phenotype (Fig. 5E,F).

We recently demonstrated that extra-ribosomal functions of RPS14/uS11 and RPL22/eL22 were linked to the regulation of the

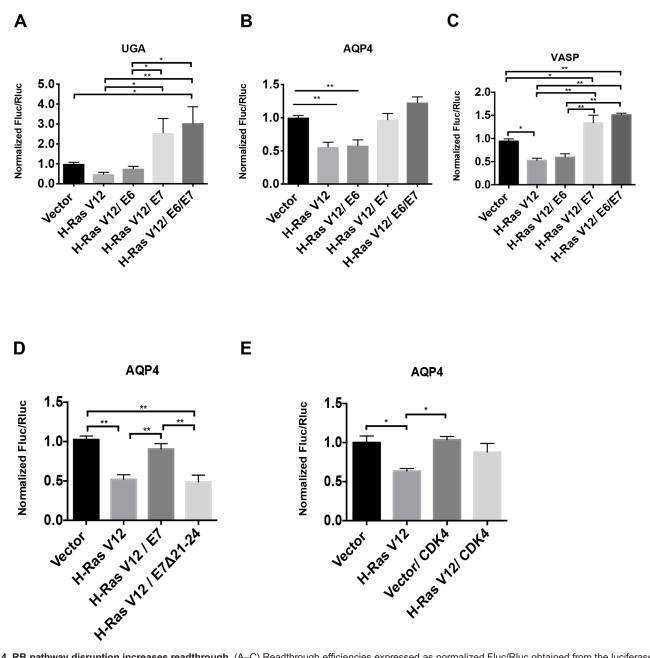


Fig. 4. RB pathway disruption increases readthrough. (A–C) Readthrough efficiencies expressed as normalized Fluc/Rluc obtained from the luciferase reporters bearing a UGA stop codon within an artificial context (A) or a stop codon within natural contexts from either AQP4 (B) or VASP (B) that were expressed in IMR-90 cells. These cells also expressed HTERT, an empty vector (Vector) or H-RasV12 and an empty control vector (pLXSN), E6, E7 or E6/E7 oncogenes to study the readthrough efficiency in proliferating versus senescent versus transformed-like cells, *n*=3. (D) Relative readthrough luciferase values from IMR-90 cells transduced with the AQP4 readthrough reporter, with an empty vector (Vector) or H-RasV12 and an empty control vector (pLXSN), wild-type E7 or E7 Δ21-24 mutant oncogene. (E) IMR-90 cells were transduced with an empty vector or H-RasV12 or CDK4 and AQP4 luciferase reporters to study the readthrough efficiency variations in proliferating versus senescent versus cells overexpressing CDK4, *n*=3. A–E. Luciferase activities were measured in non-senescent and senescent cells at day 12 post-infection. Normalizations are presented as means relative to vector-infected cells, *n*=3 with technical triplicates for each experiment. One-way ANOVA with post-hoc Tukey HSD were performed. Error bars indicate SD of biological triplicates. Tukey HSD *P*-values indicate that *=*P*<0.05, **=*P*<0.01 are significantly different.

cell cycle and senescence. We found that these two proteins interact with the CDK4–Cyclin D1 complex, inhibiting its activity and consequently activating the RB pathway (Bury et al., 2021; Del Toro et al., 2019; Lessard et al., 2019; Lessard et al., 2018). These results suggest that RPS14/uS11 and RPL22/eL22 could, as palbociclib, affect TR. We transduced IMR-90 cells with Myc tagged RPL22/eL22 or RPS14/uS11 as well as with the AQP4 readthrough reporter and measured TR efficiency at day 7, 12 and

14 after transduction. The expression of RPL22/eL22 or RPS14/uS11 was confirmed by immunoblots against the Myc tag (Fig. 5G). We also measured biomarkers of senescence such as RB, the E2F target MCM6 and the mitosis marker phospho-H3 (Fig. 5G). Cells bearing RPS14/uS11 showed a 15% decrease of TR at days 7 and 12 after transduction, and 30% decrease of TR 14 days after transduction compared to control cells (Fig. 5H). In contrast, RPL22/eL22-transduced cells showed a peak of TR

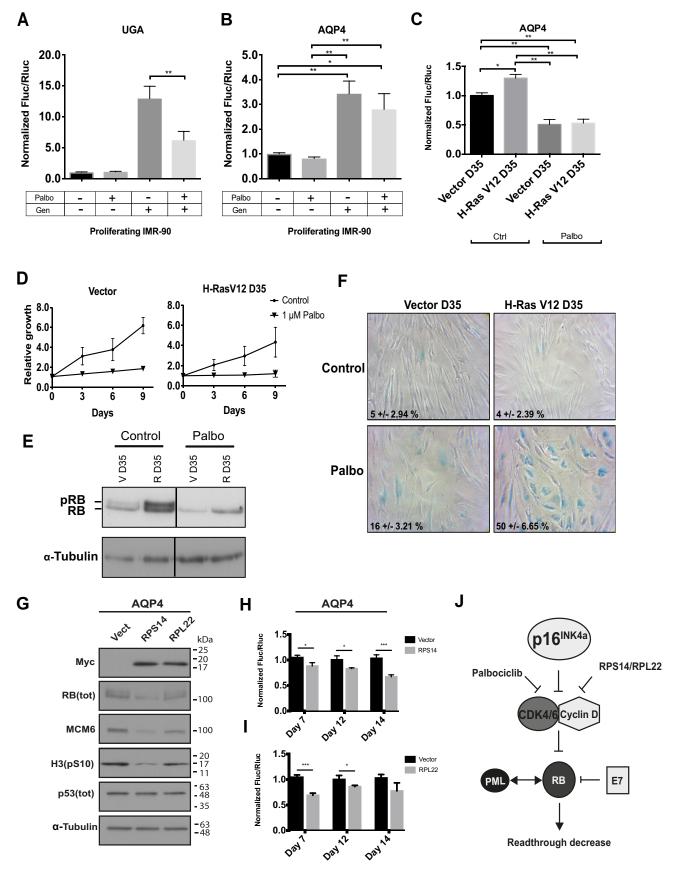


Fig. 5. See next page for legend.

Fig. 5. RB pathway activation reduces readthrough. (A,B) Normalized Fluc/Rluc ratios of IMR-90 cells transduced with luciferase reporters UGA (A) or AQP4 (B) and treated with vehicle and/or 1 µM of palbociclib (Palbo) and/or 900 µg/ml of gentamicin sulfate (Gen) for 5 days before luciferase measurements. Error bars indicate SD of three independent experiments, n=3. (C) Normalized Fluc/Rluc ratios of IMR-90 fibroblasts transduced with an empty vector (Vector) or H-RasV12 oncogene (H-RasV12) to induce OIS but cultured for 35 days until they bypassed the phenotype (D35) and with AQP4 luciferase reporter. Cells were treated with vehicle (Ctrl) or 1 µM of palbociclib (Palbo) for 5 days before measuring luciferase activities at day 35 post-infection. Normalizations are presented as means relative to vectorinfected cells, n=3 with technical triplicates for each experiment. One-way ANOVA with post-hoc Tukey HSD. Error bars indicate SD of biological triplicates. Tukey HSD P-values indicate that *=P<0.05, **=P<0.01 are significantly different. (D) Growth curves of proliferating (Vector) and ras bypassed (H-RasV12 D35) IMR-90 cells treated with vehicle (Control) or 1 µM of palbociclib (Palbo) for 5 days are shown. Data are presented as means normalized to day 0 of each condition and error bars indicate SD of three independent experiments, *n*=3. (E) Immunoblots for total RB (Tot RB) (note: upper band represents phosphorylated RB: pRB) and alpha-tubulin from non-senescent (V D35) and ras bypassed cells (R D35) following treatments with vehicle (Ctrl) or 1 µM of palbociclib (Palbo) for 5 days. Blots are representative of three independent experiments with similar results. (F) SA-β-gal of proliferating (Vector D35) IMR-90 cells and IMR-90 cells that have by-passed the senescent stage (H-RasV12 D35) treated for 5 days with vehicle (Ctrl) or 1 µM of palbociclib (Palbo) and fixed at day 35 (D35) post-infection. Data were quantified from many fields within one experiment to represent the entire petri dish. Three independent cell counts up to a total of at least 100 cells are presented as the mean and SD of positive cells. (G) Immunoblots for indicated proteins at day 7 post infection with an empty vector (Vect), pBABE-RPS14(WT)-Myc (RPS14) or pBABE-RPL22(WT)-Myc (RPL22): Myc (Myc-tag), total RB [RB (tot)], MCM6, phosphorylated H3 on serine 10 [H3(pS10)], total p53 [p53(tot)] and alpha-tubulin. Blots are representative of three independent experiments with similar results. (H,I) Normalized Fluc/Rluc ratios of IMR-90 cells transduced with an empty vector (Vector), or pBABE-RPS14(WT)-Myc (RPS14, H), or pBABE-RPL22(WT)-Myc (RPL22, I), and with the luciferase reporter AQP4. Luciferase activities were measured at days 7, 12 and 14 post infection. Normalizations are presented as means relative to vector-infected cells, n=3 with technical triplicates for each experiment Unpaired *t*-tests with equal s.d. were performed. Error bars indicate SD of biological triplicates. *=P<0.05, **=P<0.01, ***=P<0.001 are significantly different, using two-tailed Student's t-test. (J) Schema showing the RB activation/inhibition factors that modulate readthrough.

reduction at day 7 post infection, and a progressive recovery 12-and 14-days post-infection (Fig. 5I). We already reported that RPS14/uS11 is more efficient than RPL22/eL22 for inhibition of CDK4 and induction of senescence (Del Toro et al., 2019), explaining this difference. These results suggest that RPS14/uS11 haploinsufficiency in the 5q-syndrome (Ebert et al., 2008) and frequent RPL22/eL22 hemizygous gene deletions found in cancer (Ajore et al., 2017) could play a role in proteome diversity and tumorigenesis. Taken together, our results suggest that the RB pathway is implicated in translation termination accuracy (Fig. 5J).

Therapy-induced senescence and TR

To investigate whether a reduction in readthrough also applies to the senescent response induced by chemotherapeutic drugs in cancer cells (therapy-induced senescence: TIS) we treated PC3 prostate cancer cells with camptothecin for 24 h and confirmed that most of the cell population was senescent using the SA- β -Gal assay and western blots for phospho-RB, MCM6 and pH3(S10) (Fig. 6A,B). As found for OIS, TIS also reduced TR on both the UGA and the AQP4 reporters (Fig. 6C) and similar results were found in MDA.MB.231 breast cancer cells (Fig. 6D,E). TIS is not a stable

phenotype (Guillon et al., 2019; Milanovic et al., 2018; Saleh et al., 2020). After 20 days in culture, a population of growing cells emerged from the TIS population and continued to grow without signs of senescence. These cells that bypass TIS are known to be more malignant (Milanovic et al., 2018; Saleh et al., 2020) and they have an increased TR (Fig. 6F) along with higher phosphorylation of RB (Fig. 6G).

Senescence suppresses the expression of AGO1x, an AGO1 isoform generated by TR

AGO1x is an isoform of AGO1 that is expressed by TR of the AGO1 mRNA (Eswarappa et al., 2014; Ghosh et al., 2020; Singh et al., 2019). AGO1x acts as an inhibitor of the miRNA pathway (Singh et al., 2019) and in breast cancer cells it is required to maintain cell proliferation through inhibition of interferon gene expression (Ghosh et al., 2020). Senescent cells upregulate interferon gene expression (Fridman and Tainsky, 2008; Frisch and MacFawn, 2020; Moiseeva et al., 2006) suggesting that a reduced TR of AGO1 mRNA may lead to low levels of AGO1x and high levels of interferon genes in these cells. To test this idea, we triggered therapy induce senescence (TIS) in MDA.MB.231 breast cancer cells with Camptothecin (Fig. 7A,B). As expected, the expression of AGO1x was reduced in these TIS cells (Fig. 7C) but was dramatically induced after cells escaped from senescence (Fig. 7C,D). Senescence and the escape from senescence was characterized using KI67 (Fig. 7E,F) and immunoblots for RNR (a repression target of p53), p21 (an activation target of p53), MCM6 (a repression target of RB), phospho-H3 (a marker of cell proliferation) and yH2AX (a marker of DNA damage) (Fig. 7G). These results demonstrate that senescence can lead to repression of cancer driver proteins like AGO1x by reducing TR.

DISCUSSION

We show here that cellular senescence induced by oncogenic *ras*, the tumor suppressor PML, CDK4 inhibitors or chemotherapy reduces TR. Conversely, we also report that cells that bypass senescence have an increase in translational TR (Fig. 7H). The effect of senescence was demonstrated in a variety of reporters containing stop codons in a common context, within regions that stimulate endogenous TR and on an endogenous RT target, AGO1x. We propose a novel caretaker tumor suppressor activity for cellular senescence controlled mainly by the RB pathway in preventing TR and the generation of C-terminally extended proteins (Schueren et al., 2014; Stiebler et al., 2014). The potential for TR to confer advantages to cells in stress was previously reported in yeast cells expressing the prion PSI that enhances both TR and resistance to several stresses (True et al., 2004).

Senescence also reduced the stimulatory effect of aminoglycosides and the enhancer effect of CDX5-1 on TR (Manuvakhova et al., 2000). It has been reported that CDX5-1 potentiates G418-induced TR up to 180-fold compared to the aminoglycoside G418 alone (Baradaran-Heravi et al., 2016). Green and Goff reported that aminoglycosides can increase TR of the MMuLV gag-pol junction in HEK-293 cells (Green and Goff, 2015). However, using normal fibroblasts, we found that the same drugs did not have such effect. HEK-293 cells have an inactivation of the RB and PML tumor suppressor pathways due to expression of adenovirus E1A oncoprotein. In our normal cells, disruption of these pathways increases TR. It is thus plausible that in the context of an altered control in HEK293 cells, the MMuLV gag-pol junction TR is stimulated by aminoglycosides. In addition, Green and Goff used several aminoglycosides in their studies, gentamicin being the less

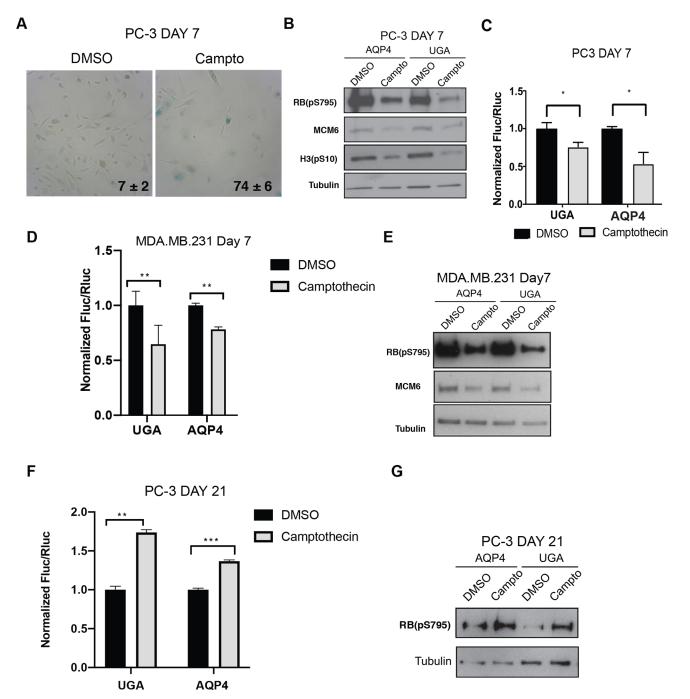


Fig. 6. Therapy-induced senescence reduces readthrough in cancer cells. (A) SA- β -gal staining of PC-3 cells treated 24 h with vehicle and/or 100 nM of camptothecin and fixed 7 days later (day 7), the percent positive cells ±SD is shown in lower corner, n=3. (B) Immunoblots in PC-3 cells transduced with luciferase reporter (AQP4, UGA) and treated as in A for the proteins: RB(pS795) [phosphorylated RB on serine 795], MCM6, H3(pS10) [phosphorylated H3 on serine 10] and tubulin. Blots are representative of three independent experiments with similar results. (C) Normalized Fluc/Rluc ratios of indicated readthrough reporters in cells as in A. Normalizations are presented as means relative to vehicle treated cells from (UGA) n=4 and (AQP4) n=5 independent experiments each with technical triplicates. (D) Normalized Fluc/Rluc ratios in of MDA.MB.231 cells transduced with the luciferase reporters (UGA, AQP4) and treated as in A. Normalizations are presented as means relative to vehicle treated cells, n=3. (E) Immunoblots for phosphorylated RB at serine 795 [RB(pS795)], MCM6 and tubulin in cells as in D, n=3. (F) Normalized Fluc/Rluc ratios of indicated readthrough reporters in PC-3 cells as in A, 21 days post-treatment when the cell population bypassed senescence. For all luciferase assays, n=3, error bars indicate SD of technical triplicates of each experiment. *=P<0.05, **=P<0.01, ***=P<0.01, ***=P<0.001 using two-tailed Student's t-test. (G) Immunoblots for phosphorylated RB at serine 795 [RB(pS795)] and tubulin in cells as in E, n=3.

active and its effects were reported as dose-independent and not consistent. Since gentamicin does increase TR in other stop codon contexts, we suggest that the pseudoknot structure of the viral signal may interfere with the binding or the action of gentamicin on the ribosome.

Our results indicate that translation termination tends to be inaccurate in cancer-like cells where the RB pathway is dysfunctional but is particularly efficient in senescent cells. Early work by Stanners and colleagues showed that SV40-mediated transformation increased mistranslation in mammalian cells

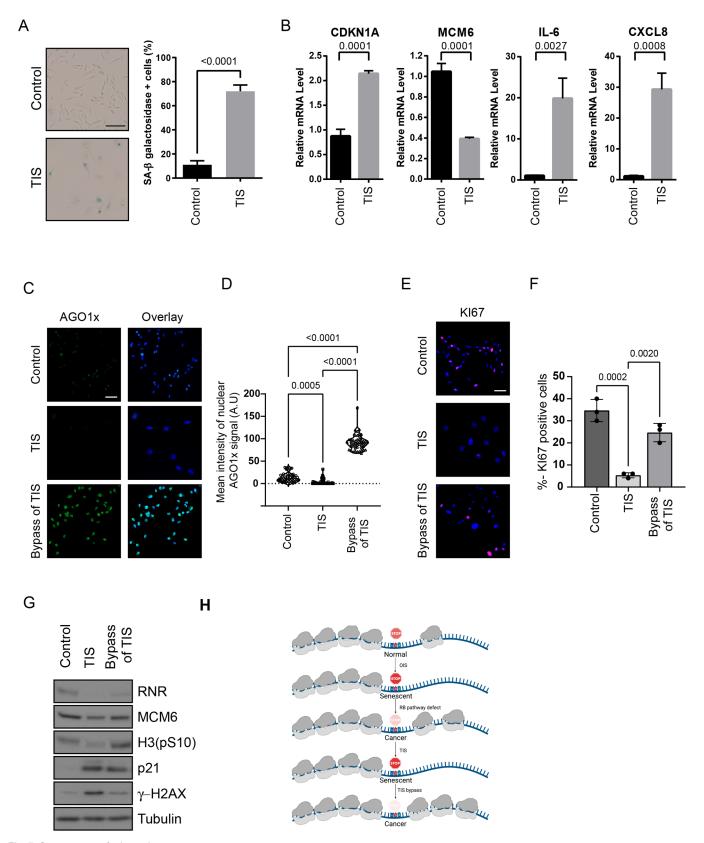


Fig. 7. See next page for legend.

