# MLL1, a H3K4 methyltransferase, regulates the TNFα-stimulated activation of genes downstream of NF-κB

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## Summary

Genes of the mixed lineage leukemia (MLL) family regulate transcription by methylating histone H3K4. Six members of the MLL family exist in humans, including *SETD1A*, *SETD1B* and *MLL1–MLL4*. Each of them plays non-redundant roles in development and disease genesis. *MLL1* regulates the cell cycle and the oscillation of circadian gene expression. Its fusion proteins are involved in leukemogenesis. Here, we studied the role of MLL1 in innate immunity and found it selectively regulates the activation of genes downstream of NF-κB mediated by tumor necrosis factor (TNFα) and lipopolysaccharide (LPS). Real-time PCR and genome-wide gene expression profile analysis proved that the deficiency of *MLL1* reduced the expression of a group of genes downstream of nuclear factor κB (NF-κB). However, the activation of NF-κB itself was not affected. The MLL1 complex is found both in the nucleus and cytoplasm and is associated with NF-κB. CHIP assays proved that the translocation of MLL1 to chromatin was dependent on NF-κB. Our results suggest that MLL1 is recruited to its target genes by activated NF-κB and regulates their transcription.

**Key words:** MLL1, MLL, Histone methylation, Transcription regulation, NF-κB signaling pathway

## Introduction

*MLL1* (mixed lineage leukemia 1) was first identified from leukemia patients ~20 years ago (Krivtsov and Armstrong, 2007; Ziemin-van der Poel et al., 1991). The N-terminal of *MLL1* is able to fuse with other partners upon chromatin translocation and this induces leukemogenesis by regulating the expression of HOX genes (Krivtsov and Armstrong, 2007; Mohan et al., 2010). The biochemical function of MLL1 was not clear until Set1, its homolog in *Saccharomyces cerevisiae*, was defined as an H3K4 methyltransferase (Miller et al., 2001). Six homologs for Set1 exist in human, SETD1A (SET domain containing 1A), SETD1B (SET domain containing 1B) and MLL1–MLL4 (Wu et al., 2008). Each of these six proteins contains a conserved SET domain, the catalytic domain for methylating histone H3K4, and its full function requires the formation of a complicated complex. Each enzyme complex contains four common units, including RBBP5 (retinoblastoma binding protein 5), WDR5 (WD repeat domain 5), ASH2L (ash2-like) and DPY30 (dpy-30 homolog) (Cho et al., 2007; Lee and Skalnik, 2005; Lee and Skalnik, 2008; Lee et al., 2007; Wu et al., 2008; Yokoyama et al., 2004). The six complexes might have different biological functions because each one also contains specific subunits (Eissenberg and Shilatifard, 2010). This idea is also supported by studies within animal models. Deletion of either *Mll1* or *Mll2* in mice is embryonic lethal, suggesting that both *Mll1* and *Mll2* have important and non-redundant roles in embryo development (Glaser et al., 2006; Yu et al., 1995).

Data from a ChIP-Chip assay has indicated that MLL1 might be a common transcription factor and essential for gene transcription (Guenther et al., 2005). However, other groups have come to different conclusions because MEFs (mouse embryonic fibroblasts) derived from $Mll1^{-/-}$ mice grow normally. Moreover, the global mRNA expression patterns in the $Mll1^{-/-}$ MEF cell also did not change much compared with that of the wild type. MLL1 has been shown to regulate only the expression of a subset of active genes in vivo (Milne et al., 2005). Genome wide ChIP-Chip assays of H3K4 trimethylation indicate that only ~5% of the actively transcribed genes have reduced methylation in $Mll1^{-/-}$ cells in comparison with the wild type (Wang et al., 2009). A similar result was also observed for a global gene expression profile (Wang et al., 2009). The function of MLL1 on the majority of gene promoters is still unknown.

How MLL1 fusion proteins regulate leukemogenesis has been heavily investigated in the past 20 years (Krivtsov and Armstrong, 2007; Mohan et al., 2010). In contrast, very few studies have explored other physiological functions of MLL1. Although methylated H3K4 seems to be related to global gene transcription (Barski et al., 2007; Eissenberg and Shilatifard, 2010; Ruthenburg et al., 2007; Shilatifard, 2008; Sims and Reinberg, 2006), deficiency of the methylation does not always lead to gene silencing. Therefore, how H3K4 methylation regulates transcription still remains puzzling. Moreover, multiple H3K4 methyltransferases exist in mammals and their functions are not redundant. Their

functions in development and other physiological events remain to be elucidated.

Recently, an MLL1 complex has been found to associate with condensed chromatin during M phase, on genes that are usually expressed preferentially in interphase (Blobel et al., 2009). It is hypothesized that MLL1 binds to these genes and regulates their methylation and transcription immediately after exit from M phase. Another report has recently suggested that MLL1 is associated with the CLOCK (circadian locomotor output cycles kaput)–BMAL1 (brain and muscle ARNT-like 1) complex and is recruited to circadian promoters (Katada and Sassone-Corsi, 2010).

The MLL1 complex is usually considered to mainly function inside the nucleus; nearly all previous studies have shown that MLL1 functions on the chromatin, and the first complex to be purified was also done from nuclear extract (Yokoyama et al., 2004). However, one study has reported that WDR5, one important subunit of the MLL1 complex, is associated with the VISA-associated complex and regulates the virus-triggered induction of type I interferons (IFNs) and the innate immune response in the cytoplasm (Wang et al., 2010). The discovery raised the possibility that the MLL1 complex might also function in the cytoplasm and methylate substrates other than H3. The NF-κB pathway is one of the key pathways involved in innate immunity and other physiological responses (Baud and Karin, 2009; Ghosh and Hayden, 2008; Smale, 2010; Spehlmann and Eckmann, 2009; Sun and Karin, 2008). This pathway can be activated by many signals, including TNFα (tumor necrosis factor), LPS (lipopolysaccharide), TLRs (TOLL-like receptors) and so on. Usually different signals will trigger different profiles of gene transcription (Ghosh and Hayden, 2008; Smale, 2010). How a single transcription factor achieves selective gene transcription has been an unsolved question for a long time. Epigenetic markers and molecules have emerged as key players in gene transcription (Campos and Reinberg, 2009; Chi et al., 2010; Eissenberg and Shilatifard, 2010; Smith et al., 2011; Suganuma and Workman, 2011; Trojer and Reinberg, 2006). MLL1 and MLL2 have been shown to be recruited by the p52 subunit of NF-κB to the promoter of *MMP9* (matrix metalloproteinase 9) in a T cell lymphoma cell line (Robert et al., 2009). It is therefore possible MLL1 is involved in the regulation of the NF-κB signaling pathway.

We investigated the relationship between MLL1 and the TNFα- and LPS-stimulated NF-κB signaling pathway in this study. Our data suggest that MLL1 selectively regulates the activation of genes downstream of NF-κB.

## Results

### MLL1 deficiency leads to a reduction of the activation of a subset of genes downstream of NF-κB

We started to investigate the role of Mll1 in NF-κB signaling pathway by checking the altered expression of NF-κB downstream genes in Mll1-deficient cells. Wild-type and $Mll1^{-/-}$ cells were treated with TNFα (10 ng/ml), and harvested 0.5 hours or 4 hours after treatment. Over thirty known NF-κB target genes were examined. The basal mRNA level of most of the genes did not show a significant change in the $Mll1^{-/-}$ cells (supplementary material Fig. S1). Only very few genes, such as *Ptges*, showed reduction of the mRNA level upon *Mll1* deficiency (supplementary material Fig. S1). Genes activated significantly by TNFα in MEFs were used for further analysis. We found that the activation of many genes was greatly impaired in the $Mll1^{-/-}$ cells, such as the *Nfkbia* (the gene encoding IκBα), *Tnfaip3* (also known as A20), *Irf1*, *Cxcl1*, *Ccl2* (also known as Mcp1) and *Traf1* genes (Fig. 1A). However, we also found a group of the NF-κB target genes whose mRNA level was not reduced in $Mll1^{-/-}$ cells, such as *Sod2* and *Tnip1* (Fig. 1B). In order to further confirm that the reduction of gene expression was the consequence of *Mll1* deficiency, the above experiments were repeated using a cell line in which a Flag-tagged *Mll1* had been integrated into the genome of $Mll1^{-/-}$ cell (designated F-Mll1). We found that the activation levels of *Nfkbia* (IκBα) (Fig. 1C), *Tnfaip3* (A20) and *Irf1* were restored to a normal level in the F-Mll1 cell line. The increase of Mll1 amount did not affect the expression of *Sod2*, as judged by comparing the expression in $Mll1^{-/-}$ and F-Mll1 cells (Fig. 1C). These data suggest that MLL1 is involved in the transcriptional activation of NF-κB target genes and selectively regulates a subset of downstream genes in MEFs. In the following studies, *Nfkbia* (IκBα) and *Sod2* were used as the representative genes for understanding the molecular mechanisms of this process.