(Pollard et al., 1982). SV40 encodes for the large T antigen that binds and inactivates the RB family of tumor suppressors (DeCaprio et al., 1988) like the E7 oncoprotein we used in this study. Recently, Ruggero et al. found that loss of SNORA24, a small nucleolar RNA

that mediates pseudouridylation of rRNA, leads to bypass of RAS-induced senescence in the liver promoting hepatocellular carcinoma. Intriguingly, cells lacking SNORA24 had an increase in TR and mistranslations (McMahon et al., 2019). Also Diaz and

Fig. 7. Senescence affects endogenous TR target AGO1x. (A) Images of senescence-associated β galactosidase assay and its quantification in MDA.MB.231 treated with 40 nM camptothecin (therapy-induced senescence (TIS)) or Vehicle (control) for 96 h. Data shows mean of three biological replicates and error bars show SD Students-t-test was performed and P value is indicated. (B) Relative mRNA levels of indicated mRNA in cells as in A. Data shows mean of three biological replicates and error bars show SD Students-t-test was performed and P value is indicated. (C) Immunofluorescence of AGO1x in MDA.MB.231 cells that were treated with 40 nM camptothecin (TIS) or Vehicle (control) or cells that were treated with camptothecin and left to recover for 14 days to allow bypass of senescence (Bypass of TIS). Scale bar=50 µm. A representative image of three biological replicates is shown. D. Quantification of results in (C). A minimum of 50 cells were scored for nuclear staining intensity using Image J. Statistical analysis was performed by ANOVA with Tukey post-test. A.U., arbitrary units. (E) Immunofluorescence of KI67 from MDA.MB.231 cells treated as in C. Scale bar=50 µm. A representative image of three biological replicates is shown. (F) Quantification of the percentage of cells expressing Ki67 shown in E. Statistical analysis was performed by ANOVA with Tukey post-test. (G) Immunoblot against the indicated proteins in MDA.MB.231 cells treated as in C. H3(pS10): phosphorylated Histone H3 at serine 10, and yH2AX: phosphorylated at serine 139 of histone H2AX variant. (H) Regulation of readthrough in senescent cells.

colleagues found that translational fidelity is decreased in the most aggressive breast cancer cell lines (Belin et al., 2009). They also reported that the p53 tumor suppressor controls translational fidelity and in particular the translation of oncogenic proteins from IRES (Marcel et al., 2013). In our experimental system, the RB pathway was more important to control TR levels in OIS. Consistent with this notion, we show that TR was reduced after TIS in p53 mutant PC-3 and MDA.MB.231 cells. However, we did notice that inactivation of p53 in cells where RB is also inactivated further increased TR, suggesting also an important role for p53 (Fig. 4A,C). Taken together, the evidence indicates that preventing translational errors and TR is a tumor suppressor mechanism.

The RB tumor suppressor pathway may repress genes that modulate TR. TR occurs when near cognate tRNAs outcompete the translation termination factors eRF1/eRF3 (Beissel et al., 2019; Cassan and Rousset, 2001). RB represses tRNA expression (Gjidoda and Henry, 2013) and this could prevent TR by near cognate suppressor tRNAs. Also, the translation initiation factor eIF3 interacts with post-initiation ribosomes and controls TR (Beznosková et al., 2013, 2015). RB could repress the expression of eIF3 subunits or sequester them in PML bodies (Vernier et al., 2011). Consistent with the latter mechanism the eIF3 subunits EIF3K and EIF3E (Int-6) localize to PML bodies (Morris-Desbois et al., 1999; Salsman et al., 2013). Viral proteins such as HTLV-I Tax can delocalize EIF3E from PML bodies (Desbois et al., 1996), an event that could facilitate TR.

Of special interest for a plausible pharmacological modulation of readthrough levels, we found that the CDK4 inhibitor palbociclib was able to reduce TR and re-induce a stable cell cycle arrest in cells that bypassed senescence. If the phenotypic plasticity conferred by C-terminal extended proteins plays a causal role in the origin of human cancers or their resistance to chemotherapy, palbociclib could be used to halt the progression of these lesions.

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Competing interests

The authors declare no competing or financial interests.

Author contributions

Conceptualization: N.d.T., F.L., J.B., J.G., S.I., V.B., L.B.-G., G.F.; Methodology: N.d.T., F.L., J.B., N.M., J.G., S.I., S.T., V.B., G.F.; Validation: N.d.T., F.L., J.B., N.M., J.G., S.I., S.T., V.B., L.B.-G., G.F.; Formal analysis: N.d.T., F.L., J.B., N.M., S.T., T.B., V.B., L.B.-G., G.F.; Investigation: F.L., G.F.; Resources: G.F.; Data curation: N.d.T., F.L., J.B., N.M., T.B., V.B., L.B.-G., G.F.; Writing - original draft: N.d.T., F.L., G.F.; Writing - review & editing: N.d.T., F.L., J.B., N.M., J.G., S.I., V.B., G.F.; Visualization: N.d.T., F.L., N.M., L.B.-G., G.F.; Supervision: F.L., L.B.-G., G.F.; Project administration: G.F.; Funding acquisition: L.B.-G., G.F.

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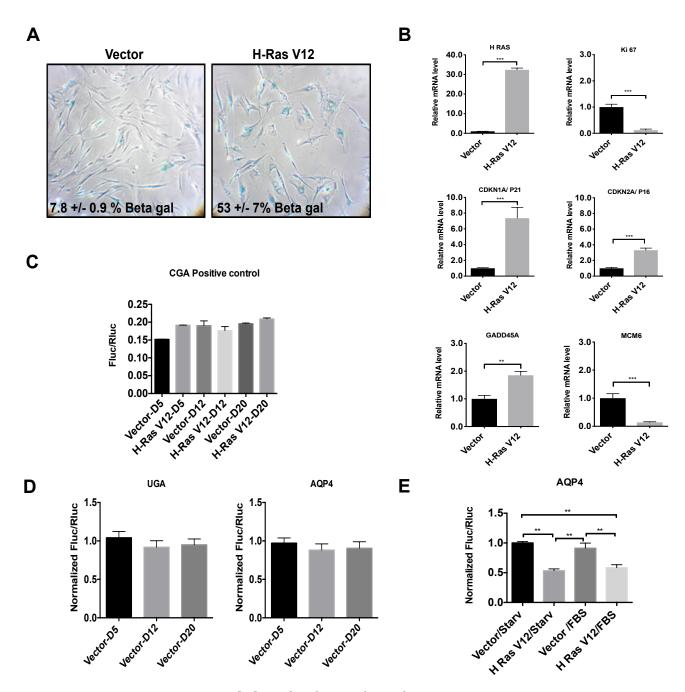


Fig. S1.Readthrough is reduced in OIS.A. SA-β-gal of proliferating (Vector) and senescent IMR90 (H-RasV12 oncogene) cells, fixed at day 12 post-infection. Data were quantified from many fields within one experiment to represent the entire petri dish. Three independent cell counts up to a total of at least 100 cells are presented as the mean and SD of positive cells. B. RT-qPCRs for senescent marker mRNAs were performed in IMR-90 cells at day 12 post-infection for cells as in (A). Data are normalized over TBP and HMBS, and presented as means relative to vector infected cells. Error bars indicate SD of technical triplicates. ** = p<0.01, *** = p<0.001 are significantly different, using two-tailed Student's t-test. C. Luciferase activities from non-readthrough control (CGA-Positive control) in proliferating (Vector) and H-RasV12 senescent cells measured at days 5 (D5), 12 (D12) and 20 (D20) post-infection. Assays are representative of 2 independent experiments with similar results with technical triplicates for each experiment. One-way ANOVA with post-hoc Tukey HSD were performed. Error bars indicate SD of technical triplicates. D. Normalized Fluc/Rluc ratios indicate that readthrough level does not change in nonsenescent cells (Vector) at day 5 (D5), 12 (D12) or 20 (D20) post-infection. Error bars indicate SD of biological triplicates. E. Luciferase activities from AQP4 reporter were measured at day 12 post-infection. Normalized Fluc/ Rluc ratios from non-senescent (Vector) and senescent cells (H-RasV12), starved (Starv) or supplied with fetal bovine serum (FBS) are represented. Starvation was performed for a week to induce guiescence. Data are presented as means relative to empty vector-infected cells, which are representative of 2 independent experiments with similar results with technical triplicates for each experiment. One-way ANOVA with post-hoc Tukey HSD were performed. Error bars indicate SD of technical triplicates. Tukey HSD p-values indicate that * = p<0.05, ** = p<0.01, *** = p<0.001 are significantly different.

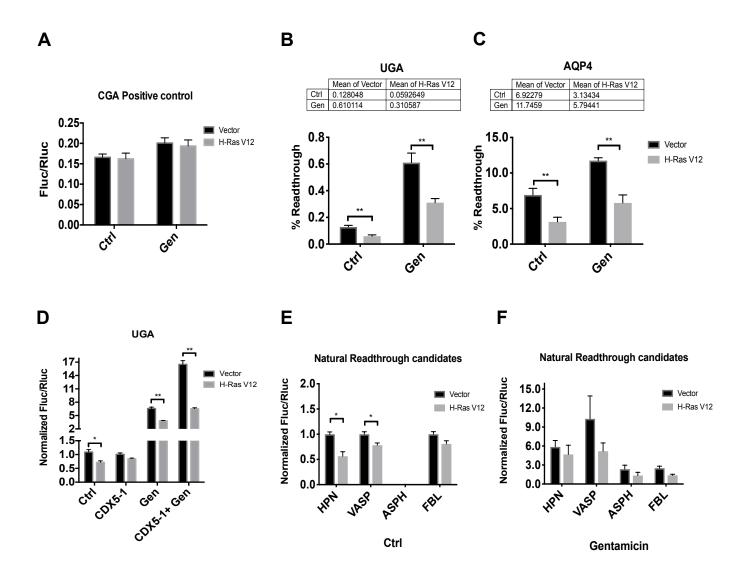


Fig. S2. Senescent cells are resistant to gentamicin-induced readthrough.A. IMR-90 cells were transduced with an empty vector

(Vector) or H-RasV12 oncogene to induce OIS and with indicated non-readthrough control luciferase reporter. Cells were treated with vehicle (Ctrl) or with 900 μg/ml of gentamicin sulfate (Gen) 24 hours before measuring luciferase activities at day 12 post-infection. Error bars indicate SD of biological triplicates. **B-C.** The percent of readthrough was determined by dividing Fluc/Rluc ratio from UGA or AQP4 luciferase reporters by Fluc/Rluc ratio from nonreadthrough controls multiplied by 100. Error bars indicate SD of biological triplicates. ** = p<0.01 is significantly different, using two-tailed Student's t-test. D. IMR-90 cells were transduced with an empty vector (Vector) or H-RasV12 oncogene to induce OIS and with a UGA luciferase reporter. Cells were treated with vehicle (Ctrl) and/or 600 μg/ml of gentamicin sulfate (Gen) and/or 25 μM of CDX5-1 72 hours before measuring luciferase activities at day 12 post-infection. Error bars indicate SD of biological triplicates. * = p<0.05, ** = p<0.01 are significantly different, using two-tailed Student's t-test. E. A stop codon within natural contexts from VASP, ASPH, HPN and FBL, was inserted in the intercistronic region of Rluc-Fluc luciferase reporter. IMR-90 cells were transduced with an empty vector (Vector) or H-RasV12 oncogene to induce OIS and with luciferase reporters. Luciferase activities were measured in nonsenescent and senescent cells at day 12 post-infection. Error bars indicate SD of biological triplicates. * = p < 0.05 is significantly different, using two-tailed Student's t-test. F. Cells as in (E) were treated with 900 μg/ml of gentamicin sulfate (Gen) 24 hours before measuring luciferase activities at day 12 post-infection. Normalized Fluc/Rluc ratios indicate the efficiency of readthrough. Normalizations are presented as means relative to vector-infected cells from three independent experiments with technical triplicates for each experiment. Unpaired Student's t-test with equal SD were performed. Error bars indicate SD of biological triplicates.

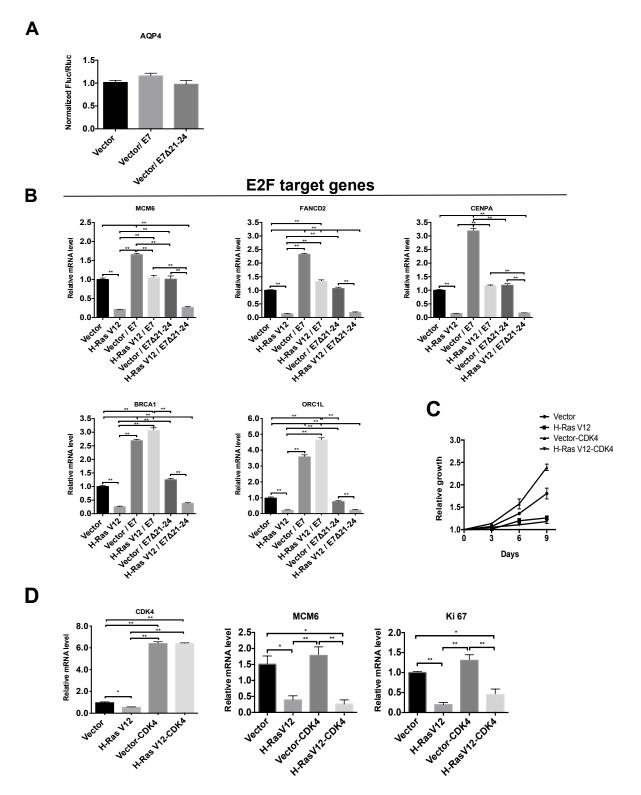


Fig. S3. RB pathway disruption affects the efficiency of readthrough. A. IMR-90 cells were transduced with luciferase reporter AQP4 and an empty vector (Vector), wild-type E7 or E7 Δ21-24 mutant oncogene. Luciferase activities were measured at day 12 post-infection. Normalized Fluc/Rluc ratios indicate the efficiency of readthrough. Normalizations are presented as means relative to vector-infected cells from three independent experiments with technical triplicates for each experiment. Error bars indicate SD of biological triplicates. **B.** Representative RT-qPCR from E2Fs' target mRNAs were performed in IMR-90 cells transduced with an empty control vector (pLXSN), wildtype E7 or E7 Δ21-24 mutant oncogene, and with an empty vector (Vector) or with H-RasV12 oncogene to induce OIS at day 12 post-infection. Data are normalized over TBP and HMBS, and presented as means relative to vector infected cells. Experiments were done three times with technical triplicates for each experiment. Error bars indicate SD of technical triplicates. Tukey HSD p-values indicate that ** = p<0.01 is significantly different. **C.** Growth curves of non-senescent (Vector) and H-RasV12 senescent IMR-90s overexpressing or not CDK4. Data are presented as means normalized to day 0 of each condition. Assays are representative of 2 independent experiments with similar results with technical triplicates for each experiment. Error bars indicate SD of technical triplicates. **D.** RT-qPCRs for CDK4, MCM6 and KI67 mRNAs were performed in IMR-90 cells as in (C) and at day 12 post-infection. Data are normalized over TBP and HMBS, and presented as means relative to vector infected cells from three independent experiments with technical triplicates for each experiment. One-way ANOVA with post-hoc Tukey HSD were performed in (A, B, D) and Unpaired Student's t-test with equal SD was performed in (C). Error bars indicate SD of biological triplicates. Tukey HSD p-values indicate that * = p<0.05, ** = p<0.01 are significantly different.

A E2F target genes

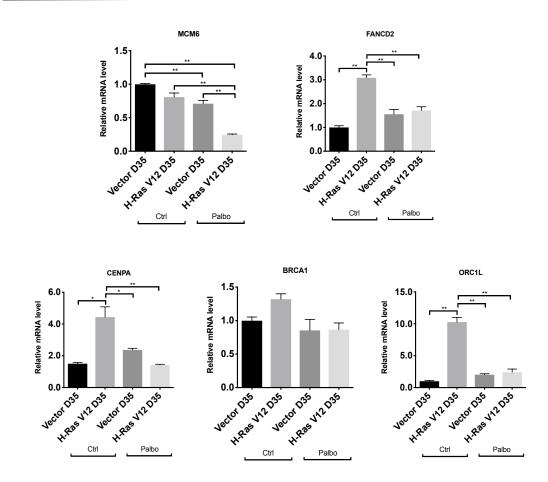


Fig. S4. E2Fs target genes.A. RT-qPCR for E2Fs' target mRNAs were performed in IMR-90 at day 35 post-infection with an empty vector (Vector D35) or with the oncogene H-RasV12 (H-RasV12 D35) and treated with vehicle (Ctrl) or with 1 μ M of palbociclib (Palbo) for 5 days before cell lysis. Data are normalized over TBP and HMBS, and presented as means relative to vector infected cells from three independent experiments with technical triplicates for each experiment. One-way ANOVA with post-hoc Tukey HSD were performed. Error bars indicate SD of technical triplicates. Tukey HSD p-values indicate that * = p<0.05, ** = p<0.01 are significantly different.

Table S1. PCR cloning primers

Name	5' forwad primer (5'-3')	3' reverse primer (5'-3')
pMSCV-RLUC-FLUC	GGAAGAAAGCGGCCGCTTCAGATCCGCTAGAGCC	TGGATGCATGAATTTCGTCATCGCTGAATAC
UGA STOP CODON	CCAAGCTTGCACCAGTGACCAGCAAGGTGTACG	CGTACACCTTGCTGGTCACTGGTGCAAGCTTGG

Table S2. Readthrough region

	Gene name		Readthrough context
AQP4	Aquaporin 4	NM_001650.4	atctggagaggtattgtcttcagta tga ctagaagatcgcactgaaagcagacaagactccttagaa
ASPH	Aspartate beta hydroxylase	NM_004318.3	AGAACAGCAGGAAGTACCACCAGATACT TAA AGCTTCAAAAAGACTGCCCCTACCACCGGGCC
FBL	Fibrillarin	NM_001436.3	GTACAGGCCACCCCCAAGGTGAAGAAC TGA AGTTCAGCGCTGTCAGGATTGCGAGAGATGGG
HPN	Hepsin	NM_182983.2	TCGAGGCCAGCGGCATGGTGACCCAGCTC TGA CCGGTGGCTTCTCGCTGCGCAGCCTCCAGGG
MMuLV	Moloney Murine Leukemia Virus		CTAGGGAGGTCAGGGTCAGGAGCCCCCCCCTGAACCCAGGATAACCCTCAAAGTCGGGGGGCC
VASP	Vasodilator-stimulated phosphoprotein	NM_003370.3	GGAGCTGAGGAAGCGGGGTTCTCCC TGA CCACAGGGACCCAGAAGACCCGCTTCTGGGCCCCA

Table S3. Readthrough candidates

Readthrough code		peptides found by MS analysis		« confistop-DNA 3/UTR TGA:DASAGEACCCASEBBERCCCSEBBBERCCCASECTEBBEBCCCASECTACASCCAGETTACACCT TGA:DASAGEACCCACASEBBERCCCOSEBBBERCCASECTACASCCAGETTACACCCAGETTACACCT TGA:DASAGEACCCACASBERCCACCBBBBERCCASECTACACCCAGETTACACCCAGETTACACCT TGA:DASAGEACCCACASBERCCACCBBBBBERCCASECTACACCCAGETTACACCACACC	RTP (readthough propensity)(Ref 22)	RTP Linfs3 (Ref 22)
RT_012331.1 RT_006854.1	FAM19A5 family with sequence similarity 19 (chemokine (C-C moti ZNF182 zinc finger protein 182	f) APSEDGLRLR YGSKFSLSSFHLSHNPK	NP_001076436. NP_001171570.1, NP_001	TGArasacraegoccctpagggecctggggetggccttggtcccggpatgcccaegitctagccaegitctcact Moreotype Continue Contin	0.309 0.143	0.646 0.215
RT_020801.1 RT 017649.1	ACADS acyl-CoA dehydrogenase, C-2 to C-3 short chain ACSLS acyl-CoA synthetase long-chain family member 5	LGGPAGAPWGPQMGSVLPPR VLKYLPAHCALLVR	NP_000008.1, N NP 976313.1, NP 976314	TGAgcccqcgqcggctqccccaggactqcgggaaggcqccgggagcctcaacccaacc	-0.077 -0.08	0.066 -0.226
RT_009441.1	ADCK2 aarF domain containing kinase 2	AGGHSQEPLLWQLGR	NP_443085.2 XP_01151	To-language-gategocicitytegocicityteappactuge-gategocicityteappactucicitatigocaptugga-cq 664 tittaaantugga-ca-cantita-aantiga-cct-cragetyga-gategocicityteitytego- To-language-ty-cquartita-aantiga-cct-cragetyga-gategocicityte-cragetyga-gategocicityte-cragetyga-gategocicityte-cragetyga-gategocicityte-cragetyga-gategoci-cragety-cragety-companya-cragety-cragety-cragety-cragety-gategocicityte-cragety-gategocicity-cragety-gategocicity-cragety-gategocicity-cragety-gategocicity-cragety-gategocicity-cragety-gategocicity-cragety-gategocicity-cragety-gategocicity-gateg	0.237	0.065
RT_013024.1	ADCY7 adenylate cyclase 7	GLLLDSEK	NP_001105.1 XP_01152	ccacpccaatccaaagcatgcagatgcttgtgcatgttggcttttggactgcactggaggatttctagacacat 9511 excacapattteetctpaagacaccatspaccataa	-0.029	0.028
RT 020165.1	ADGRES adhesion G protein-coupled receptor ES	MVLDGPAAPVATAALYTK	NP 510966.1, N	1 Ghaggeyangguttegasegeccagangeterigtegaceangeaguttighacegangacantententectett 6373 opteraceantentententeraceterieterietega. 7373 opteraceantentententeraceterieterieterieterieterieterieterieter	0.084	0.12
RT_004627.1	AES amino-terminal enhancer of split	LGGGTEGRQR	NP_945320.1, NXP_00672	TAGcagegagccaggacaggaagttaggaaggttaggaagggagaagagggaagagaaga	0.232	0.107
RT_024040.1	AGAP2 ArfGAP with GTPase domain, ankyrin repeat and PH domain	2EGLVHGR	NP_055585.1, NXP_00526	402 aggrescritagetttictrateceatticegetttictrictrictegragetgglagatactigettigs algegagesageta 403 aggrescritagetttictrateceatticeggettictrictrictrictegragetgglagatactigettigs algegagesageta 404 aggrescritagettictrictrictrictrictrictrictrictrictric	0.059	0.072
RT_009047.1 RT_002208.1	AK1 adenylate kinase 1 AKAP8L A kinase (PRKA) anchor protein 8-like	QRWSRFPSSEPRPTPS PELGAGGAR	NP_000467.1, XP_01151 NP_001278407.XP_00525	5273 TAGeaacpetiggagecgettecccagetcageacccgeccetga 924 TGAcccagegetgggggggggcgcggagetcggagetggaacctaa	0.054 0.42	0.424
RT_017612.1 RT_022128.1	alpha-(1,3)-fucosyltransferase 9 AMOT angiomotin	NFSSLAHLINILMR SRAADYOOK	NP_006572.2 XP_01153 NP_573572.1 NXP_01152	652 T∆∆aatttttratractteraractteraraatatttteateraatattteateraagatatraggagataraggagateraaratactartttetetraraatttttatttatraccetetragggtaa	-0.081 0.051	-0.089 -0.11
RT_021756.1	ANKLE2 ankyrin repeat and LEM domain containing 2	EGRVICLLLNCQK	NP 055929.1, XP 00526	3141 TAPaccgccaaatcaagagctgcagattatcagcaasaatgcttttaa 2085 TAGgcttggcgctgggctctcggttgttcttcatttttaaagaggaagggtcatatgttattgctaaactgtcaaaaaggaatatattctgattaa	-0.028	-0.11
			ctactcactagactaga	gagggringscarcccrccrccgrccqmtmathtmtmataacccctrcqrcqsagcrtggagccccaggaatgagcaggcaggagactgagaatgagaatgagaatgaga எதுர்துதுக்கு நேர் நக்கு நக்		
RT_002681.1 RT_001281.1	ANKRD13D ankyrin repeat domain 13 family, member D ANO10 anoctamin 10	AIAPGGLARPLPAR GLCLCHTCHGGRGGTRGSIVAPER	NP_997237.2, XP_01154 RNP 001191762.XP 01153		0.041 0.236	0.066
RT_005833.1 RT_021610.1	APLP1 amyloid beta (A4) precursor-like protein 1 APPL2 adaptor protein, phosphotyrosine interaction, PH domain an	AOTSPLPGAPEPOLPA	NP_001019978.1, NP_005 NP_060641.2, NXP_00671	2785 TGAcctacttgcgcccgtracccttraccccttagagcccagaacctccctcttacttgagccccagaaccccaactccagctgg 20075 TAActacttgcgcctgtgggggaggagaacaaggaagggaggactacctcctaagggttttaacgtcttgacattacaggcacattgactgatttcgaaggtgacaatcgtttgggaatgtaa	0.271 0.027	0.432 0.147
_				AUV5 IAActeatregecrigtggggaagageaaasaggaagareactectaaaggirttaaegectegaataaaggeacatrgattecgaaggeggaacaategttigtggaatgtaa TGAgecrigtggggaagteaaggaaggetgaactegagaaggetgettagetgistetgetgistetgetgetgetgaaggetgaaggaaggaaggaaggaagg	0.027	
RT_023876.1 RT_007575.1	AQP12B aquaporin 12B ARHGAP17 Rho GTPase activating protein 17	ALGSSKAAARSPVAR RTWRPPLK	XP_01150 NP_060524.4, NXP_01154	Ti-Gegracteggggegrtcanagerdepagracegggategtragetregterdeptschangszer Ti-Gegractegggategtraangerdeptschangszereggategtragetregterdeptschangszer Ti-Gegractegggategtraangerdeptschangszereggategtragetregterdeptschangszereggategtragetregtragetregterdeptschangszereggategtragetregtragetreggategtragetreggategtragetreggateggat	0.214 0.319	0.066
RT_018159.1 RT_023604.1	ARHGEF1 Rho guanine nucleotide exchange factor 1 ARPP21 cAMP-regulated phosphoprotein 21kDa	IGGLFFNIYYLR KLOMFRNSK	XP_00525 NP_001254545.XP_00671	8679 TGAattgaaggtttatttttaatatatatatataagaaggasttigtigtigtiga 4165 TGAaaactgcaaatggaaaggaattcaaaaggaatttagattaaaagttaaatta	0.186	0.382
RT 026723.1	ASB14 ankyrin repeat and SOCS box containing 14, predicted transc	riSSSAWEAEAGGLLHLGRSR	XP 00526	2744 TAAtranacratictaatoganagotataatttigcagcigtatticttaanattiracttagagticatgattrattittigctigaagatraatgiraatgiraatgiraatgiraagagtiraaga	0.161	0.151
RT_011768.1	ASPH aspartate beta-hydroxylase	KTAPTTTGGPA	NP_001158227.1, NP_001	5997 TAAspetteaaaaspatgecectaccaccacagagagaccagcctaac TGAgggagagtattgccctcqtgagcacagagactctcctagggaggggag	0.123	0.033
RT_021372.1 RT_013285.1	ASTN2 astrotactin 2 ATGRA autophany related RA	GRVLPSVSTETLHGR DSSLIPR	NP_054729.3, N NP_076990.4. NP_001070		0.001	0.028
RT_006517.1 RT_003127.1	ATG9A autophagy related 9A ATP10D ATPase, class V, type 10D	DFEEVSLQAR	NP_065186.3, XP_00524 NP_775965.2 XP_01152	1866 T Microsagettyag-caggitrictytigscrusgsagsagsagscarcetytecrdecatecgictycctgccateggag-ggetricttyagtyticctggcccacetytigtggittytigtytictytictgcctagccaagggagstyccaacateggctigccaacateggagsagsagsattigggagagagsattictcaagca	0.203	0.444
RT_003127.1	ATP11C ATPase, class VI, type 11C	QNPNLELPMLLSYK	NP_775965.2 XP_01152	3127 TA-kagsantegsantettgsacegctatigtstittgitchesasgespartegsestgitstasegscatus TGAsaggieretterdspantgeratigtsgiteretestgitergetegsgeggsaceceaaraggec cegggggggaacecegocceaaceceaaceaaggstigtseagretigetegstittgittgittgittgittgittgittgittgittgi	0.129	0.152
				agccatccgctggcttggccagcagaaccagccccaagccactttggtaaataaa		
RT_007887.1 RT 027025.1	ATP13A1 ATPase type 13A1 ATP6V0B ATPase, H+ transporting, lysosomal 21kDa, V0 subunit b	CLPEMAVLVPTAHPGCR LGVQGPPCTPLLLR	XP_01152 NP_004038.1, NP_001034	666 aaaaaaaaaaaaaaaaaaaa. 2970 TAGatgatatgtgtgggtggggccgtgcctcacttttatttat	-0.032 0.123	0.056 0.127
RT 025167 1	RCORL1 RCI 6 coregressor-like 1	LONFAUR	NP 068765 3 XP 00526	TGAccagagaaacagcccctcctcttctttcttcccagattcgcccttccccacctccttgtcttttccccaaccaga	0.176	0.341
RT_020389.1	C10orf105 chromosome 10 open reading frame 105	WGVHKHAPTSP	NP_001161862.XP_01153	6940 carcagastgragaadgaggcaataatacggaccaacaagaagccgccttatcaatgccagcattag 9533 TAAtgggggtgtccacaacacagccccccaatcccctag	0.056	-0.113
RT_023564.1 RT_024012.1	C1GALT1 core 1 synthase, glycoprotein-N-acetylgalactosamine 3-be C1orf186 chromosome 1 open reading frame 186	IPNIFNGVOFSMDSYL	NP_064541.1 XP_00524 NP_001007545.XP_00527	1008 TGAasgaaaatcatgaatgaacaaaggtaa 10908 TGAattccaaatattttaatgaggtccagttctctatggattcttacatttaa	0.112 0.197	0.056
RT_024012.1 RT_021492.1 RT_007816.1	Clorf186 chromosome 1 open reading frame 186 Cls complement component 1, s subcomponent C22orf15 chromosome 22 open reading frame 15	YIPPASPR GDGLHTVVR	NP_958850.1, NXP_00525 NP_872326.2. XP_00526		0.001 0.116	-0.075 -0.15
RT 019768.1	C22orf23 chromosome 22 open reading frame 23	LTAPSAEK; QSPSIPTRTCV	NP_001193991.XP_00526	555 Talegagagattgaractigletgagattactartiger 1593 Taletteritoragagattgaractigletgagattactartiger 1593 Taletteritoragagattgaractigletgagattactartiger 1593 Taletteritoragagattgaractigergattgartactattgagattgagattgartactattgaga	0.131 0.364	-0.134 0.122
RT_013060.1 RT_024351.1	C5orf60 chromosome 5 open reading frame 60 CACNA1A calcium channel, voltage-dependent, P/Q type, alpha 1A	VTGITGLCHR stTHPTRGAAQRPR	XP_01153 NP_001120694.1, NP_075	NOS TAGEGRAPHICEA AND AGRAPHICE AND AGRAPHICE AND AGRAPHICE AND AGRAPHICE AND AGRAPHICE AND AGRAPHICE AGRA	-0.086	-0.112 -0.112
RT 018787.1	CAPN1 calpain 1, (mu/l) large subunit	OPRPPVPSPPSHHR	NP_001185797:XP_00671	gittatttgctragge-agaattgitgigg-cctigctrigtge-catagge-cragge-tragga-tgga-tcctggg-cccaccc 1683 attgc-aager-aagga-aagge-agget-tcttgtctrage-catagge-ccagge-tcct-gag-	0.169	0.119
RT 005409 1	CASK calcium/calmodulin-dependent serine protein kinase (MAGU)		NP 001119527.XP 00672		-0.161	-0.156
RT_005409.1 RT_010840.1	CASK calcium/calmodulin-dependent serine protein kinase (MAGU) CCDCS8 coiled-coil domain containing 58	REILFFFFFFFFRTGSSHK	NP_001119527.XP_00672 NP_001017928.XP_00524	1200 graggichatggicrotegapetherchetgischatgdigg 3766 TAAgapagantettimittimittimittimittimittaggardiggischetzafangagetha2 TGAgapagantettimittimittimittimittimittimittimitt	-0.161 0.285	-0.156 0.259
RT_004671.1	CCL3 chemokine (C-C motif) ligand 3	GVQKLR	NP_002974.1, N	Linggggtctagaagtctagggccagtggggggggggggggg	0.291	0.028
RT_012415.1 RT_004395.1	CCNH cyclin H	PFEVDFSMLTNQEK NWTVPGK	NP_001230.1, NP_001186		0.402	0.48
	CD72 molecule		XP_00671	105a agaatagastagastagastagastaga TG-Aggragetgetatecceatetecetgectegaetetagaggettetetetetetagg		
RT_016795.1 RT_006924.1	CD82 molecule CDH23 cadherin-related 23	TLLPILTESRGLSGA FILEGGK	NP_002222.1, NXP_00671 NP_001165402.XP_01153	4030 gettgecteccaetteactgepaagaccetctggecatectgactgaaagtagggggcttagectettggggettagectettggggtttgetgggttttettetggggttttgetgttgetge	0.065 0.136	0.119 0.035
RT_019066.1 RT_008545.1	CDK2AP2 cyclin-dependent kinase 2 associated protein 2 CEACAM4 carcinoembryonic antigen-related cell adhesion molecul	LDLSGHCRAPASPWPSSR	NP_005842.1, N XP 01152	digitactaneacaircaggatterigiterigiterigiteggatecetecaggatecaggatecetecagga digitactaneacaircaggatterigiterigiteggatecetecaggatecaggatecaggateggatecetecagga digitactaneacaircaggatterigiterigiterigiteggatecetecaggatecaggateagateggateggate	0.153 -0.015	0.152 -0.122
RT_022767.1 RT_002593.1	CEPS7L1 centrosomal protein 57kDa-like 1	QNSKTVTLMNFVSETLNCLKWF ISYTRODKTEK	NP_001077004.XP_00526 XP_01153	8129 TAAcaaaacagcaaaactetcaccttaateaacttigtcagtgagaccttgaattgtctaaagtggttttaa	0.29 0.333	0.468
RT_023936.1	CFAP54 cilia and flagella associated 54 CFHR3 complement factor H-related 3	GSIVTLNVCPTSTFPLLTLMVSK		1470 TGAatatectatacaegggatgataaaactgagaaaataa 9546 TAAggeagcattgttacectaaatgtatgtecaacttecactttecactttecacttetcactettatggtetcaaagcttgeaaagatagttetgatattgttaatttetactttatttecaaagaaaattaatataa	0.059	-0.059
RT 003463.1	CHRNA1 cholinergic receptor, nicotinic, alpha 1	AENELSLALPWNLPEQRRAGEED	SNP 000070.1, N	TGAgcagaaatgagctgagcttagctctgccctggaacctaccagagcagagagggagg	0.219	0.292
RT_021669.1	CLEC12A C-type lectin domain family 12, member A	SVGGGGSRL	NP_001193939.XP_01151	2968 TGAppratraatraaatacatttaappaptetappppptetapppptttappctatap	0.238	0.119
RT_010570.1	COG3 component of oligomeric golgi complex 3	SLAVCRTPR	NP_113619.2, XP_01153	T-Magangercegroupgertyterschambigteitgignagsgapgaraggettagsambitteragtertgeraggarancc 3531 gaggamtegtatgtaggamegterccegamaccancegagetgigetgercagtgetga	0.213	0.114
RT_016946.1	COL1A1 collagen, type I, alpha 1	TPSIPTWLPPTQPTFPPTR	NP_000079.2 XP_01152	TAAntectctateceacetagetceteceacetagettececeaacettececeaacetggaaacageaacegaaacegaa 390 ctga 886 TAGagaatgcgaaattaccaacatgtgccaagagaaacttectagggggctaagacttectagactgtgctaag	0.046	-0.078
RT_004138.1 RT_014034.1	COL4A4 collagen, type IV, alpha 4 CORO2A coronin, actin binding protein, 2A	RMRNSPTR AETSALLTLR	NP_000083.3, XP_00524 NP_438171.1 NXP_01151	886 TAGsgasategasastacacasacgtsgccasagasastactcasgasgctasgacttctagactsgctasg 20475 TGAscassactctsectcatcasectsaccatcsectcasterseaseattsease	0.2 0.259	0.215
RT_024782.1 RT_011692.1	CPS1 carbamoyl-phosphate synthase 1, mitochondrial CREB3L4 cAMP responsive element binding protein 3-like 4	HPSPIIK AGTDLPGPLPDHK	NP_001116105.XP_01150 NP_570968.1, NXP_00671	20475 TG/gerapsgacctt/gecetectacectagggeaccate/gegetectagggggggttag 5966 TA/gegrapsgacaccate/gegetectaggggaggttag 6767 TG/gerapsgacaccate/gegetectagggaggttag 6767 TG/gerapsgacaccate/gegetectagggaggaggttag 6767 TG/gerapsgacaccate/gegetectagggaggaggttag 6767 TG/gerapsgacaccate/gegetectagggaggaggttag	0.222 0.075	0.215
RT 021761.1	CUX1 cut-like homeobox 1	GAAAIGRAAR	NP_001189472.XP 01151	671 TG/eg/tgpas-aga-cttict/ggcccattictgalca-aggsalct/gggcttettatggctttgctccca/gggaltccta-ttaggtgttgccct-aggggtccaaattacttraggca-accccaaggagtgtctttagtcttgcctga TG/ggggccg-gggcctggggg-gggg-gggg-gggg-gggg		0.008
				2074 cagggcangactegagggtgattegaggggtgattettgecagggggggggg		
RT_013213.1 RT_019282.1	CYBS61 cytochrome b561 CYBSD2 cytochrome b5 domain containing 2	RLQDCRLR AVASSVNNTQRALPST	NP_001906.3, NXP_00525 NP_001241685.XP_01152	12262 ccggagatggctttggcagcagggggggggggggggggg	0.292	0.156 -0.112
RT_011989.1	CYGB cytoglobin	APVNQKHMAQVPQHAARPALPT	LP XP_01152	12296 TGAccaeastagecccgggctggctectgetectecteccectettercgtrageacecaeacaagaagtgggggtectggtetggctggagecaageca	0.393	0.658
RT_016292.1	DAAM2 dishevelled associated activator of morphogenesis 2	PGELATQEAGRQGLVR	NP_001188356.XP_00671	12479 ttaa TGAstctttctgttgasgasatccstgttatagasasgasctttgcagtcsgasattcgtcagasas	0.226	0.373
RT_018283.1	DACH1 dachshund family transcription factor 1	VLLRELPEFCVLMFFK	NP_004383.4, NXP_01153	Lowertuncegrapageautrcagtrangassagaantregrapticagearangeragggasagrungsassa 5699 aaatasagtrangggaartregrattinggataategritumtgataatagruntsagaatragagtrangassassassassagtitticaatgattitacatga	0.121	0.44
RT 013666.1	DENND2A DENN/MADD domain containing 2A	LGSSLDEDLGAAWEDSPRKGAR	NP 056504.3 XP 00525	acctggggccgcctggggggcagccccagaaagggagcccgagaccagcgtgtcgccgacatgcaaatgggttgttt 6495 tggtggttgggtttttttttacttagatattaa	0.12	0.536
RT_013306.1 RT_022377.1		RLASWALLAWPR LSSVPWSDHK	NP_690618.2, NXP_01151		0.227	0.151
RT_007395.1	DHODH dihydroorotate dehydrogenase (quinone) DOCK11 dedicator of cytokinesis 11	GNADVRDNETDLSQEYLELCK	NP_001352.2, XP_00525 NP_653259.3 XP_00526	1337 TG-Aggasangcrighatgagsangcrighattgasactiticraaggantatgagsangcritigiscriggartagasaggaaggacticratitgagcragtiticrccragcratiggasggcagctigcartgasaggactagcragtiticracragcraggartagaaggacticratitgagcragtiticracragcratigasg	0.306	0.345
RT_023489.1	DOCK4 dedicator of cytokinesis 4	TFSVGTLITYSAPSMNGIK	NP_055520.3, XP_01151	786 TAAgicactttictatgtacctgcgatgcattctttgcccgtttacaaaataagaagtatgatgaagaagaacatttagtgtaggcactttaataacttactcagctccttcgatgaatga	0.054	0.17
RT_013182.1	DOCK8 dedicator of cytokinesis 8	EKPSSFVETVALQPWR	NP_982272.2, NXP_01151	2611 attgccacccaggactga TAGggccccaccctcacccggagctcccggaggactcttgagggccgctccccccgcagagctttggcgtctaaaccg	0.054	0.103
RT_017352.1	DOHH deoxyhypusine hydroxylase/monooxygenase	SSPAELWR	NP_001138637.XP_01152	gytgitgitgiaaateggitgitatigettigtittigtigggegealiggitgettigetegeeeestettigggacegaagga 1607 getgeegitgitgitgitgitgitegeeeeste	0.047	-0.103
RT_009530.1	DPPA4 developmental pluripotency associated 4	ATSMVINGRK	NP_060659.3 XP_01151	TAGastatcaggaaaaaggccacatctatggtaattaatggcagaaaagctggagagttggattctgcggtgctgctgac 23756 aggtgaactctggtcctctgcacctgtttatgggccatgcagactggtggggtggcagatgttagcctaa	0.046	-0.134
RT 024102.1		NSVSLSECR	NP 060840.2. XP 00526	TGAagaaagaagtcagtctcactcagtgaatgtcgcaggccatttctaaaagtgctacagagagacagac	0.267	0.437
RT_014648.1	DRAM1 DNA-damage regulated autophagy modulator 1 DUSP18 dual specificity phosphatase 18	AIPRAPALESEVQIYC	NP_689724.3, NXP_00672	636 gaggcraccctga 4973 Tolgacrancccangagcccctgcarttggagtragaggtragagtrag	0.109	0.066
RT_024715.1	DUSP22 dual specificity phosphatase 22	LGRGAVVVADEDR	NP_001273484.XP_01151	Index_marge_accept_content.cacept_marge_marge_age_age_age_age_age_age_age_age_age_a	0.23	0.307
RT 0069931	FDN3 endothelin 3	EPPI YROEVNI PGAEHPPK	NP 996917.1. NXP 01152	Augusgangacquagequrugganggcutuguangcracachasgungantucacturum tagacasganggantuguctuggganggcutuguangcracachasgungantucacturum tagacasganggantuguctugggangganacaccactcasaasgantuccacturum tagacasacquantuguctugganguccacgututuctangagtaa 11113 anduccasactcanatquaccacagututuctangagtaa	0.450	-0.258
N1_000773.1	- MANUAL F	LINGEVILL GHERFER	550517-1, PAF_01132		0.153	3.4.30