We further tested whether Mll1 also regulates gene expression downstream of NF-κB under other stimuli or in other cell lines. LPS was used to stimulate the above MEF cell lines. The expression of *Nfkbia* (IκBα) and *Sod2* was similar to that upon TNFα treatment (Fig. 1D). HCT116, a human colon cancer cell line, and HL7702, an immortalized human liver cell line, were used to verify the effect of *Mll1* on activation of genes downstream of NF-κB. siRNA against *MLL1* was transfected into the above cell lines and the mRNA levels of genes were assayed. Data suggest Mll1 also regulates NF-κB target genes in the above cell lines (supplementary material Figs S2, S3). In order to verify whether the protein levels of these genes were also impaired in the MLL1-deficient cells, an ELISA experiment was performed for IL6 in the HL7702 cell line. Similar to the results with mRNA (Fig. 1E, top right), the amount of secreted IL6 in the medium was greatly reduced after *MLL1* knockdown (Fig. 1E, bottom). Thus, we conclude that MLL1 is involved in the activation of downstream genes of NF-κB mediated by TNFα and LPS in multiple cell lines.

### A genome-wide gene expression profile proves Mll1 regulates the NF-κB signaling pathway

In order to identify the genes downstream of NF-κB that are regulated by Mll1 on a genome-wide scale, a gene expression profile was analyzed by next-generation sequencing. $Mll1^{+/+}$ and $Mll1^{-/-}$ MEF cells were treated with TNFα for 4 hours, and then isolated mRNA was reverse transcribed and subjected to next-generation sequencing. The raw data have been uploaded to the GEO database (http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE36567). The identified genes with different expression levels in each cell line are listed in supplementary material Tables S2 and S3 ($P<0.01$). The numbers of genes upregulated by TNFα were calculated (Fig. 2A). The numbers of genes upregulated more than 1.5-fold were very close in wild-type and knockout cells. However, for genes upregulated more than 2-, 3- or 4-fold, the numbers in the $Mll1^{-/-}$ cells were much less than those in $Mll1^{+/+}$ cells. This suggests that some of the genes are stimulated to a lesser extent by TNFα in the absence of *Mll1*.

Genes that were upregulated more than 2-fold in $Mll1^{+/+}$ cells were picked for clustering analysis in all the four samples ($P<0.01$ in all four samples) (Fig. 2B). The genes were clearly

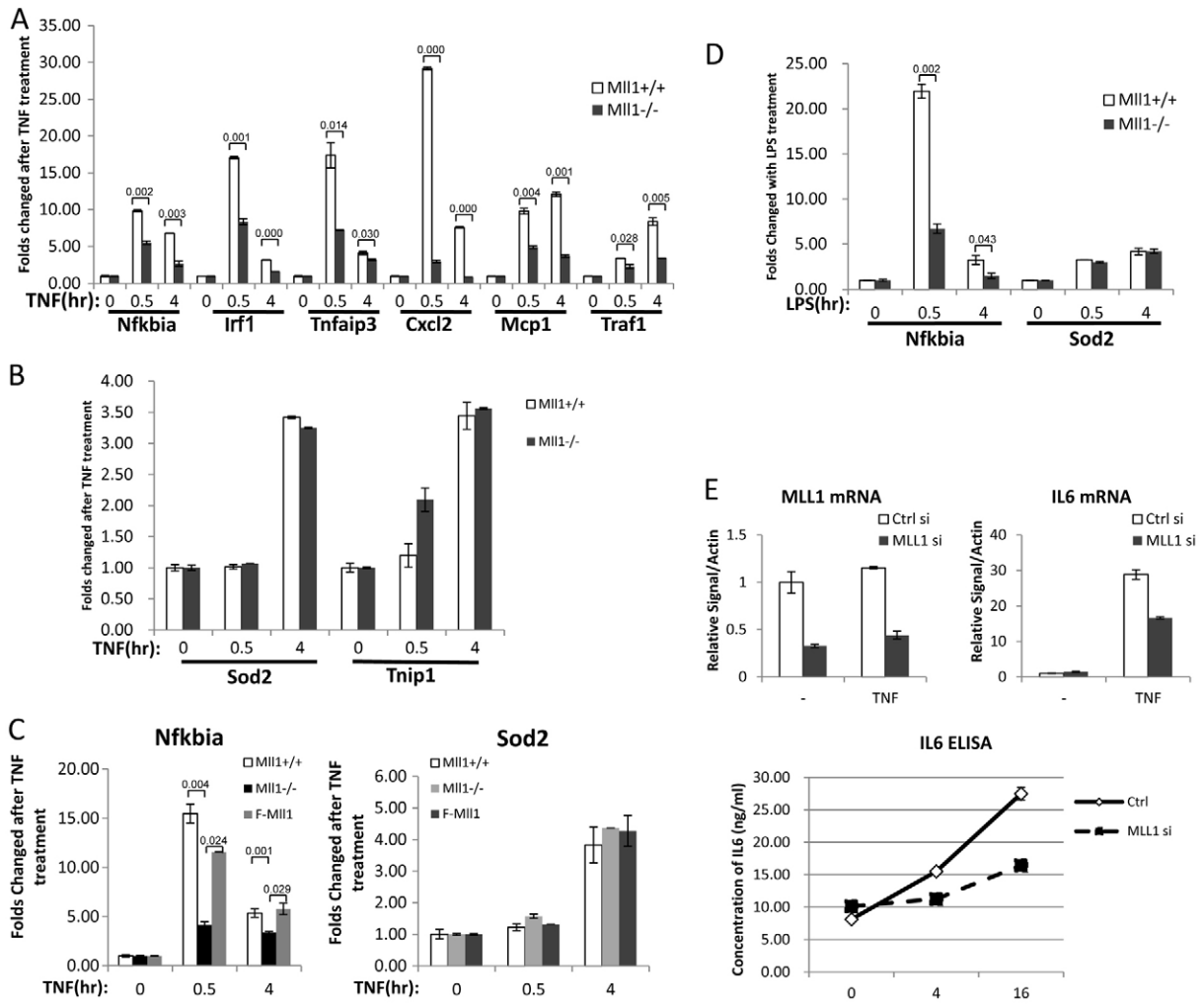


**Fig. 1. MLL1 regulates the expression of genes downstream of NF-κB.** (**A**) Cells were treated with TNFα and the levels of mRNA for various genes were assayed. The activation of genes downstream of NF-κB [*Nfkbia* (IκBα), *Irf1*, *Tnfaip3* (A20), *Cxcl2*, *Mcp1* and *Traf1*] was reduced in *Mll1*$^{-/-}$ cells. (**B**) The activation of *Sod2* and *Tnip1* was not reduced in *Mll1*$^{-/-}$ cells. (**C**) The activation of *Nfkbia* was restored in the F-Mll1 cell line. (**D**) LPS was used to activate the NF-κB signaling pathway. The activation of the IκBα-encoding gene was also impaired in *Mll1*$^{-/-}$ cells, but not that of *Sod2*. (**E**) *Mll1* was knocked down by siRNA in HL-7702 cells (top left). Levels of IL6 in the medium were assayed by ELISA. MLL1 deficiency caused the reduction of mRNA (top right) and protein of IL6 (bottom). The *P* value of significantly different results is indicated above the corresponding columns.

categorized into two groups, *Mll1*-dependent and *Mll1*-independent genes (Fig. 2B). These data correlated very well with our studies using real-time PCR and further proved that Mll1 selectively regulates TNFα-induced genes downstream of NF-κB on a genome-wide scale. We searched the two groups of genes using the Gene Ontology database. Among the 61 *Mll1*-dependent genes, 27 genes (~45%) are related to the inflammation and immune response. For the *Mll1*-independent genes, 11 out of 37 genes (29%) are related to the inflammation and immune response. We conclude that *Mll1*-dependent genes seem to be enriched in those related with inflammation and immune response.