RT_023670.1	EFCAB6 EF-hand calcium binding domain 6	TPLLCAQRDDSHR	NP_942153.1, hXP_00526	10512 TAGaraccectgctgtgtgcccagegggacgacagggacgatgtaagggctaataaaatcetataa TGAtcctcctcttaacccaggccaattaaggggcaaggaccaaggicgctaaggtgctcatggtcatccctgc	-0.017	0.162
RT_001248.1 RT_026532.1	EPHA1 EPH receptor A1 ERCC4 excision repair cross-complementation group 4	TLLCTPENLFVLK TVMAVFLSHACTFQRLLAR	NP_005223.4 XP_00671 NP_005227.1, XP_01152	gr.cctt.cca.ac.tgr.cajac.tagctalregigi.gct.tttgcccatttlaggagapacctgi.ctgc.cccag 5193 assacctttigmtaaaggaggaggaggaggaggaggaggaggaggaggagga	0.158 0.218	0.103 0.384
RT 003934.1		MYGDLETSR	NP_005227:1, XP_01152 NP_001116297.	TGAaagatgtatggggatcttgaaacctccagacacaagaaaacttctagcaaattcaggggaagtttgtctacactcag		0.384
RT 002612.1	ESRP1 epithelial splicing regulatory protein 1 EVPL envoplakin	TPLASEQPHPR	NP_001116297. NP_001979.2 XP_01152	8815 grügerajamittragenaartiga 1GAnaceggernaagsgeragigggagaagigrajtytittiggerengistagsniaegistacarictitgerengagere 1GAnaceggernaagsgertereteitgerenaenaenaenaenaenaenaenaenaenaenaenaenae		0.056
K1_002612.1	EVPL envoptakin	TPLASEQPHPK	NP_0019/9.2 XP_01152	aus tracccage agggeric recregic casaccagimisma immacinas aggigas FAGINITE cyclic reclamacing agging cyclic planting crabbge gatalightec Icaaaaaaaactetitige cigentee gigtis casacagine attituae casate casactagine casacagine attituae casate casactagine casacagine attituae casace casactagine casacagine attituae casace casacagine attituae casacagine attituae casacagine attituae casacagine attituae casacagine attituae casace casacine attituae casacagine attituae cas	0.216	0.421
RT 018437.1	FAM 192A family with sequence similarity 192, member A	TVHAAYR	NP 079222.1, XP 00525	caccegogacegostegistegistegisticische accessoriege consociale cons	0.236	0.104
K1_010437.1	PAW132A falling with Sequence similarity 132, member A	TVINALIN	NF_0/9222.1, XF_00323	TGAcagagaggtgtgaggggggagagccttggcctccgaggatctgggtggcgtctgctgccctaaggtgtgctggaag	0.230	0.104
				tracettiganganetigitrzgagagegetigggiggetiggetighetighetighetigheti		
RT 011736.1		AEMGLIPPGGVGGPWRLSGDGF		Banangang-regaggat-rap-tic-ag-anggat-paggat-	0.316	0.33
RT 012764.1	FAM213B family with sequence similarity 213, member B FANCE Fanconi anemia complementation group E	GPPSWCSITSFLK	NP 068741.1. XP 00524	21033 caaggictittactga 4680 TGAccaticaccaagggaccacccictiggigeticataccagcitictipaagggcattictiteticaccaccitigitiga	0.371	0.658
RT_025932.1	FBL fibrillarin	SSALSGLR	NP_001427.2, XP_00525	120 TGAagttrapcgctgtrapgattgcpapgaattgtgtttgatactgttgctactgttgttttttcattaa TGAggacacagacctgcttrapggccaagcctggatgggtgctcagaggagctaaggtggaattactgcctgaaaagacc	-0.004	0.153
RT_026099.1	FBXO10 F-box protein 10	GHRPASGPSLDGCSEELRWK	NP_036298.2, XP_01151	ceptercitecteduceritapaanaalaggatecaggatecteanaacaggatecteapaanaattiragtetaacag 488 cetatagatagatagatagatagtiittitagaggatagaaggatgaggatticagaanaagatiitataa TAnagtitagaggagatattigatettittittitettigetitettiettitattita	0.195	0.345
RT_024737.1	FBXO21 F-box protein 21	LHGALGTCCTRK	NP_055817.1, N	2900 cggagccctcgggacctgctgcaccaggaaagccactccaccagtagtgctggttgcctcctactaa	0.081	-0.025
RT_011219.1 RT_007474.1	FGFRL1 fibroblast growth factor receptor-like 1 FMNL2 formin-like 2	GPMARRNGQHPR TCVLLMVPK	NP_001004356.XP_01151 XP_01150	7158 TAGarggrancgitattgraptgggrancggggggcraggcagacagacagacaggaggaggaggaggaggaggagg	-0.033 0.136	-0.155 0.345
RT_020024.1	FRK fyn-related Src family tyrosine kinase	TLEKNIK	NP_002022.1 XP_01153	386 TG-harcetigg-pag-pashterashtas TG-harcetigg-pag-pashterashtas TG-harcetigg-pag-pashterashtashtas TG-harcetigg-pag-pag-pag-pag-pag-pag-pag-pag-pag-p	0.046	0.384
RT_019443.1 RT_026450.1	FRMD4B FERM domain containing 4B GDF9 growth differentiation factor 9	SHTSVPCKLYLSSERMFVLET QMVLLKP	NP_055938.1, XP_00671 NP_001275753.XP_01154	7924 TAAcaaatggtcctcttaaaaccttga	0.206 0.24	0.1 0.468
RT_014494.1	GGT5 gamma-glutamyltransferase 5	TVARTRPR	NP_001289393.XP_01152	6149 TAAgactgriagpaggtgcagaggggactcaaagaccggggccagaaccagacccagagggcggtgtctttctga TGAgcggtggcaccccctctctgctggtgccagtgggagactgccctctttgacctgaagcctggtgtgctgccc	-0.034	-0.123
				caccectracter-assage at circ transplant agree acting properties agree to care transplant agree agree transplant agree to care transplant agree to care transplant agree to care transplant agree transp		
				acctaagccigcagggaaaggiggaggictigggciitiggciitiggciitiggciitiggciitigciitigtiggiititictacagccigciittigti gccapggcigtigggcigtictitagggicggaggacgctataalogaitigccogcciitiggciitigciitigtiggiititictacagacgciitigaa acquirectiitigaggacgtacaagacgacgacgacgacgactataagacgacgacgacgacgacgacgacgacgacgacgacga		
RT 003442.1	GLB1L2 galactosidase beta 1-like 2	SISLSSNLR	NP 612351.2, XP 00671	tgg.cs.atcctatigg.cccattratcccgaatcctgggtigtcaccagigtage.ggtiggggaaggggigtct 5181 ccctquagtag 11807 TAGccccggaasaaactgcagiggiiitattactticcctga		-0.025
RT_007096.1	GLYATL3 glycine-N-acyltransferase-like 3	PSKKLQWFYYFP	NP_001010904.XP_01151	11307 TAGCCCaptasasasartgcagtggtttatacttcctgs TGAcceptasasartgcagtggtttatactttcctgs TGAcceptasactgcagtggtttatactttcctgs	0.129	0.21
RT 024798.1	GPR17 G protein-coupled receptor 17	AGGAVOAER	NP 001154887.	TGAgcaggaggcqccgatcaggccgagcagactgtttaggactcagcaggaccagccag	0.133	-0.025
RT_023626.1	GRID2 glutamate receptor, ionotropic, delta 2	SLHCFFFR	NP 001501.2, NXP 01153	TGAncetcase assetztice reletite tittitannacter titter asnange asetatase statenanactase	0.19	0.292
=			5	1		
				gcaggctctaggccagtgtftgggtttahtctctcagagtttttagggtttttaaggtgccagcgggaaagcc aaggccaaggaagcactgcctcttctaggccaaactcactgcccctcaacticctccagagtttagaagttttgcc		
RT 000656.1	GRIK3 glutamate receptor, ionotropic, kainate 3	AOI GWGPOAWGI GRGK	NP 000822.2. XP 01153		0.122	0.07
RT 006083.1	GRK6 G protein-coupled receptor kinase 6	APFTVLHSDLPHCPLK	NP 002073.2, XP 00671	g Gegetetegengeggenegeggenegengenegenegeneg	0.05	0.107
RT 002849.1	H2AFV H2A histone family, member V	RDALTNPLPPR	NP_958844.1, N	TAGaggargicitaaccaacccittccccgcatigtacigtaactgagacagaagaataatggggataigtigg 14036 aatitttaacaacagttaa	0.214	-0.102
RT_012910.1 RT_012805.1	HAGH hydroxyacylglutathione hydrolase HAUS2 HAUS augmin like complex subunit 2	GRPAPSADLGIR SSTLELLNYV	NP_005317.2, NP_001035 NP_060567.1. NXP_00672	2154 TGApproprotegrandtrapropatttappotetttap	0.028	0.119
RT 006180.1	HEATR9 HEAT repeat containing 9	OSILIFR	NP 689994.2 XP 00527	7221 Molecularsactutututugictularilangiguig TAAgicaatututggectactuccegatecetecetgaagaigetictagagaacaatetatact SSI7 taicticegagaataa	0.115	0.100
RT 023343.1	HOXB8 homeobox B8	ASAGTARAAAAR	NP_076921.1 XP_00525	TAGentrageteggarterragegergergergergergergergergergergergerge		-0.215
K1_023343.1	HOABS HUITIEODUX BS	ASAGTARAGOAR	NF_070921.1 XF_00323	1334 ccgapapagtttigsccgctiag TGAcqgapagttigscccgcagcccapaggtgatccgptggtgagatccacqcttgggctaaggataggg	-0.2	-0.215
RT_007294.1	HPN hepsin	STGPRTPSLQGPLFHSGGPTQPR	DHNP_892028.1, hXP_00672	acguitte intringegezegetranagetranggerangegeranezettezetranggegereteintecanglegezegezen 1019 tengerezegegeranezenatearezeteteger TGABBERGEREGEREGEREGEREGEREGEREGEREGEREGERE	0.314	0.341
RT_010197.1 RT_012273.1	HSPA12B heat shock 70kD protein 12B IDS iduronate 2-sulfatase	VGAGETIVLQSAPFHALQPR VI PTM DGK	NP_443202.3, hXP_00526 NP_001160022.1, NP_000	т отнуворо ре- кор уструктор и под посторо и под посторо и под	0.142	0.028
K1_012273.1	ios iudionate 2-suriatase	VEFIMIDAK	NF_001180022.1, NF_000	TAGegactegcteccctegaccegaeggcaeggcaeggegetaeggegegegegegegegegegegegegegeg	0.075	0.209
RT 004577.1	IFFO1 intermediate filament family orphan 1	GRGWGCTEGNISCSSAPGR	NO. 5 40750 0 1 NO. 00574	gettetecagggetetgggggtgtgggggggggggggggg	-0.066	0.215
KI_004577.1	IFFO1 Intermediate filament family orphan 1	GRGWGCTEGNISCSSAPGR	NP_542768.2, NXP_00671	3056 cetgectte.acg.gtggggtitgetactteccatatttaa TGAccggergeatecttge.acgecegggggetietetecatiggtageccagggegetiggengaccatageteegeetiete	-0.066	0.215
				Conggorange (Internally lighters and plage page and an another than the pa		
RT_016397.1	IGHMBP2 immunoglobulin mu binding protein 2	WQTMLRLHQGHRGAEGPMGE	ER NP_002171.2, XP_00527	tgs.ceptcentrecettactecegecaaacecageceteggagaaggttecaggeggaaggttecaggega 4725 abeccagggect-caaacttga 1AAggectrectrecggececececcaggecaececaggaaaggersaaggatgecgectletegetectgec	0.278	0.341
RT_011586.1	IKZF1 IKAROS family zinc finger 1 (Ikaros)	KSTRTAAFSLPPAA	NP_001278768.XP_01151		-0.107	0.033
				"Tildigengggeticscognisticsggggigt tilgiggs; egsangsanstiggstiggsancceggsangspagectits ganctipanistic tilggggggticstogggggggangspagecamistic tilgicstanceggsangsicsangs conspictorsgapeticsgap		
				cregitrocregogy gitrocitrocitrocitation attitucing an expansion and control of the control of th		
RT_023045.1	IL17RE interleukin 17 receptor E	IPCLTGRKSQPSPR	NP_705616.2, NXP_00671	日本の主義を表現していません。 日本の主義を表現しています。 日本の主義	0.154	0.292
RT_008965.1	IL33 interleukin 33	RELGLPDPLK	NP_254274.1, NXP_00525	770 not found TGA-ctgtractttggcatcctctgatgaactacacatgcctcagtgcaaaagaacagggatgctggctcttg		
				gctapagegigtic apasitisgearacticasitiscic gogagearatacccapacacegiritgistictic taasagtiing gaid (traiter casaftycctec schaesgeeggaagtilgachtect casaftycctec schaesgeeggaagtilgachtectacageciritigisciiligitiiti citecraftycciiligiscii		
				caacagacagcttttaaggctaacgtccagctgtatttacttctggctgtgcccgtttggctgtttaagctgccaattgt		
RT_025506.1	ILSRA interleukin 5 receptor, alpha	LTSSCIYFWLCPFGCLSCQL	NP_783853.1, NXP_01153	4995 ag TAGccaaaacagctggcaggactgccggtcacacaccagcacgtccacctigtgctcacggattttattacacagatag	0.208	0.623
RT_020939.1	JMJD8 jumonji domain containing 8	GGQEHKLCIGAGGFCPGLPWTR	NP_001005920.XP_00525	tion of the properties of the	0.182	0.435
				TGAgircququegggs, grafqqrager.acct.cccaagggsqagctargagggsqagcccraggarttgagarger.cccggarttgagarger.ccctccccqagtggcccaggcccccaggartgagcccagggsacct.caggggartcaggggccccagggartcagggggccccagggartcaggggartcaggggartcaggggartcaggggartcaggggartcaggggartcaggggartcagggartcaggggartcagggartc		
RT_010302.1	JUND jun D proto-oncogene	ARPPGIPPPRGCPGLDK	NP_005345.3, N	752 gestject:tittecccgesgegocgccregittgcasaaccqsgegittgggftgcasaaccqsgegttcggftgcasaaccqsgegggggggggggggggggggggggggggggggggg	0.187	0.348
RT_009378.1	KCNG2 potassium channel, voltage gated modifier subfamily G, me		XP_01152	TGA-kgcreftgeregereaneggagaereeringereeringsgeringsgaereeringsgegereeringsgagereeringsgargeringsgageri		0.485
RT_000486.1	KCNU1 potassium channel, subfamily U, member 1	KILPTFTLLNSLVDWK	XP_01154	14663 agrantgecetti 146geccrapaggicpachtegrapaggantipaggecrapitgecattercregggecrapscreggsreptivaceca crepulspacetgrapaggaccapscregaggaccrapaggecratitegrecomposite transparations of the company of the c	0.108	0.373
RT_003017.1	KIAA0513	RTEAMCHSPGPSARPSPHPMTC	MINP_001273495.XP_00525			-0.156
RT_021510.1 RT_003800.1	KIAA1191 KIAA1683	SPLSRDSGK DPGSLQWGLRGR	NP_001274264.XP_00526 NP_079525.1, NXP_00526	8568 TAGsgecctetticagggatitiggtaaaggiggtititigtaatecaticectitiactitiggettiga 3408 TAGgaecctggetecctgeaggggatitiggtaaaggatititigggatgaateaggeteitiggggataata	0.014	-0.011 -0.167
				transportung of the control of the c		
RT_010079.1 RT_005240.1	KMT2D lysine (K)-specific methyltransferase 2D LAMTOR2 late endosomal/lysosomal adaptor, MAPK and MTOR act	RGSSQSQDPGLGLPAD tis NDHLEGR	NP_003473.3, XP_00526 NP_054736.1, NP_001138	6602 ctgspagerag-nagstyssgaangaagstytigsgccpggctctx-augroctigstgctcxctga 2906 TAA-cgcattggtggaagctggggtcagaaangagaaatgaccatttggaaggggggggctctctagaaagaa	0.021 0.198	0.103 0.216
RT_017114.1	LIPG lipase, endothelial	TSCYPSPWRKVTAEDPPNGR	NP_006024.1, XP_00525		0.063	0.028
RT_023299.1	LMTK2 lemur tyrosine kinase 2	VAANAHARVRGCSPGAAPLRPQ	PE/NP_055731.2 XP_01151	5528 gazeczeczaligosagamient inzerosopo- Haftigia incensenta przed prze	0.16	0.035
RT_001154.1	LOC102723730 adhesive plaque matrix protein-like	SPWPTGLR	XP_01150	17842 TAditccatattictagccteigctagigaagttictgcctttacttcagaagiccaagiggigaagagcctiggcccacaggictaggaacgaaaaggccgctctga TGActggtccacgacgaagagaggaagctactgtgggattcatttictacatttiggacttacacagtaa	-0.025	0.207