### MLL1 depletion does not affect the activation of NF-κB by TNFα

In order to further understanding of the role of MLL1 in the activation of the NF-κB signaling pathway, we checked whether activation of the pathway was impaired in *Mll1*$^{-/-}$ cell lines by using a luciferase reporter assay. *Mll1*$^{+/+}$ and *Mll1*$^{-/-}$ cell lines were treated with TNFα and the luciferase activity was assayed 12 hours later. The result showed that the NF-κB pathway was activated in *Mll1*$^{-/-}$ cells to a similar level to that in wild-type cells (Fig. 3A). We also studied the translocation of the p65 subunit of NF-κB into the nucleus by immunofluorescent staining and CHIP assays in the *Mll1*$^{-/-}$ cell. Immunofluorescent staining indicated that p65 was still translocated into nucleus after TNFα treatment in the absence of *MLL1* (supplementary material Fig. S4). The results of CHIP assay showed that the ability of p65 to bind to DNA had no obvious difference between *Mll1*$^{+/+}$ and *Mll1*$^{-/-}$ cells (Fig. 3B). Taken together, these data suggest that MLL1 deficiency does not affect the activation of NF-κB by TNFα.

### MLL1 depletion affects the oscillation of IκBα upon TNFα treatment

To study the effect of MLL1 on the NF-κB signaling pathway, we analyzed the degradation of IκBα, which is one of the