RT_013953.1	LOC105373926 putative HERV-K_Xq28 provirus ancestral Pol protei	in GIHFSYILDLHSKGFN	XP_01151	8461 gggetteaactga TGAeggeteaceabaaagccaaaatggggaectgteaaaaatgttttagecaaactatggetteaggaagatgcc	0.399	0.623
RT_000939.1	LOC643355 uncharacterized LOC643355	KMPRPK	NP_001257874.XP_00527	8225 sagaccaagggregraacttaa TGAacaaccaagggregraacttaa	0.209	0.394
RT_024143.1	LRIT2 leucine-rich repeat, immunoglobulin-like and transmembran	e TTQAMGWK	NP_001017924.	801 intracepose governments of the control of the c	0.205	0.384
RT_007580.1	LRRC4B leucine rich repeat containing 4B	GGGAGRARGVEPPTQVPAR	NP_001073926.XP_00672	1548 gparccrcaptaagsaneggggggetcaggaggetcaggaaggacgtcaggaggaggaggaggaggaggaggaggaggaggaggagg	0.16	0.119
RT_026848.1 RT_006265.1	LRRFIP1 leucine rich repeat (in FLII) interacting protein 1 MAOB monoamine oxidase B	TVASLALR RERVSVITLSSYCIWDMSLGK	NP_001131022.XP_01151 NP_000889.3, XP_01154	ccaggagecccagecaccaggicctegitectettepaapcccaggccggcagecagecagecagecages UII 3 gattettaaagaccaegggccctgggagectettegatega 6600 TAAgagagagaggtetgatacacticttittettettattgiattigggaatagata TAAgagagagaggtettgatacacticttittettettattgiattigggaatagatagatagatagaccaggacggagagaagccaggcagg	-0.019 0.26	0.204 0.259
RT_023252.1 RT_013519.1	MAP3K6 mitogen-activated protein kinase kinase kinase 6 MAP7D1 MAP7 domain containing 1	ELNEGIIGQTGPR EGLPWIR	NP_001284538. NP_060537.3, NXP_00671	5739 gggaggggtactugggaggggcactaggtutttaaaaattttttigtigccgggcatgtgctctagcctgtaatccagcactttgggaggccaaggtgggcagatcaggaggagatactgaggagatcaggagataatcaggatagctaagctggaatcaggagataagagataatcaggataagataagagataatcaggataagagataatcaggataagagataagagataatcaggataagagataagagagataggataagagataatcaggataagagataatcaggataagagataagagatagagataagagatagagagagataggatagagataagagatagagagatagagagagagagagagagataagagagagagagagataagagagagagagagagagagagagagagagagagagaga	0.059 -0.005	-0.036 -0.214
RT_011694.1	MAPK9 mitogen-activated protein kinase 9 MARK2 MAP/microtubule affinity-regulating kinase 2	VATPLLISLHR	NP_620707.1, N	ganceaparagarithatorictparceggaccitipanggatepapatanggitaganatagitaganatagitang 3409 catigangganchicaetricetpaggaccitya 509 TAAcaggangeapangaggacggangganggangganggacaparagarggangganggargaccaccitipagangganggangganggangganggangganggangga	0.151	0.396
RT_022686.1 RT_022228.1	MCAT malonyl-CoA-acyl carrier protein transacylase	QAARSGGGGGGPAGR LQGAQMR	NP_001034558.XP_01154 NP_775738.3 XP_01152	10785 TGActgcagggggctcaaatgcgatga	0.181 0.257	0.152 0.623
RT_027052.1 RT_014431.1	MED1 mediator complex subunit 1 MED12L mediator complex subunit 12-like	EPYFLKETGPEEK RHDVLCLH	NP_004765.2 XP_00525 NP_443728.3 XP_00671	10723 TAGgaacttatticctaaaagaaacaggccagagaaaaaaactattgataagtttatag S365 TGaatctgcaagaggagaagacatgccgtttatgtttgcactga	-0.112 0.257	0.058
RT_022201.1	MEI1 meiotic double-stranded break formation protein 1	SSGLEGPEVER	NP_689726.3, XP_01152	SSSS (GARCTERGRAGGECGRAGAUGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG	-0.087	0.103
RT_017809.1 RT_013659.1 RT_001122.1	MGATS mannosyl (alpha-1,6-)-glycoprotein beta-1,6-N-acetyl-gluco MID1IP1 MID1 interacting protein 1 MIS12 MIS12 kinetochore complex component	ssi Shagtlara KMVAGDGR LLSSQKEEPVK	NP_002401.1 XP_00526 NP_067065.1, NP_001092 NP_001245146.XP_00525	1213 ang-triquesgganttegunaspactup Half Tolkgegtegerdeggetegenesgenestettlepsecattetacicitettettasakettiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiii	0.125 0.154 0.066	0.107 0.119 0.116
RT_019879.1	MITF microphthalmia-associated transcription factor MPV17L MPV17 mitochondrial membrane protein-like	RILPALHSHK FVKDSI K	NP_937802.1, NXP_01153		0.278 0.219	0.488
RT_021866.1 RT_021358.1	MSL3 male-specific lethal 3 homolog (Drosophila)	NVVGSVR; ATALSSLALWVPGE	NP_001121895.XP_01152 NP_523353.2, NXP_00527	1849 Tülkapatigagacitethaaagggactacatittitiaccha 1844 TAAsaigtigtiggtictjaagagcacigcitetgittiggticcaggigaataa	-0.003	-0.089
RT_010471.1 RT_020347.1	MTR methionine synthase MTSS1 metastasis suppressor 1	FAVLGTMVMK VHKKCAGGE	NP_000245.2, NXP_00527 NP_055566.3, NXP_00671	1933 in found 427 TAGISTIC-aagasatigscoggieggeatigs TGhgistic-aagasatigscoggieggeatigs georgegegegegegegegegegegegegegegegegege	0.134	0.067
RT_025500.1	MYO9B myosin IXB	LKSDVRWAPAPSAESR	NP_004136.2 XP_01152	ggraggapaggcrggrtggagcraggcrccttsgracgragcrccenaatchtggargraccacat 1548 citeractsgraggcrtacatchteceachcecttttgtacgtttaa	0.079	-0.036
RT_006029.1 RT_009713.1	NCAM2 neural cell adhesion molecule 2 NCAPH2 non-SMC condensin II complex, subunit H2	QQYYRGLNNTTK	NP_004531.2, XP_01152 NP_001171940.	1/10/3 TA-Ascardanthracagggerigae-ascardicaga-ageigningstregs Tolk-gloggga-garcagga-ageigningsga-garcaggerigae-garcaggerigae-garcaggerigae-garcaggerigae-garcagae-garcaggerigae-garcagae-garcaggerigae-garcagae-garcagae-garcagae-garcaggerigae-garcagae-garc	0.29	0.468
_		LSSCPAPGDGDPSLK	=	TGAggggctgcgccacgccacggccccgctggagctggggccacaggactggaccggctctcttcatgcccaggcccccgg	0.233	0.257
RT_014759.1	NCKAPSL NCK-associated protein S-like	LSSCPAPGDGDPSLK	NP_001032895.XP_00671	3669 aganggggacccctcctganagggaccanggagganaaganggtganaagagggttcctggcacccccaccaccactgcttcggcgatga TGActcagaacagggsgcgggggggttagggtccagcgagccaaggaacggccttgraggagagggggtgaacggcccaccaccaatggatcccaccacaaggaagg	0.164	0.028
RT_015970.1	NCOR2 nuclear receptor corepressor 2	HPCLSKALTK	NP_001070729.	The contraction of the contracti	0.265	0.714
RT_006054.1	NEB nebulin	AFQSITLVCR	NP_004534.2, NXP_01150		0.092	0.07
				TAGentigagic catigs:aaaaggitaagccataigas:aatticaaaatigcatiggatiggaggcticaaaacagaacg ggitt:cccatigggggctcagaggactatigutticitticitiiiiiiiiiiiiiiiiiiiiiiiii		
RT_001896.1	NEFM neurofilament, medium polypeptide	VLPWGLQTLYFTLCNMR	NP_005373.2, N	19012 gataxitmagggggapittmigapatpatmigcapagbachurgapggcaptcapatraagtg TGMcargccaccccccccaccacracpagaagaaggeggecgggggapttcpaggcaptcaagtg		-0.182
RT_019335.1 RT_016847.1	NFASC neurofascin NFIC nuclear factor I/C (CCAAT-binding transcription factor)	QWPGAVPRAVPAVK LPKLFISSPPAAR	NP_001005389.XP_00524 NP_995315.1, NP_001231	254 gccgggt-aggctggtga 7251 a Chacaaggtettetteeteeteetetteteategteetteteategteetateageeggeaggea	0.407 0.104	0.658 0.424
RT_008486.1 RT_015312.1	NLRCS NLR family, CARD domain containing 5 NPL N-acetylneuraminate pyruvate lyase (dihydrodipicolinate synth	WPPQDLWNPAK ia: EDCLSRRTLNY	NP_115582.4, XP_00672 NP_001186985.1, NP_001	274 TGAtageccecteaagacetttggaatcagecaagtga	0.086	0.065 0.281
RT 016124.1	NPLOC4 NPL4 homolog, ubiquitin recognition factor	GACPLLARTGPSPALPEAR	NP 060391.2, XP 01152	turo ungangangunutunggancunganunga Hagagarcintentungkunggancunggancapcungcungungung 846 ciginantipuccuntanginggangunggancanggangungungungungungungungungungungungungun	0.029	-0.103
RT_009589.1 RT_003245.1	NUDT18 nudix (nucleoside diphosphate linked moiety X)-type motif NXN nucleoredoxin	1 APSSADLSPSEGGKR GCMAFAKSLAFGEGSARVSWAE	NP_079091.3 XP_01154 NP_071908.2, hXP_00525	angering-part-anggari tiligiar-itaggari tiligiar	0.128 0.25	0.215 0.203
RT_016280.1	OLFML1 olfactomedin-like 1	CITAVR	NP_940876.2, XP_00525	TAAlgeattacagretgiagaaagagcactgitgscagretgitchacaggacagtgagcattagcccctcaca 2996 satatgatecctchatcacacaggaagagtgitgs TGateraacretetetercreasagagaagagtgitgs	-0.12	-0.022
RT_014428.1	OLFML2A olfactomedin-like 2A	VETCAPRRGAAVR	NP_872293.2, NXP_00671	ccgcasalithattaggggccagccagggctaggcatggcaggatggcaggatggcaggatggagttcctcaggaccc 974 agtgggtastacttgcttccacttgcagcacccgttgcagcacttcccacacacttacccgtttga	0.315	0.257
RT 010142.1	OPA1 optic atrophy 1 (autosomal dominant)	IVLIISSAYI	NP 570850.2. N	Takattasastegarciasastegarcigarciarciarciasasteriarciarciarciarciarciarciarciarciarciar	0.054	0.204
RT 015055.1	PAQR7 progestin and adipoQ receptor family member VII	WEOGLVK	NP 848509.1 XP 01153	TGAaggegganggcatteggraggaaggaaggtahgttggggacaagggstrigggtttggctscaggtgggancaagg 3864 creptpraangttetttegtctgecccacagtea	0.138	0.12
RT_005430.1	PARP10 poly(ADP-ribose) polymerase family member 10	APEGGVGDGGQQRPR	NP_848509.1 XP_01153 NP_116178.2, XP_01151	3568 TAAcqaagggccaccninggccitcigethccaggctccagctccgactaggtctcccqcccaactgtggcqcctpagctccccggggacqcccctgcctcctctgcgggctcagggggggggg	0.138	0.12
RT_017560.1	PAX2 paired box 2	VGQDGWSRGR	NP_001291498.	Son	0.08	0.388
RT_014634.1	PCBP2 poly(rC) binding protein 2	NNADSSIIPFCCSPPPMIHLCSF	NP_005007.2, NP_001122	4813 T/AGaseangcagentacricanhacterittegitaticas can canceagnaterating lagatitutga T/AGaseangcagettingcanhacterittegitaticas canceagnagentaggatitutga T/AGaseangcagettingcanhacteratingcaneagnagentaggatitutga Capasaccentituticanhasaanasaanaterateggatitutgatitutgatituttegitatinaterateggati	-0.054	-0.075
RT_026547.1	PEBP4 phosphatidylethanolamine-binding protein 4	IAGFAIR	NP_659399.2 XP_01154	6085 ggggaatag	0.365	0.444
RT_014747.1	PHF14 PHD finger protein 14	FAAYVIADKISNCKMLNCK	XP_01151	TÄÄaagaittitgaaagittigtagteettitigaaagittig-ragtiaaaattittaatigtaaadigttaaa 1005t tigtaaastittigta	-0.055	-0.122
RT_013650.1	PIAS2 protein inhibitor of activated STAT, 2	NMTALLLLVPYCQVR	NP_775298.1 XP_00672	TGAstacasastasacasatattigatttatgagatgasaacagctatitt:aaggasaastatgactgccttatt 3105 sittg-tagtgccatatigtaggtgcgastgtgcatatgtag igastgccatatigtaggtgcastgtgcatagtgagtgatcatasasttga	0.22	0.666
RT_010003.1 RT_023912.1	PICK1 protein interacting with PRKCA 1 PLAC1 placenta specific 1	GLGGGRSPSPAPCGRSHCPR SSGLGSPEDAISR	NP_036539.1, NXP_01152 NP_068568.1 XP_01152	2783 Tó-Afgroccogaga-talgatur-cogagaga-gagaga-gagaga-gagaga-gagaga-gagaga-gagag-ga-ga	0.28 0.131	0.257 0.103
RT_006100.1 RT_023238.1	PLCB4 phospholipase C, beta 4 PLCZ1 phospholipase C, zeta 1	THSQTSEHKLHG QLMINDISLAMHRNK	NP_000924.3, XP_00526 NP_149114.2, XP_00525	S813 TG/lagcage.saaccex.saagcatcaaagactactus.saactictgaacacaaactcatggaiga 1169 TAAcagctaatgataatgactatcattus.gaactagaacagccaaaaggaatgcttitatgtttictttttaaacataaagaaaaataattactcataa	0.127 0.028	0.211 0.152
RT_009701.1	PLDS phospholipase D family, member 5	GLEERKNTLICLFF	NP_689879.2, NXP_01154	TAA: atgatgaagaaactga: aggacagcictgtatticatattatacataaaggacttgaggagaaaaacacttt 259 aatatgactctittittag	0.334	0.184
RT_008256.1 RT_023570.1	PMPCA peptidase (mitochondrial processing) alpha PNPLA7 patatin-like phospholipase domain containing 7	RSEFPETAK SPDAASSVGLSPR	XP_00526 NP_689499.4, NXP_00671	219 F Mayageactraaghtaylagsgapaaggortughaaggotgatusathganggaptigaadgaatgaatgaatgaatgatacgthectggcaaggaqttraagcccaagthactggcccaahgaggaccccaahgaggaccccaahgaggaccccaahgaggaccccaahgaggaccccaagthactgaagccccaagthactgaagccccaa	0.075	0.259
RT 009079 1	POUZF3 POU class 2 homeobox 3	ISTINEPR	NP_001231611.XP_01154	Source of the state of the stat	-0.045	0.102
RT_020178.1	PPP1R12B protein phosphatase 1, regulatory subunit 12B	LASSISPP	NP_001231611.XP_01154 XP_01150	44os cząpsanccasactogama; 97 TGActtgcraginacyticaccititga TGAggariantitracgogictcraggaccagtigtiggcctiggaasgcagatigtiagcttt	0.383	0.655
RT_020123.1	PPT2 palmitoyl-protein thioesterase 2	GYIQGSPGTPR	NP_619731.2, N	11122 ggistgrutsga Täbere rispettisteraepeatteenseepeepeepaaarateensaattaetrepranta	0.174	0.345
RT_023177.1	PRRC2C proline-rich coiled-coil 2C	SDNAGSQRGK	NP_055987.2 XP_00524	1964) creating diges creating intelligent distribution for the control of the con	-0.016	-0.058
RT_027064.1	PTP4A3 protein tyrosine phosphatase type IVA, member 3	HLRALVSEERGAPR	NP_116000.1, NXP_00525	8250 decreagescrapeagggetreagggetragedgecreantering intercepts activity and a secretage of the page of	0.19	0.491
RT_009826.1	PTPN4 protein tyrosine phosphatase, non-receptor type 4	KNEELK	NP_002821.1, XP_01150	1000 asatgcattitacasasasasatgaagaactcasasasacttigacattitigacattitigititias T-AGCtcastiggaatggaagaactcasasasacttigacattitigacattitigititias T-AGCtcastiggaatgggaagaagaagactcattigacatgaatgacattactig	0.052	0.103
RT_023418.1	PTPRT protein tyrosine phosphatase, receptor type, T	LNGMGNLPESR	NP_008981.4, PXP_01152	1995 gercageactiga TGActrageaccagaccageccageccciccgcccccccccccgccctgaccagcctggttgactigttcgtctgacgacatgcaggaggaacatgcciccactttcttgggactiggaggaggagaaca	0.357	0.491
RT_016814.1	PVRL2 poliovirus receptor-related 2 (herpesvirus entry mediator B)			11516 granactegacttetecontectua	0.418	0.373
RT_002300.1	RASAL2 RAS protein activator like 2	ALSVEGDR	NP_733793.2, PXP_01150	The agent the grant agent ago ago and garceact tectal tectage certage 1999 gitter ago ago ago ago and garceact tectal tectage certage 1996 gitter ago	0.261	0.394
				TGAcagectagipaggetipasgarcatutigeccegaccanganggeggitacanganggetictritegec agecaptiggangcritegitimgecritegitimgeringgangcritegitimgeringgitimanganggetictritegec agecaptiggangcritegitimgecritegitimgeringgeticanggeticanggeticangangcritegitimgering acceptagingangcritegitimgeringgeticangcritegitimgeringgitimgenggitimgengangang		
RT_014669.1 RT_013497.1	RASSF7 Ras association (RalGDS/AF-6) domain family (N-terminal) RBM14 RNA binding motif protein 14	m SQLGTCQAPK APIMITCGRLR	NP_003466.1 XP_00525 NP_001185765.1, NP_001	See the conference of the conf	0.289 0.152	0.33 0.119
RT 024372.1	RFPL3 ret finger protein-like 3	AATAKKNR	NP 006595.1, N	TAAgccgccactgcaasaasaacagggtcagaasaattattgggggggtagacttaggaatttictacttggtaasagc 7405 attatacagtcataggagaaagatatggggacatttctatatcattttaatttga	0.076	-0.112
= '			= '			