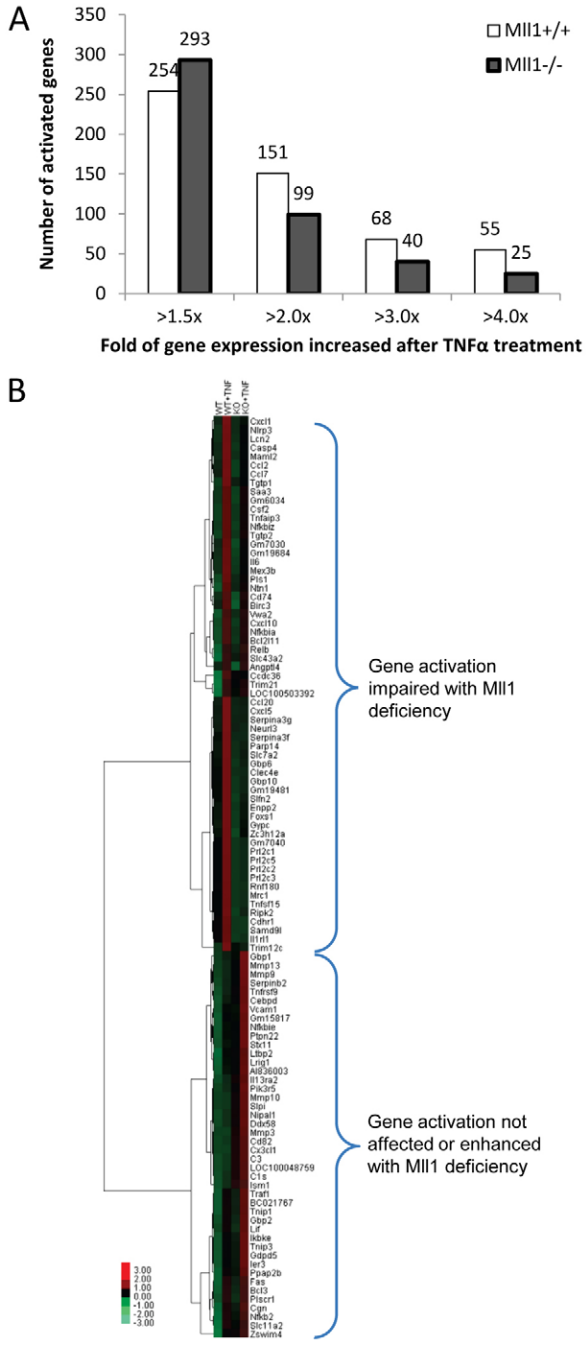


**Fig. 2. The expression profiles of genes downstream of NF-κB regulated by MLL1, as analyzed by RNA sequencing.** *Mll1*$^{+/+}$ and *Mll1*$^{-/-}$ cells were treated with TNFα and extracted RNA were subjected to a gene expression profile analysis. (**A**) The number of genes upregulated by the indicated amount in both cell lines was calculated. The number of genes upregulated by >1.5-fold was not substantially different in the two cell lines. The number of genes upregulated genes by a greater amount (>2-, 3- and 4-fold) was less in the *Mll1*$^{-/-}$ cell, which suggests that the level of activation of some genes was reduced in the absence of MLL1. (**B**) All the genes activated by TNFα in the *Mll1*$^{+/+}$ cell (i.e. with a >2-fold increase at $P<0.01$ in all four samples) were subjected to gene clustering. A total of 61 of these 97 genes showed an *Mll1*-dependent regulation.

hallmarks of NF-κB activation. In *Mll1*$^{-/-}$ cells, the protein level of IκBα rapidly decreased 30 minutes after TNFα treatment (Fig. 3C). However, at 4 hours, its protein level did not recover to the same extent as that seen in wild-type cells. Instead, the protein levels of IκBα at 0.5, 4 and 12 hours were almost the same (Fig. 3C). The level of *Nfkbia* mRNA (i.e. that encoding IκBα), and the bound p65 on the *Nfkbia* promoter were also analyzed at the above time points (supplementary material Figs S5, S6). The oscillation of IκBα protein levels is a typical characteristic of prolonged NF-κB activation and is known to be the consequence of degradation and synthesis of IκBα at the same time. The levels of IκBα expression in *Mll1*$^{-/-}$ cells is consistent with the above data, and is due to the impaired mRNA synthesis of *Nfkbia* (supplementary material Fig. S5). However, the amount of p65 on the *Nfkbia* promoter was not different between the two cell lines (supplementary material Fig. S6), which is consistent with the above data.

### WDR5 and RBBP5 are present in both the nucleus and cytoplasm

The MLL1 complex exerts its function on the chromatin and until recently no study had reported whether it is present outside the nucleus. Wang et al. reported recently that WDR5 localizes to both the cytosol and nucleus (Wang et al., 2010). We studied the localization of endogenous RBBP5 and WDR5 by western blotting and immunofluorescent staining. Wild-type MEF cells were separated into three fractions, those from the cytosol, soluble and insoluble fraction of nucleus. The results of western blotting showed that RBBP5 and WDR5 are present both in cytosol and nucleus (Fig. 4A). Histone H3 was used as the control for the nuclear fraction. p65, the transactivation subunit of NF-κB, resided in the cytoplasm without upstream signals (Fig. 4A). The results of immunofluorescent staining showed that the majority of WDR5 and RBBP5 are localized inside the nuclear. However, we also observed substantial amount of the above proteins in the cytosol (Fig. 4B). These data suggested that WDR5 and RBBP5, two subunits of the MLL1 complex, are localized both in cytosol and nuclear.

### Generation of a cell line expressing triple-Flag-tagged MLL1

MLL1 is usually expressed at a very low level in many cell lines. In order to further study the localization of Mll1, we generated a knock-in cell line derived from a colon cancer cell line, HCT116 (Fig. 4C). A triple Flag tag and streptavidin-binding peptide (SBP) were knocked into the C-terminal of the *MLL1* gene in one of the chromosome copies. Because the SET domain, which is responsible for the catalytic activity of MLL1, is located at the very C-terminus of the MLL1 protein, the addition of the tags meant the resulting protein (designated 3F-MLL1) was unable to methylate histone H3 (data not shown). We did not get homozygous clones, which suggests that the complete loss of MLL1 catalytic activity causes cell death. However, the heterozygous clones were still useful.