				70		
RT 016562.1	RGMA repulsive guidance molecule family member a	SPGVSTMAPONAR	NP 064596.2. N	TAGasgastapatetgapaggapaggasgasgasgasgasgasgasgasgasgasgasgasga	-0.048	-0.155
RT_020305.1 RT_020623.1	RGN regucalcin RGS4 regulator of G-protein signaling 4	GQVFFPAR FSPEGRGMKCQDSMLWK	NP_690608.1, NXP_00672 NP_001095915.1, NP_005	13379 TGAggaraggirttittittittittittigtiggaggarattigaaggaraattig 2129 TAMittitactigaaggaggaggaggaggaaattigaaggaraattig TGAdritticerigaaggaggaggaggaggaaattigaaggaraattigaagraggagaaattigaaggagaaattigaaggagaaggaggaggaggaaattigaaggaaaattigaaggagaaggaggaggaggaaattigaaggaaattigaaggagaaggaggaggaggaaattigaaggaaattigaaggagaaggaggaggaggaaattigaaggaaattigaaggagaaggaggaggaggaggaaattigaaggagaaattigaaggaggaggaggaggaggaggaggaggaggaggaaattigaaggagaaggaggaggaggaggaggaggaggaggagga	0.238 0.216	0.345
RT_015540.1 RT_016579.1	RILPL1 Rab interacting lysosomal protein-like 1 RNF183 ring finger protein 183	LSDLRMDIEKLTPNSK EAVLTTELHSK	NP_847884.2, XP_00671 NP_659488.2 XP_01151	grigetinagetininggiqeagigeacetgaaastjacetcinaaasgantigitigiitigiiggagiggartig 1994 aasaastgaqeeaasettaagaaagiitiitiitiacetgagagattacetgiitiitaa 387 Tokkigetiiceegaaagaaagiitiitiitiitiitiitiitiitigiitiityitigiitigiitigiitigiitiitiitiitiitiitiit	0.197 0.144	0.373 0.257
RT_016183.1	RNF212 ring finger protein 212	SFEVISK	XP_01151	TGAsgittigaagicatittaaagacaaagitsigitittiacegegaciticaatgecteetgeggacetgeteacettg 15579 gggeagigacacetga	0.188	0.153
RT_014053.1	RNF43 ring finger protein 43	SQNFGRPR	XP_01152	T-Adtr.cragaactitggeaggctraggtgggtggtccttgaggcraggagttcnaggcraactatggtga 1416 ascretzettetetasaastatgcaggatgtgtggtggggcrattataa 416 ascretzettetetasaastatgcaggatgtgtggtgggtggttatataa	0.056	-0.075
		TVSIRIPR		TGAaccgistcctgaagattccagacaggaatagaaccatttccigtcacccaagacctggsctgigtgt tyggittiggccigtigtttictgacqicgggaatcacttcacagacctcagaggittigtaaa		
RT_014228.1	ROBO4 roundabout guidance receptor 4		NP_001288017:XP_00671	GO43 acasatgs TAAsgccctcctgggganttaggastcagtcagtcagtcagtcagtgtgttttcgtgggancaactgggc	0.338	0.159
RT_014154.1 RT_002043.1	RPL13 ribosomal protein L13 RRAS2 related RAS viral (r-ras) oncogene homolog 2	SPPGDLESVGSHAGSPR QMITMLALDEEAG	NP_000968.2, N NP_001170785.1, NP_036	3890 (oggangsgattrantgrigter 2021 Maanteentragittingsteransgecrapspaangeertanthictintelectragittingsteertittageertagsterantgittingsteertitingsterantgittingsteertitingsterantgittingsterantgittingsteertitingsterantgittingsterant	-0.067 -0.013	-0.134
RT_016126.1	SAPCD2 suppressor APC domain containing 2	SI WAAWAPR	NP 848543.2 XP 01151		0.021	
RT 024884.1	SAPCD2 suppressor APC domain containing 2 SECISBP2L SECIS binding protein 2-like	LSISSCGR	NP_848543.2 XP_01151 NP 055516.2, N	1984 ccangectigecccagategetracquaregategethga TAnctraggasagtinggetrichteteragtigegasagggtigeagecethacetttatgetteatetrasactit \$500 specingtegethitas	0.021	0.536
K1_U24004.1	Secisor2e Secis unumg protein 2-like	LSISSCOR	NF_033310.2, I	TMG-glateggatean-gasaaccigctcacgggaatcagtcactccaaggtatcccactcaaagtatcccat ccaaatcaagagtccctgcagtttcccgctcagggaatcagtcactccaagtatcccatcaagagaacagacagacacagac	0.277	0.330
RT_024986.1	SEL1L2 sel-1 suppressor of lin-12-like 2 (C. elegans)	TLLPICHLGDLVPRYE	XP_01152	construings (a. v. a. v.	0.051	-0.226
RT_022798.1	SERINC4 serine incorporator 4	DTQGVISVWAEVNTMNWKK	NP_001244960.	atacttaaggacacagggagttattcgttigggctgaagttaatactatgaactggaagaggtgtcaaacacag 5671 teta	0.178	0.17
RT_023546.1	SETBP1 SET binding protein 1	LHLGPRELTR	NP_056374.2 XP_00525	TAGgerggittgggrittgarcitggggattggarggarggarggarggggggggggggggg	0.015	-0.103
RT_006972.1	SF1 splicing factor 1	RGEQMVLGK	NP_973724.1, NXP_01154	143 To Agitanting iggs acgs antegos acac reference to the control of the control	0.323	0.289
RT_014701.1	SGOL2 shugoshin-like 2 (S. pombe)	ESKQKYSIKKMKCLMK	NP_689737.4, XP_01150	gasalgettastgasasgettiittiligticttiggettieatiggetgitastitigteestictastgittistt 268 aa TGAggggracktaceceggeagetchagecasgetgeecetgeecegteentgettastitteeteetggetgastg	0.044	0.153
RT 006725.1	SGSM1 small G protein signaling modulator 1	ERGPGVCSQAWSSVRK	NP_001035037.		0.073	0.028
RT_008135.1	SH3RF2 SH3 domain containing ring finger 2	DTNSLASK	XP_00526	591 clagacages page page gas page control of the co		
RT_017390.1	SLC38A8 solute carrier family 38, member 8	WAASAGQEGALR	NP_001073911.XP_01152	To signification and the state of the state	0.088	0.065
RT_013448.1	SLC9A3R2 solute carrier family 9, subfamily A (NHE3, cation proto		NP_001123484.XP_00525	1985 ag-ectra-signa-signage-gic-signage-signag	0.091	0.066
RT_018371.1 RT_018499.1	SLC9A8 solute carrier family 9, subfamily A (NHE8, cation proton a SMOC2 SPARC related modular calcium binding 2	inti GLAEMRASSSPFKT AHTPKAVPR	NP_001247420.XP_01152 NP_071421.1, NP_001159		0.189 0.184	0.485 0.172
RT_018427.1	SNX29 sorting nexin 29	RHPHGPGCTGELASRGVITHR	XP_01152	TAGegeatecceatageceatggeaeggggaattagecetegeggagtataeceatgaetgaattecetggt 6366 gaaaactgagttagecagtggttectaa	0.251	0.171
RT_021657.1	SPACA7 sperm acrosome associated 7	SLLEPPPTSLRNR	NP_660291.2, XP_01153	1398 TGAgecreageccrageccragecragecragecragecrage	0.012	0.119
RT_009922.1 RT_005096.1	SPAG11B sperm associated antigen 11B SPAM1 sperm adhesion molecule 1 (PH-20 hyaluronidase, zona pel	AGMLKYPK II u LAEMNNMSILK	NP_478108.2, hXP_00527 NP_001167515.XP_01151	335 satasatattigtiga 3094 TAMIqçcagettagıcıpasiqascastatgiccatttasagtgiqcittittgactasitas	-0.046 0.092	-0.089 0.116
RT_002817.1	SPATA21 spermatogenesis associated 21	QELLLGFAFVAW HLYSQLLK	NP_940948.1, XP_01153 XP_01151	TGAccritiggaggctgacttaggcagctgtraaggctgtagacagalgggccaccaggaggtgctgctgggg 4868 attgcttttgtggcctggtga	0.219	0.432
RT_006931.1 RT_019025.1	SPDYE3 speedy/RINGO cell cycle regulator family member E3 SPOCK3 sparc/osteonectin, cwcv and kazal-like domains proteoglyc		NP 001238896.XP 01153	2077)e ne trouve pas le pespide Toditagnage aging paste arba anisi ne attiti casanti pastago ciatifiasa antiaciti: 588 cocca anisa paste apiticiasa cocca ciatifiasa antiaciti citti 588 cocca anisa paste apiticiasa cocca contrati mitigia anisa mitigia an	0.272	0.294
11_013013.1	an overal sport portromistering level with mazor miss community proteogrys		in _ooisabsum_oiis	Mokangitapan tiges sang pangang mingan nga napan tegang unga magan tigan mintang a quence pangan pan	0.1/1	0.234
RT_004780.1 RT_026612.1	SPTB spectrin, beta, erythrocytic STIL SCL/TAL1 interrupting locus	QVGLAGAAESGRAETGQPRPWI PFNSLPF	PPLNP_001020029.XP_00526 NP_003026.2. NXP_01154	11848 app.catgpanatycatagccagcccctaggggcatga	0.137 0.112	0.107 0.195
RT_009155.1	SUPT7L SPT7-like STAGA complex gamma subunit	EMFCPDLLDPTEK	NP_001269661.XP_00526	691 Yakanganangggapajimtikrcapicthchapiccacaaqpanagittiijathapiartijittictaanatipittiatriqtiittaani aranjigittictaaticaanggan-tigacqtaccaanaagittijittitiitiitigicticaaticagittiitiitiitiigicticaaticagittiitiitiigictiitiitiigiagiticaagittiitiitiigiagitiitiitiigiagiticaagittiitiigiagigicaagitiitiitiigiagitiitiitiitiigiagiticaagitiitiitiitiigiagitiitiitiitiigiagitiitiitiitiigiagitiitiitiitiitiitiitiitiitiitiitiitiiti	0.058	-0.122
RT_010002.1	SWI5 SWI5 homologous recombination repair protein	AGSSPLVHSSQGQK	NP_001035100.XP_00525		0.325	0.292
RT_002713.1 RT_026555.1	SYCE2 synaptonemal complex central element protein 2 SYT15 synaptotagmin XV	CAGHCFRSTDQQR PFAQHRGSALGADHPR	XP_01152 NP_114118.2, XP_01153	5976 TGAcacttggggtcagattgcaggccactgcttcagaagtacagaccaacagagatggtga 12022 TGAccettggccagcaccgggttccgctttgggaagccaacatcttggcagttgcatgga	0.325 0.336	0.421 0.432
RT_026388.1 RT_019228.1	T T brachyury transcription factor	AQVPKDAVTFCRGSQW MVWIRIR	NP_001257413.XP_01153 XP_00671		0.237	0.211
RT_019228.1 RT_007777.1 RT_026131.1	TCTE3 t-complex-associated-testis-expressed 3 TET3 tet methylcytosine dioxygenase 3 TEX26 testis expressed 26	AVSVVLLPSYLGAGWGCR IVOMKK	XP_00671 NP_001274420.XP_01153 NP_689538.1, XP_01153	McCreatina gantea gantea gantea gantea con que gono mango gantea con que que gantea gantea gantea que gantea con que gantea gant	0.379 0.008 0.169	0.491 0.035 0.373
RT_013769.1	THUMPD2 THUMP domain containing 2	TVTQMNLELK	XP_00671	1363 TGNanaggaaastagte.caatgaagsaastctga 7276 ot found TANanactgeanyagaggattanagaagaastctattgatattctatactctatactctatactctaatgaagaggatittcctaat	0.109	0.373
RT 001050 1	TMEM1068 transmembrane protein 1068	KLEEMDLK	NP_060844.2, hxP_00524	remain (ppany) my pagaritang paga	0.046	0.195
RT_012578.1	TMEM1068 transmembrane protein 1068 TMEM155 transmembrane protein 155	RMTSHSHLQNLK	XP_01152	121 not found	0.040	0.193
RT 017166.1	TMEM185A transmembrane protein 185A	WTGTHSLR	NP 001167563.	TMGalgccattrcggggat-apagethaagtgaartgggateggatectactrcgccttectatgcccctcatgtcaccceg cagactagaarcagatectggatectaggtacagtcatattratagccttgttgcatcaagcacc 1338 tecracagateggateggateggateggatecagtgatcaagcaccatcaggategategategateggateg	0.008	0.127
			E	Tolegogutaritetigeccageccegategecactaggacceteragecactetigtgaccageccaggatitec tggasetigacgactetigtgaccaggeccaggatitec tggasectigagaggettcaateggacccaggatecaateggaccaggatitecaacceteticeccaaccaaccagecca		
RT_019558.1	TMEMS4 transmembrane protein S4	TLQATLLCDQARIPGAGLR	NP_277039.1 XP_00527	13000 etgenetgaantga Ti Gutta gede dae dae na aktituse ale angazete etgene angazete etgana angazete etgana a	0.14	-0.036
RT_022387.1	TMEM92 transmembrane protein 92	VTSCLESCHQQPPPQCLLDQAR	NP_001161687:XP_00672	ccccaggastaticcdgccarticdgcdgttctdgttattttggatttacttttggatttactttttggatttc	0.304	0.348
RT_004139.1	TNFRSF25 tumor necrosis factor receptor superfamily, member 25		NP_683871.1, NP_683868	1064 TGA-asggecrcattgecacttagesgettetgagsgecttagasgagsctnagtsagstattatgetgtag TGA-aggagsgargetgigsgtlagsartagsgtgastattsgapsartcagsgagsgagsagsagsgagsgagsgagsgagsgagsga	0.343	0.421
RT_024642.1 RT_019102.1 RT_005492.1	TNFSF14 tumor necrosis factor (ligand) superfamily, member 14 TNK2 tyrosine kinase, non-receptor, 2	GALDMGLTRGELR DASGEPEGLPEGIT SYLLGKCPR	NP_742011.2, NXP_00525 NP_005772.3, NXP_00526 NP_055643.1 NP_001290	5902 gasagcasagetigaggetigatgatteritetigaa 7393 Tikagatigetitegasgagetigatgaggetigetigaggetigetigag	0.123 0.092 -0.102	0.12 -0.004
RT_005492.1 RT_015033.1	TOX4 TOX high mobility group box family member 4 TPCN1 two pore segment channel 1	SYLLGKCPR APEGPSQGDPSPGSSR	NP_055643.1, NP_001290 NP_001137291.XP_01153	793 Tokaping integraps percepagang-circular paggantacetga 193 Tokaping integraps percepagang-circular paggantacetga 193 Tokaping integraps percepagang percepagang integraps percepagang integraps percepang integration percepang integration percepang integration percepang integration percepang integration percepang integration percepang integraps percepang integration percepang integration percepang integraps percepang integration percepang integration percepang integraps percepang integration p	-0.102 0.143	-0.119 0.21
RT_019778.1	TPCN2 two pore segment channel 2	LAYTGAR	NP_620714.2, XP_00527	Tokeptroggeduceptroagenggggggggggggggggggggggggggggggggggg	0.186	0.426
RT_002189.1 RT_024775.1	TPM1 tropomyosin 1 (alpha) TPM3 tropomyosin 3	PWFSLLASCLRARHTLCFLLYR LSPFLLCSGSAPFTPR	XP_00525 NP_689476.2, XP_00671	2616 tragificationary consequence of the control of	0.262 0.264	0.432 0.433
RT_000591.1 RT_020019.1 RT_006402.1	TPRA1 transmembrane protein, adipocyte associated 1 (lipid met TRIM68 tripartite motif containing 68 TRIM7 tripartite motif containing 7	ab EEASRPRVPRGGGPGQGTFCGQ GLELGLAPMGLGGPSH VTVANRAGEQGLWTPEGVPFLR	NP 001291425 1 NP 060	Towards, must expect (edges) and edges (edges) geographic (edges) edges) edges (edges) edges) edges (edges) edges) edges (edges) edges) edges) edges (edges) edges)	0.262 0.15 0.102	0.362 0.103 0.028
RT_014420.1	TSPEAR thrombospondin-type laminin G domain and EAR repeats		NP_659428.2, N	TGAggcqcgqtqccqgcagcaattggggtqgccagtgaggcqggaccccagcactccccaattaacctgacctg	0.073	0.119
PT 012052 1	TSPO translocator protein (18kDa)	VPGPPGTAAAPAGAITLVMWWI		412 gg-agggantentroactstaggetritige 1Gelgetroactsagggartentroggartentroggetroactstaggetrogggartentr	0.183	0.257
RT_008971.1 RT_021416.1	TSTA3 tissue specific transplantation antigen P35B TTC13 tetratricopeptide repeat domain 13	TGSGASGPSAGR LFFKTWNYK	NP_003304.1, XP_01151 NP_001116307.XP_00671	3290 TAGttctgctgctgtatttatacaagtaaagggccggacctcttgcttcttaagttatttttaaaacatggaattataaagaaattaggtcctctattacttttgataccaatttttataggaattga	-0.078 0.125	0.211 0.162
RT_021425.1 RT_003336.1	TTC39B tetratricopeptide repeat domain 39B TTC7A tetratricopeptide repeat domain 7A	WKNDLVNK QQGTWVR; REGGAGQR	NP_001161813.XP_01151 NP_001275882.XP_01153	4525 TGAtcagaacttgaaggatttttcctcaattagcatcggcatctgctatagattcaccttatattaagtggaaaaagalcttgtgaataagagcaaaaaaacagttttttgtcaattatttctatcatctgaagatttactgttggtctacataatttttttcctatggaatggcattctatattatc 17188 TGAcgacctgcagcagcaggaagggagggctggccagagggagg	0.324 0.4	0.329 0.71
RT_022743.1	TUBGCP2 tubulin, gamma complex associated protein 2	KGVGSAGTGANGSR	NP_001243547.	To New Critical tip are again again gain gain great gr	0.052	0.066
RT 023684.1	TUFT1 tuftelin 1	AISIFLO	NP 064512.1, NXP 01150	ngccmgacuccagacqueccuggecaccaggaccugggcuaccauccaggccuggecaccauccaggcc acctaagctgggcagacgaggacaggcacggcac	0.196	0.008
			, , , , , , , , , , , , , , , , , ,		0.250	

				TGAscagasatgcctctasacagaaccctcttactatttagtttatctgggcagaaccagatigttatgtcctttgttcc		
RT 007176.1	UBA2 ubiquitin-like modifier activating enzyme 2	TEMPLNRTLLLFSLSGONOIVMSF	VINP 005490.1. XP 00525	2127 asagggasasasattgacagcagtga	0.25	0.384
RT 009758.1	UBL5 ubiquitin-like 5	RILIFLPR	NP 001041706.1, NP 077	9141 TAGatranaatecteatetteetreeceenttteeteteeateeteateeeeatan	0.097	0.127
				TAAcagccacacccgaccagtgacagcagggcctgggcagggctcgggggtcactgggggacctccaggggacctccagggggactccactgggcacagtgacagggggtgacgggggtgagggagg		
RT 022085.1	uncharacterized LOC105371419	APPGHSDRGRGVR	XP 01152	4152 attrccagagggaaggcagggaaggacgcgtag	0.172	0.152
RT 000368.1	UNG uracil DNA glycosylase	SSAEGWPLR	NP 550433.1, NP 003353	4500 TGAtcatcagctgaggggtggcctttgagaagctgctgttaa	0.157	0.329
				TAGagageggggccagtgcactggcatcagcacttictcctctgccagtgtctcaggacagcagagtgggcttgggt		
RT 023844.1	UVSSA UV-stimulated scaffold protein A	AGPSALAISTFSLCOCLR	NP 065945.2, XP 01151	5089 triggcagtaaccatgctitigtctatatcitigttittgatgtaaa	0.028	0.215
RT 012400.1	VASP vasodilator-stimulated phosphoprotein	TTOECIVPTPHPTWK	NP 003361.1. XP 00525	921 ToAccasagggaeccagasagaccegetictectiticegeacaccaggecigicaccetectiticegeactactiticetiticegeacaccaggeatiggetigaccetegeacaccagggaatiggaeccagacaggaatiggaeccagacaggaatiggaeccagacaggaatiggaeccagacaggaatiggaeccagacaggaatiggae		0.658
RT 001270.1	VDAC3 voltage-dependent anion channel 3	ASDLSLEVKRNEPTMFWP	NP 001129166.XP 00671	4076 TAAkstyngtitsangaaangcatcapatitytxcctigsaagtyaagagaaantgaaccactatgittingccttaa		-0.081
RT 022463.1	VMO1 vitelline membrane outer laver 1 homolog (chicken)	AAVVSRR	NP 001138413.1. NP 001	21723 ToApecagetigtigtigtigtigtigtigtigtigtigtigtigtigt		0.066
RT 017770.1	VPREB1 pre-B lymphocyte 1	SAEEAEPLSISWSCSVAVNPHWR		4587 TGAactgaagacaggaggcaggcatcccttggagagagattgtatggaagggtggagttgccgccgaagggctgagccactcagcatctctggtcctgcagtgttctgcagtgttctgcaatccccattggagactgcattag	0.129	0.1
RT 013079.1	WDFY3 WD repeat and FYVE domain containing 3	FNKLSGDHGL	NP 055806.2. XP 01153	7738 TGAsgattcascasagctpastgasgacataggtctgtag		0.437
				TGAttigcacqtigcagatacaatigctcctgagaagacagcattttccacaggaggctgtttcctcccctiggtggatttaa		
RT 019157.1	WDR19 WD repeat domain 19	ADTMLLR	NP 079408.3. XP 01151	8174 gagacggtcttttcggatacagagaaatga	0.269	0.294
			,	TGAgccccqtqtqcaaccaccacctccqtqqaaqtqctqqaacqqttccaagctqcqqqctccc		
				tggcaggatgctgagcttgtcttttctgctpaggaaggtacttttctgggtttctgcaggcatccgtgggggaaaaaa		
				astritragagectrisaciatitritricaaccasticigitricacctricecagagaccageccagetricteg		
RT 004152.1	WNT7A wingless-type MMTV integration site family, member 7A	MLSLSFLLR	NP 004616.2 XP 01153	7432 cggctggaaccaagccttctgcagcaggaactctggacccctgggcctcatcacagcaatattaac	-0.001	0.066
RT 022489.1	ZCCHCS zinc finger, CCHC domain containing 5	GGPHVGOSTNMRPPLFOYPCLIH	Y(NP 689907.1 XP 01152	9291 TAAgagagacccacqttggccaatctacaaatatgcgtcccctctcttccaatatccatgtctcatacactatggcttactgttgaaatccaactgggaagaagataattctttgagcaagca	0.007	-0.15
				TGAatttacactgcsaagaaaaactatgaatgtatggaatttttaaaaagaagtataatgccttacttcagagaactct		
RT 023327.1	ZNF140 zinc finger protein 140	NYECMEFFKK	NP 001287707.XP 01153	894 treasageasecttatetrasagtrateactetrasetas	0.218	0.382
				TAGENCTRENCESPRICE		
				gagestectoggeacegectraacttetegagtgeettgggacactgggecacagatggteatraggggaageca		
RT 027047.1	ZNF282 zinc finger protein 282	GAERPRAPPSHLLECPGTTGPOM	IVINP 003566.1. XP 00671	5072 crangenaticcenaniccitita	-0.116	-0.103
RT 014705.1	ZNF283 zinc finger protein 283	VVKEYFVCVYRQLIIIRTLTLEK	NP 001284681.XP 00525	4338 TGAttgaaagttgtbaaagaatattttgtgtgtgtatagacaacttatcataataagaactettactcttgagaaaccttgtgaatgtaugggttgtgcaaaagccattcatttctgtttatgggcaattatcttgctatccagcaattcttgctactagtga	0.227	0.294
RT 010661.1	ZNF34 zinc finger protein 34	FIAADLR	NP 001273699.1, NP 085	7548 TAALagtingcgcggtgtccgagggcagagtccagctpagcacticagctpagcacticctgcatgcgccccggcacctpactctigccctttatigtattatccacagagtgtttcacagagtgaaaggacgttictcattaaaacaaacctcttttcttaaaacaaagcagtgcatgtccagtgaaaggacatgtgaaaggacagtgccag	0.201	0.152
RT 002045.1	ZNF410 zinc finger protein 410 (glycosylation candidate)	ATLSDLKMR	NP 067011.1. NP 001225	5300 TGAscettaggific tractic transpagaços activat tratic assisting activate transpagaços activate tractic assisting activate tractic activate transpagaços activates activates activate transpagaços activates a	-0.098	-0.025
				TGAgcatagatacatagacetagacetagacetagacetacatecatacatacatagacatatagataagacatacatagatacata		
RT 023991.1	ZNF512B zinc finger protein 512B	VALPLIR	NP 065764.1. XP 00526	3859 tgtc:trcagttetrcateccrcaccccgccttttatrcgtccagtagagcagccagccactetcccttcattcctpaaggtggcccttcccctgttaaggctgccacaggggaacacctgggttggggctcccaaaggtgtgcccagaggtgtgccagaagtgcaatag	0.074	0.292
RT 010258.1	ZNF580 zinc finger protein 580	RGVGAPAPGGGTSALGSR	XP 01152	1229 not found		
			-	TAAagagctacaggagtaatccagcaccaggacactcatagtgaggggaaaccaagaaggcacactgaggcagct		
				ttcccacclagettccagttgtgggcaacagcaagaagtccatgtggcagagaagctgttcaaatgcagtgactgttgggaa		
RT 005360.1	ZNF584 zinc finger protein 584	RATESSSTRTLIVR	XP 00525	8735 ggtgttcttaa	0.176	0.259
			=			

Table S4.

change	Relative Fluc fold change	Relative Fluc fold change
Norm Flucifiles SD Norm Flucifiles SD	Condition Norm FlucRible SD SD SD SD SD SD SD S	Condition Norm Fluc/Rise QP
Condition Name Flucifilities SD Name Flucifilities N	Condition Norm FaucRise SD Norm FaucRise	Condition Norm Flucifile Vector 1.000 Vector Palbo 0.702 Vector Palbo 0.702 Vector Palbo 1.222 Vector Palbo + Gen 1.222
Name	Condition Norm FlucRitise SD Norm Flu	50 Condition Norm FluciBit. L. Vector D35 H-Ras V12 D35 H-Ras V12 D35 H-Ras V12 D35 Palbo H-Ras V12 D35 Palbo 0.535
No. No.	Condition None Fig.(R)ts SD None Fig	
Condition Non-Placified SD Non-Placified SD Non-Place SD SD SD SD SD SD SD S	Condition Num FlatNote ED Num FlatNote	Condition Norm Flucible
Condition Nom-ParipRole S	Condition Numm Furthless 10 Numm Furthless 50 Numm Furthle	Condition Norm PlucRis
PMLERAONT Com 2,200 1,200 3,988 0,600 6,000 0,600	Condition Non-Facilities SD Storm Facilities SD SD SD SD SD SD SD S	\$\frac{1}{2}\$ VASP-Vector 0.9999998 \$\frac{1}{2}\$ VASP-H-Ras V12 0.749281 \$\frac{1}{2}\$ ASPH-H-Ras V12 \$\frac{1}{2}\$ FBL-Wector FBL-H-Ras V12 0.641645
Vector Gen 3.7800 0.7600 2.8350 0.9966 PML-ER Gen 2.9820 0.3866 2.9700 0.2400 Vector 4 OHT Gen 2.7990 0.4541 2.4750 0.161 PML-ER 4OHT Gen 1.8230 0.1799 2.0780 0.8581	Condition Non Florible SD Non Florible	Condition
Confident Som Part Som Part	Hafter VEREFAIN-34 2,9595 50,000	### ASPH-Vector 3.696 ### ASPH-Nas V12
	Condition Num Planiffilms SD Num Plan	Condition Num Fuerities 20

Relative Fluc f	old change						
		N1		N2		N3	
UGA Fig 5A	Condition	Norm Fluc/Rluc	SD	Norm Fluc/Rluc	SD	Norm Fluc/Rluc	SD
2	Vector Vector Palbo	1,372	0.08361	0.8938	0.3002	1.076	0.2082
Æ	Vector Palbo Vector Gen	1.372	2 396	10.8938	1 821	7.828	1.838
š	Vector Palbo + Gen	11.23	1.73	1.708	0.1734	5.699	1.172
		N1		N2		N3	
5B	Condition	Norm Fluc/Rluc	SD.	Norm Fluc/Rluc	SD	Norm Fluc/Rluc	SD
AQP4 Fig	Vector	1.0000	0.1549	1.0000	0.1802	1.0450	0.1230
4 4	Vector Palbo	0.7022	0.0392	0.9950	0.2310	0.7346	0.0666
ą	Vector Gen Vector Palbo + Gen	1.5200	0.2612	4.8140 5.2490	0.5472	3.9550 1.8240	0.5800 0.3738
	Vector / ando / Gen		0.1100		0.7314		0.07.00
50		N1	SD	N2		N3	
Fig.	Condition Vector D35	Norm Flue/Rlue	SD 0.1425	Norm Fluc/Rluc	SD 0.123	Norm Fluc/Rluc	SD 0.2231
AQP4 F	H-Ras V12 D35	1.466	0.1292	1.25	0.2135	1.178	0.147
ğ	Vector D35 Palbo	0.573	0.2292	0.7346	0.06662	0.2108	0.02081
	H-Ras V12 D35 Palbo	0.5395	0.08137	0.7351	0.1591	0.3108	0.05771
S	1	N1		N2		1	
E S	Condition	Norm Fluc/Rluc	SD	Norm Fluc/Rluc	SD	l	
E	Vector D5	1.0000	0.2828	1.0820	0.1161		
8	Vector D12 Vector D20	0.8620 1.0000	0.3315	0.9551 0.8995	0.1077	l	
	Vector D20	1.0000	0.1937	0.0995	0.2043		
-		N1		N2		1	
AQP4 FigS1	Condition	Norm Fluc/Rluc	SD	Norm Fluc/Rluc	SD		
4	Vector D5	0.9991	0.2331	0.931	0.1098	l	
á	Vector D12	0.7887	0.1582	1.004	0.2469	l	
₹	Vector D20	0.7829	0.1559	1.066	0.2165		
ш		N1					
				N2			
S	Condition	N1 Norm Fluc/Rluc	SD	N2 Norm Fluc/Rluc	SD		
FigS1	Vector/Starv	Norm Fluc/Rluc	0.05281	Norm Fluc/Rluc	0.04788		
P4 FigS1	Vector/Starv H Ras V12/Starv				0.04788		
AQP4 FigS1	Vector/Starv	Norm Fluc/Rluc 1 0.4751	0.05281	Norm Fluc/Rluc 1 0.5905	0.04788		
AQP4 FigS1	Vector/Starv H Ras V12/Starv Vector/FBS	Norm Fluc/Riuc 1 0.4751 0.928 0.5003	0.05281 0.05073 0.2528	Norm Fluc/Rluc 1 0.5905 0.8961 0.669	0.04788 0.04545 0.213		
AQP4 FigS1	Vector/Starv H Ras V12/Starv Vector /FBS H Ras V12/FBS	Norm Fluc/Riuc 1 0.4751 0.928 0.5003	0.05281 0.05073 0.2528 0.1221	Norm Fluc/Rluc 1 0.5905 0.8961 0.669	0.04788 0.04545 0.213 0.01713	N3 Name Shailling	en .
Fig 8 AQP4 FigS1	Vector/Starv H Ras V12/Starv Vector /FBS H Ras V12/FBS	Norm Fluc/Rluc 1 0.4751 0.928 0.5003 N1 Norm Fluc/Rluc	0.06281 0.05073 0.2528 0.1221	Norm Fluc/Riuc 1 0.5905 0.8961 0.669 N2 Norm Fluc/Riuc	0.04788 0.04545 0.213 0.01713	Norm Fluc/Rluc	SD
Fig 8 AQP4 FigS1	Vector/Starv H Ras V12/Starv Vector /FBS H Ras V12/FBS Condition HPN-Vector	Norm FluciRiuc 1 0.4751 0.928 0.5003 N1 Norm FluciRiuc	0.05281 0.05073 0.2528 0.1221 SD 0.075251	Norm FlucRluc 1 0.5905 0.8961 0.669 N2 Norm FlucRluc 0.9999999	0.04788 0.04545 0.213 0.01713 SD 0.050515	Norm Fluc/Rluc	0.253091
Fig 8 AQP4 FigS1	Vector/Starv H Ras V12/Starv Vector /FBS H Ras V12/FBS	Norm Fluc/Rluc 1 0.4751 0.928 0.5003 N1 Norm Fluc/Rluc	0.06281 0.05073 0.2528 0.1221	Norm Fluc/Riuc 1 0.5905 0.8961 0.669 N2 Norm Fluc/Riuc	0.04788 0.04545 0.213 0.01713	Norm Fluc/Rluc 1 0.5758567	
Fig 8 AQP4 FigS1	Vector/Starv H Ras V12/Starv Vector /FBS H Ras V12/FBS Condition HPN-Vector HPN-H-Ras V12	Norm Fluc/Riuc 0.4751 0.928 0.5003 N1 Norm Fluc/Riuc 1 0.3838983 0.9999998	0.06281 0.05073 0.2528 0.1221 SD 0.075251 0.384538 0.008484	Norm Fluc/Rluc 1 0.5905 0.8961 0.669 N2 Norm Fluc/Rluc 0.999999 0.7287598	0.04788 0.04545 0.213 0.01713 SD 0.050515 0.218933 0.292373	Norm Fluc/Riuc 1 0.5758567 1	0.253091 0.060332 0.008485
Fig 8 AQP4 FigS1	Vector/Starv H Ras V12/Starv Vector /FBS H Ras V12/FBS Condition HPN-Vector HPN-H-Ras V12 VASP-Vector VASP-H-Ras V12	Norm FluciRluc 1 0.4751 0.928 0.5003 N1 Norm FluciRluc 1 0.3838983	0.05281 0.05073 0.2528 0.1221 SD 0.075251 0.384538 0.008484 0.05589	Norm Fluc/Riuc 1 0.5905 0.8961 0.669 NZ Norm Fluc/Riuc 0.9999999 0.7287598 0.9999998	0.04788 0.04545 0.213 0.01713 SD 0.050515 0.218933	Norm Fluc/Rluc 1 0.5758567	0.253091
Fig 8 AQP4 FigS1	Vector/Starv H Ras V12/Starv Vector /FBS H Ras V12/FBS Condition HPN-Vector HPN-H-Ras V12 VASP-Nector VASP-Nector	Norm FluciRiuc 1 0.4751 0.928 0.5003 N1 Norm FluciRiuc 1 0.3838983 0.9999998 0.7492877	0.06281 0.05073 0.2528 0.1221 SD 0.075251 0.384538 0.008484 0.05589	Nom FluciRiuc 0.5905 0.8961 0.669 N2 Nom FluciRiuc 0.9999999 0.7287598 0.9999998 0.8763331	0.04788 0.04545 0.213 0.01713 SD 0.050515 0.218933 0.292373 0.225433	Norm Fluc/Rluc 1 0.5758567 1 0.7188824 0	0.253091 0.060332 0.008485
Fig 8 AQP4 FigS1	Vector/Starv H Ras V12/Starv Vector /FBS H Ras V12/FBS Condition HPN-Vector HPN-H-Ras V12 VASP-Vector VASP-H-Ras V12 ASPH-Vector ASPH-H-Ras V12	Norm FluciRiuc 1 0.4751 0.928 0.5003 N1 Norm FluciRiuc 1 0.3838983 0.999998 0.7492877 0	0.06281 0.05073 0.2528 0.1221 SD 0.075251 0.384538 0.008484 0.05589	Nom FluciRiuc 1 0.5905 0.8961 0.669 N2 Nom FluciRiuc 0.9999999 0.7287598 0.9999998 0.8763331 0	0.04788 0.04545 0.213 0.01713 SD 0.050515 0.218933 0.292373 0.225433	Norm FluciRluc 1 0.5758567 1 0.7188824 0 0	0.253091 0.060332 0.008485 0.018714 0
Fig 8 AQP4 FigS1	Vector/Starv H Ras V12/FBS Condition HPN-Vector HPN-H-Ras V12 VASP-Nector VASP-H-Ras V12 ASPH-Vector ASPH-Ras V12 FBL-Vector	Norm FluciRfue 0.4751 0.928 0.5003 N1 Norm FluciRfue 1 0.3838983 0.9999998 0.7492877 0 0 1	0.06281 0.05073 0.2528 0.1221 SD 0.075251 0.384538 0.008484 0.05589 0	Nom FluciRiuc 0.5905 0.8961 0.669 N2 Nom FluciRiuc 0.9999999 0.7287598 0.9999998 0.8763331	0.04788 0.04545 0.213 0.01713 SD 0.050515 0.218933 0.292373 0.225433	Norm FluciRiuc 1 0.5758567 1 0.7188824 0 0	0.253091 0.060332 0.008485 0.018714 0 0
Nat Rth candidates Ctrl Fig 8	Vector/Starv H Ras V12/Starv Vector /FBS H Ras V12/FBS Condition HPN-Vector HPN-H-Ras V12 VASP-Vector VASP-H-Ras V12 ASPH-Vector ASPH-H-Ras V12	Norm Fluc/Riuc 0.4751 0.928 0.5003 N1 Norm Fluc/Riuc 1 0.3838983 0.9999998 0.7492877 0 0 1 0.6416453	0.06281 0.05073 0.2528 0.1221 SD 0.075251 0.384538 0.008484 0.05589	Nom FluciRuc 0.5905 0.8961 0.669 N2 Nom FluciRuc 0.999999 0.7287598 0.8763331 0 0.9999999 0.8305688	0.04788 0.04545 0.213 0.01713 SD 0.050515 0.218933 0.292373 0.225433 0.050515	Norm FluciRluc 1 0.5758567 1 0.7188824 0 0	0.253091 0.060332 0.008485 0.018714 0
Nat Rth candidates Ctrl Fig 8	Vector/Starv Vector (FBS H Ras V12FBS H Ras V12FBS H Ras V12FBS HPN-Vector HPN-H-Ras V12 VASP-Vector VASP-H-Ras V12 ASPH-Vector ASPH-H-Ras V12 FBL-M-Ras V12 FBL-M-Ras V12	Norm Fluc/Riuc 0.4751 0.928 0.5003 N1 Norm Fluc/Riuc 1 0.3838983 0.9999998 0.7492877 0 0 1 0.6416453	0.06281 0.05073 0.2528 0.1221 SD 0.075251 0.384538 0.008484 0.05589 0 0.178778 0.164848	Nom FluciRiuc 0.5905 0.8961 0.669 N2 Nom FluciRiuc 0.9999999 0.7287598 0.8763331 0 0.9999999 0.8305688	0.04788 0.04545 0.213 0.01713 0.01713 SD 0.050515 0.218933 0.292373 0.225433 0 0.197851 0.006193	Norm FluciRiuc 1 0.5758567 1 0.7188824 0 0	0.253091 0.060332 0.008485 0.018714 0 0
Nat. Rth candidates Ctrl Fig § AQP4 FigS1	Vector/Starv Vector FBS H Ras V12/FBS H Ras V12/FBS Condition HPN-Vector HPN-H-Ras V12 VASP-H-Ras V12 ASPH-Ras V12 ASPH-Ras V12 ASPH-Ras V12 ASPH-Ras V12 Condition Condition	Norm Fluc/Ritue 0.4751 0.328 0.5003 N1 Norm Fluc/Ritue 1 0.383883 0.9999998 0.7492877 0 0 1 1 0.6416453 Norm Fluc/Ritue	0.06281 0.05073 0.2528 0.1221 SD 0.075251 0.384538 0.008484 0.05589 0 0.178778 0.164848	Nom FlucRiuc 0.5905 0.8961 0.669 N2 Nom FlucRiuc 0.9999999 0.7287598 0.9999998 0.8763331 0 0 0.9999999 N2 Nom FlucRiuc N9 NOM	0.04788 0.04545 0.213 0.01713 SD 0.050515 0.218933 0.292373 0.225433 0 0 0.197861 0.006193	Norm FluciRiuc 1 0.5758567 1 0.7188824 0 0	0.253091 0.060332 0.008485 0.018714 0 0
Nat Rth candidates Ctrl Fig 8	Vector/Starv Vector/Starv Vector/FBS H Ras V12FBS Condition HPN-Vector HPN-H-Ras V12 VASP-Vector VASP-H-Ras V12 ASPH-Vector FBL-Wector FBL-H-Ras V12 FBL-Wector FBL-H-Ras V12 FBL-Wector FBL-H-Ras V12 FBL-Wector FBL-H-Ras V12	Norm Fluc/Rive 0.4751 0.4751 0.4751 0.5003 Norm Fluc/Rive 0.5003 0.3838983 0.9999998 0.7492877 0 0 1 0.6416453 Norm Fluc/Rive 8.0240	0.06281 0.05073 0.2528 0.1221 SD 0.075251 0.384538 0.008484 0.05589 0 0.178778 0.164848	Norm FlucRlue 1 0.5905 0.5905 0.8961 0.669 N2 Norm FlucRlue 0.999999 0.7287598 0.9999998 0.8763331 0 0.9999999 0.8305688 N2 Norm FlucRlue 3.5987	0.04788 0.04545 0.213 0.01713 0.01713 0.050515 0.218933 0.292373 0.225433 0.0197851 0.006193	Norm FluciRiuc 1 0.5758567 1 0.7188824 0 0	0.253091 0.060332 0.008485 0.018714 0 0
Nat Rth candidates Ctrl Fig 8	Vector/Starv Vector/Starv Vector/FBS H Ras V12FBS Condition HPN-Vector HPN-H-Ras V12 VASP-H-Ras V12 ASPH-H-Ras V12 FBL-Vector FBL-M-Ras V12 Condition HPN-Vector	Nom FluciRiuc 0.4751 0.928 0.5003 Nom FluciRiuc 0.3838983 0.999998 0.7492877 0 0 1 0.6416453 N1 Nom FluciRiuc 8.0240 7.9446	0.05281 0.05073 0.2528 0.1221 SD 0.075251 0.384538 0.008484 0.05589 0 0.178778 0.164848 SD 0.9762 2.6363	Norm FlucRuc 1 0.5905 0.8961 0.8991 0.8991 0.8999 Norm FlucRuc 0.999999 0.7287598 0.999999 0.8763331 0 0 0 0.999999 0.8305688	0.04788 0.04545 0.213 0.01713 SD 0.050515 0.218937 0.225433 0.225433 0.0197851 0.006193 SD 0.4123 0.1470	Norm FluciRiuc 1 0.5758567 1 0.7188824 0 0	0.253091 0.060332 0.008485 0.018714 0 0
Nat. Rth candidates Ctrl Fig § AQP4 FigS1	Vector/Starv Vector (FBS H Ras V12/Starv Vector (FBS Condition HPN-Vector HPN-H-Ras V12 ASPH-Vector ASPH-H-Ras V12 FBL-Wector FBL-H-Ras V12 ASPH-Vector ASPH-H-Ras V12 ASPH-Vector HPN-H-Ras V12 FBL-Wector HPN-Wector HPN-H-Ras V12 VASP-Vector HPN-H-Ras V12 VASP-Vector HPN-H-Ras V12 VASP-Vector HPN-H-Ras V12 VASP-Vector	Norm FluciRiue 1 1 1 7 1 7 1 9228 0.5003 Norm FluciRiue 1 0.3839983 0.7492877 0 1 1 0.5416453 Norm FluciRiue Norm FluciRiue 1 1 0.5416453	0.05281 0.05073 0.2528 0.1221 SD 0.075251 0.384538 0.008484 0.05589 0 0.178778 0.164848 SD 0.9762 2.6363 1.8238	Nom FlucRuc 0.5905 0.9961 0.5690 N2 Nom FlucRuc 0.5999999 0.7287598 0.999999 0.7287598 0.999999 0.8105688 Nom FlucRuc Nom FlucRuc 1.5999999 0.8305688	0.04788 0.04545 0.213 0.01713 0.01713 SD 0.050515 0.2182373 0.225433 0.225433 0.050515 0.06193 SD 0.4123 0.1470 0.3532	Norm FluciRiuc 1 0.5758567 1 0.7188824 0 0	0.253091 0.060332 0.008485 0.018714 0 0
Nat Rth candidates Ctrl Fig 8	Vector/Starv Vector /FBS If Ras V12/FBS Condition HPN-Vector HPN-Vector HPN-Vector VASP-H-Ras V12 ASPH-Vector FBL-H-Ras V12 Condition HPN-Vector FBL-H-Ras V12 Condition HPN-Vector HPN-Vector HPN-Vector HPN-Vector HPN-Vector HPN-Vector HPN-Vector HPN-H-Ras V12 VASP-Vector VASP-H-Ras V12 VASP-Vector	Norm FluciRiuc 1 1 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	0.05281 0.05073 0.2528 0.1221 SD 0.075251 0.384538 0.008484 0.05589 0 0.178778 0.164848 SD 0.9762 2.5363 1.8238	Norm FlucRluc 1 1 0.5905 0.5905 0.98951 0.669 Norm FlucRluc 0.3999999 0.728798 0.9999999 0.58763331 0 0 0.3999999 0.8306689 0.8306689 Norm FlucRluc Norm FlucRluc 3.9697 4.4482 3.1289	0.04788 0.04545 0.213 0.01713 0.01713 0.050515 0.218933 0.292373 0.225433 0.0197851 0.006193 0.4123 0.4123 0.4123 0.3532 1.0182	Norm FluciRiuc 1 0.5758567 1 0.7188824 0 0	0.253091 0.060332 0.008485 0.018714 0 0
Nat. Rth candidates Ctrl Fig § AQP4 FigS1	Vector/Starv Vector (FBS H Ras V12/FBS Vector (FBS H Ras V12/FBS Condition HPN-Vector HPN-H-Ras V12 VASP-Vector VASP-H-Ras V12 FBL-Wector FBL-H-Ras V12 FBL-Wector FBL-H-Ras V12 VASP-Vector VASP-Vector VASP-H-Ras V12 ASPH-Vector VASP-H-Ras V12 VASP-Vector VASP-H-Ras V12 VASP-Wector VASP-H-Ras V12 VASP-Wector	Nom FluciRiuc 1 1 0.4751 0.9282 0.5003 N1 Nom FluciRiuc 1 0.383983 0.7492877 0 1 0.5451645 N1 Nom FluciRiuc 8.0240 7.946861 19.0749	0.05281 0.05073 0.2528 0.1221 SD 0.075251 0.384538 0.008484 0.05589 0 0.178778 0.164848 SD 0.9762 2.6363 1.8238 1.1154 0.4123	Nom FlucRiuc 1 1 0.5905 0.9895 0.9895 0.98961 0.6699 N2 Nom FlucRiuc 0.9999999 0.7287598 0.9999998 0.8763331 0 0 0.9999999 0.830588 Nex 2.84033 4.44482 4.4482 1.10000	0.04788 0.04545 0.213 0.01713 0.01713 0.050515 0.218933 0.292373 0.292373 0.292373 0.0506193 0.197861 0.006193 0.4123 0.4123 0.1470 0.3532 0.1470 0.1502 0.1470 0.1502 0.1470 0.1502 0.1470 0.1502 0.1470 0.1502 0.1470 0.1502 0.1470 0.1502 0.1470 0.1502 0.1470 0.1502 0.1470 0.1470 0.1502 0.1470 0.1	Norm FluciRiuc 1 0.5758567 1 0.7188824 0 0	0.253091 0.060332 0.008485 0.018714 0 0
Nat. Rth candidates Ctrl Fig § AQP4 FigS1	Vector/Starv Vector #B8 I Ras V12/FBS Condition HRN-Vector HRN-Vector HRN-Vector VASP-H-Ras V12 ASPH-Vector FBL-M-Ras V12 Condition HRN-Vector FBL-M-Ras V12 Condition HRN-Vector HRN-Vector HRN-Vector ASPH-N-Ras V12 ASPH-Vector ASPH-Ras V12 ASPH-Vector ASPH-Ras V12 ASPH-Vector ASPH-Ras V12 ASPH-Ras V12 ASPH-Ras V12 ASPH-Ras V12	Norm FluciRiue. 1 1 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	0.06281 0.05073 0.2528 0.1221 SD 0.075251 0.384538 0.008484 0.05589 0.178778 0.164848 SD 0.9762 2.6363 1.8238 1.1152 0.4123 0.1470	Nom FlucRiuc 1 1 0.5905 0.5905 0.5905 0.5905 0.5905 0.5909 Nom FlucRiuc 0.3999999 0.7287598 0.8763331 0 0 0 0.5909999 0.5305698 NZ Nom FlucRiuc 3.59997 2.4933 4.4442 3.1289 1.10000	0.04788 0.04545 0.213 0.01713 SD 0.050515 0.21893 0.292373 0.292373 0.292373 0.197851 0.006193 SD 0.4123 0.1470 0.3532 1.0182 0.4716 0.0323	Norm FluciRiuc 1 0.5758567 1 0.7188824 0 0	0.253091 0.060332 0.008485 0.018714 0 0
Nat. Rth candidates Ctrl Fig § AQP4 FigS1	Vector/Starv Vector (FBS H Ras V12/FBS Vector (FBS H Ras V12/FBS Condition HPN-Vector HPN-H-Ras V12 VASP-Vector VASP-H-Ras V12 FBL-Wector FBL-H-Ras V12 FBL-Wector FBL-H-Ras V12 VASP-Vector VASP-Vector VASP-H-Ras V12 ASPH-Vector VASP-H-Ras V12 VASP-Vector VASP-H-Ras V12 VASP-Wector VASP-H-Ras V12 VASP-Wector	Norm FlecRise. 1 1 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	0.06281 0.05073 0.2528 0.1221 SD 0.075251 0.384538 0.008484 0.05589 0 0 0.178778 0.164848 SD 0.9762 2.6363 1.8238 1.1154 0.4123 0.4470	Nom FlucRiuc No	0.04788 0.04545 0.213 0.01713 SD 0.050515 0.218933 0.292373 0.2254333 0.292373 0.0197851 0.006193 SD 0.4123 0.1470 0.1572 1.0182 0.4716 0.0323 0.3116	Norm FluciRiuc 1 0.5758567 1 0.7188824 0 0	0.253091 0.060332 0.008485 0.018714 0 0
Fig 8 AQP4 FigS1	Vector/Starv Vector #B8 I Ras V12/FBS Condition HRN-Vector HRN-Vector HRN-Vector VASP-H-Ras V12 ASPH-Vector FBL-M-Ras V12 Condition HRN-Vector FBL-M-Ras V12 Condition HRN-Vector HRN-Vector HRN-Vector ASPH-N-Ras V12 ASPH-Vector ASPH-Ras V12 ASPH-Vector ASPH-Ras V12 ASPH-Vector ASPH-Ras V12 ASPH-Ras V12 ASPH-Ras V12 ASPH-Ras V12	Norm FluciRiue. 1 1 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	0.06281 0.05073 0.2528 0.1221 SD 0.075251 0.384538 0.008484 0.05589 0.178778 0.164848 SD 0.9762 2.6363 1.8238 1.1152 0.4123 0.1470	Nom FlucRiuc 1 1 0.5905 0.5905 0.5905 0.5905 0.5905 0.5909 Nom FlucRiuc 0.3999999 0.7287598 0.8763331 0 0 0 0.5909999 0.5305698 NZ Nom FlucRiuc 3.59997 2.4933 4.4442 3.1289 1.10000	0.04788 0.04545 0.213 0.01713 SD 0.050515 0.21893 0.292373 0.292373 0.292373 0.197851 0.006193 SD 0.4123 0.1470 0.3532 1.0182 0.4716 0.0323	Norm FluciRiuc 1 0.5758567 1 0.7188824 0 0	0.253091 0.060332 0.008485 0.018714 0 0
Nat. Rth candidates Gen Figs Nat Rth candidates Ctrl Fig S AQP4 FigS1	Vector/Starv Vector /FBB If Ras V12/FBS Condition IHPN-Vector IHPN-H-Ras V12 VASP-Nector ASPH-H-Ras V12 FBL-M-Ras V12 FBL-M-Ra	Norm FlecRise. 1 1 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	0.06281 0.05073 0.2528 0.1221 SD 0.075251 0.384538 0.008484 0.05589 0 0 0.178778 0.164848 SD 0.9762 2.6363 1.8238 1.1154 0.4123 0.4470	Nom FlucRiuc No	0.04788 0.04545 0.213 0.01713 SD 0.050515 0.218933 0.292373 0.2254333 0.292373 0.0197851 0.006193 SD 0.4123 0.1470 0.1572 1.0182 0.4716 0.0323 0.3116	Norm FluciRiuc 1 0.5758567 1 0.7188824 0 0	0.253091 0.060332 0.008485 0.018714 0 0
Nat. Rth candidates Gen Figs Nat Rth candidates Ctrl Fig S AQP4 FigS1	Vector/Starv Vector /FBB If Ras V12/FBS Condition IHPN-Vector IHPN-H-Ras V12 VASP-Nector ASPH-H-Ras V12 FBL-M-Ras V12 FBL-M-Ra	Norm FlucRisue. 1 1 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	0.06281 0.05073 0.2528 0.1221 SD 0.075251 0.384538 0.008484 0.05589 0 0 0.178778 0.164848 SD 0.9762 2.6363 1.8238 1.1154 0.4123 0.4470	Norm FlucRisc Norm F	0.04788 0.04545 0.213 0.01713 SD 0.050515 0.218933 0.292373 0.2254333 0.292373 0.0197851 0.006193 SD 0.4123 0.1470 0.1572 1.0182 0.4716 0.0323 0.3116	Nom FlucRiuc 1 0.5759567 1 0.7188824 0 0 1 1 0.9574316	0.253091 0.060332 0.008485 0.018714 0 0
Nat. Rth candidates Gen Figs Nat Rth candidates Ctrl Fig S AQP4 FigS1	Vectorifistry NEAR VIT/28/28/29 I Rau VIT/28/28/29 I Rau VIT/28/28/29 Condition HPN-Vector PRI-M-Rau VIT/28/29 VASP-M-Rau VIT/2 ASPH-M-Rau VIT/2 ASPH-M-Rau VIT/2 FBL-M-Rau VIT/2 FBL-M-Rau VIT/2 SPH-M-Rau VIT/2 ASPH-M-Rau VIT/2 ASPH-M-Rau VIT/2 FBL-M-Rau VIT/2 ASPH-M-Rau VIT/2 FBL-M-Rau VIT/2 Condition Condition Condition Condition Vector Vecto	Norm FlucRisse. 1 0.4751 0.9276 Norm FlucRisse. 1 0.3838083. 1 0.3838083. 0.99999986 0.7492877 0.00 0.7492877 1.058418453 Norm FlucRisse. 1 0.4416453 Norm FlucRisse. 1 0.7492877 1.7986 Norm FlucRisse. 1 1.7986 Norm FlucRisse.	0.02818 0.05073 0.2528 0.1221 SD 0.075251 0.394538 0.05589 0.90762 2.63636 1.8228 0.11154 0.4123 0.14743 0.16438	Norm FlucRiuc 1 0.5505 (1.5005	0.04785 0.04545 0.213 0.01713 SD 0.050515 0.21933 0.225433 0.00785 0.197851 0.006193 SD 0.4123 0.4470 0.3532 0.4470 0.00323 0.4716 0.00323 0.4716 0.00323 0.4716 0.00323 0.4716 0.00323 0.4716 0.00323 0.4716 0.00323 0.4716 0.00323 0.4716 0.00323 0.4716 0.00323 0.4716 0.00323 0.4716 0.00323	Norm FlucRisc 1 0.5759507 1 0.7188824 0 0 0 1 0.9574316 Norm FlucRisc Norm FlucRisc	0.253091 0.060332 0.008485 0.018714 0 0 0.144858 0.076049
Nat Rth candidates Ctrl Fig 8	Vector/Bary Net Nat 1728A Condition HPN-Vector ASPH-H-Ray 172FB Condition HPN-Vector HPN-Vector	Norm FlucRise 0.3538963 0.9005 N1 0.3538963 0.999998 0.749287 0 0.541963 Norm FlucRise 8.0241 1.7049 1.7049 1.7049 1.7049 1.7049 1.7049 1.7049 1.7049 1.7049 1.7049 1.7049 1.7049 1.7049 1.7049 1.7049 1.7049 1.7049 1.7049	0.06281 0.06273 0.2528 0.1221 SD 0.075251 0.384538 0.008484 0.05589 0 0.7625 0.164848 SD 0.9762 2.6363 1.8238 1.1154 0.4123 0.4123 0.4123 0.4123 0.4123 0.4123 0.4123	Norm FlucRisc Norm F	0.04783 0.04545 0.01713 SD 0.050515 0.21893 0.222473 0.222473 0.222473 0.006193 SD 0.4123 0.4	Nom FlucRiuc 1 0.5759567 1 0.7188824 0 0 1 0.9574316	0.253091 0.060332 0.008485 0.018714 0 0 0.144868 0.076049

			_				
o	Condition	N Fluc/Rluc	1 SD	N Flue/Riuc	2 SD		
SIC	Vector D5	0.1513	0.01336	0.1522	0.0328		
£	H-Ras V12-D5	0.1915	0.03523	0.1917	0.02881		
ш.	Vector D12	0.177	0.02829	0.2036	0.05782		
800	H-Ras V12-D12	0.1877	0.05967	0.1653	0.01256		
ö	Vector D20	0.1976	0.01948	0.1937	0.03903		
	H-Ras V12-D20	0.2119	0.02777	0.2063	0.04968		
SZA		N		N		N	
66	Condition	Fluc/Rluc	SD	Fluc/Rluc	SD	Fluc/Rluc	SD
윤	Vector	0.1586	0.03595	0.1653	0.0114	0.1709	0.0308
-	H Ras V12	0.1553	0.007879	0.1812	0.06017	0.1478	0.0294
800	Vector Gen	0.1961	0.05043	0.2048	0.04365	0.1997	0.0381
o	H Ras V12 Gen	0.229	0.009903	0.2198	0.006688	0.1437	0.00597
		N		N		N	
	Condition	Fluc/Rluc	SD.	Fluc/Rluc	sn sn	Fluc/Riuc	sn sn
					0.154	1.000	0.25
m		1 000	990.0				
828	Vector H Ras V12	1.000	0.066	1.000 0.748	0.154	0.620	0.03
g S2B	Vector						0.03
Fig S2B	Vector H Ras V12	0.625	0.162	0.748	0.063		0.03
A Fig S2B	Vector H Ras V12 Vector CDX5-1	0.625 0.973	0.162 0.099	0.748 1.045	0.063 0.094		
UGA Fig S2B	Vector H Ras V12 Vector CDX5-1 H Ras V12 CDX5-1	0.625 0.973 0.837	0.162 0.099 0.178	0.748 1.045 0.860	0.063 0.094 0.020	0.620	1.05
UGA Fig S2B	Vector H Ras V12 Vector CDX5-1 H Ras V12 CDX5-1 Vector Gen	0.625 0.973 0.837 7.038	0.162 0.099 0.178 0.741	0.748 1.045 0.860 5.910	0.063 0.094 0.020 0.425	0.620 5.430	1.05 1.22 0.82

Table S5. Real time PCR primers

Gene Name	5' forward primer (5'-3')	3' reverse primer (5'-3')
BRCA1	GGTTGTTGATGTGGAGGGGCAA	CCAGATTCCAGGTAAGGGGTTC
CDKN1A/p21	ACCCTTGTGCCTCGCTCAGG	GCGTTTGGAGTGGTAGAAATCTGT
CDK4	CAGTGCAGTCGGTGGTACCTGA	GGCAGAGATTCGCTTGTGTGG
CENPA	AATGGATTCTGCGATGCTGTCTGG	TTTTCAGGCCTTTGGAACGGTGTT
FANCD2	CCTTAGTAGCCGACTGAAACAGG	TGCAAGTAATGGACGCTCTG
GADD45A	TTGCAATATGACTTTGGAGGAA	CATCCCCCACCTTATCCAT
HMBS	GGCAATGCGGCTGCAA	GGGTACCCACGCGAATCAC
H-RAS	TTGCCATCAACAACACCAAGTC	ATCCGAGTCCTTCACCCGTTTG
KI67	AGAAGACAGTACCGCAGATGA	CGGCTCACTAATTTAACGCTGG
MCM6	ATCCCTCTTGCCAAGGATTT	GAAAAGTTCCGCTCACAAGC
ORC1L	CCCGGCTCAAGCATCYAAAGG	TCGTGCATCTCCAGACAGTCT
TBP	GCTGGCCCATAGTGATCTTTGC	CTTCACACGCCAAGAAACAGTGA
MCM6	ATCCCTCTTGCCAAGGATTT	GAAAAGTTCCGCTCACAAGC
IL-6	CCAGGAGCCCAGCTATGAACTC	AAGGCAGCAGGCAACACCAG
CXCL8/IL-8	GGCACAAACTTTCAGAGACAGCA	GGCAAAACTGCACCTTCACACA