### MLL1 is associated with RBBP5 in cytoplasm

Next, we separated nuclear and cytoplasm fractions of the 3F-MLL1-expressing cells and performed immunoprecipitation with anti-Flag antibody for each fraction. We detected 3F-MLL1 in both fractions (Fig. 4D). Interestingly, this result also indicates that cytoplasmic MLL1 is associated with RBBP5 (Fig. 4D), which raises the possibility that the MLL1 complex might be intact and catalytically functional outside of nucleus.

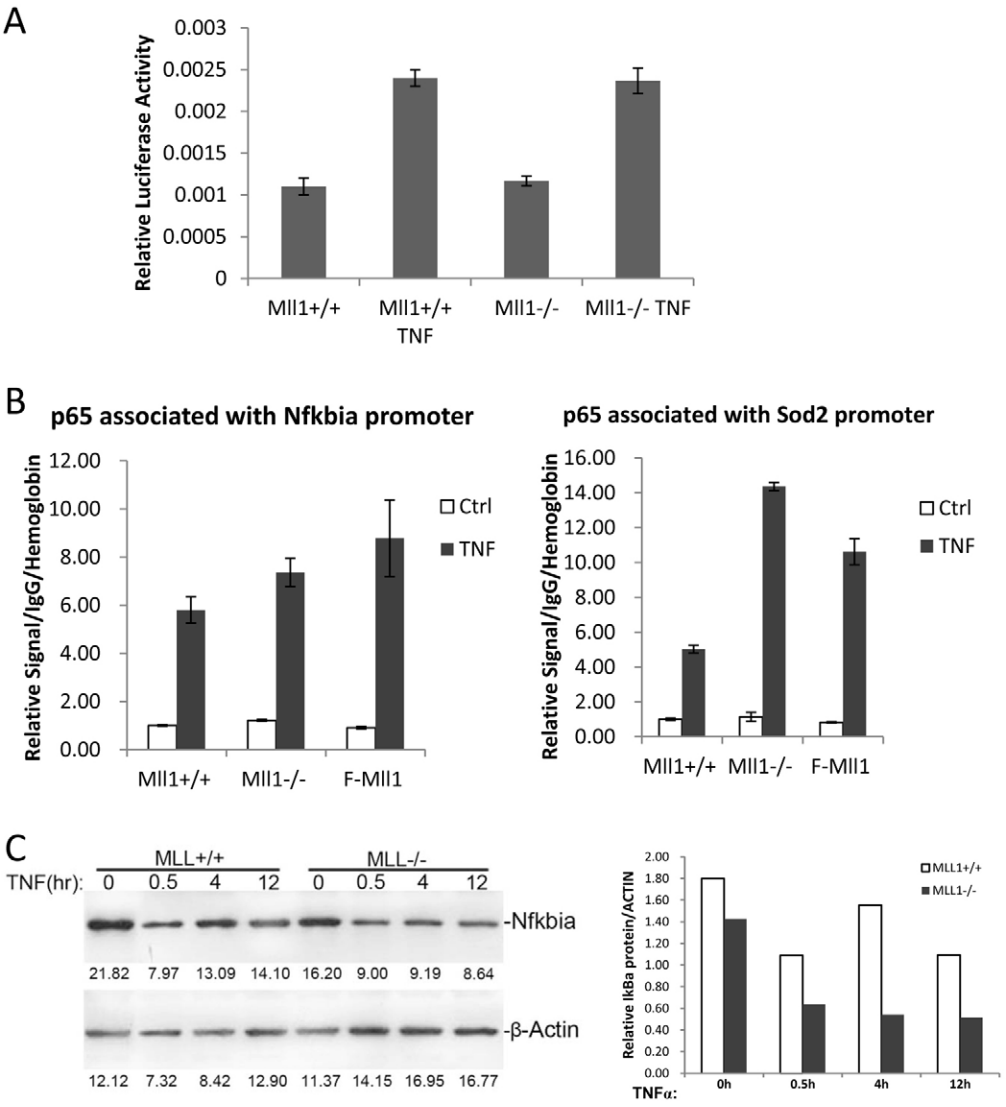


**Fig. 3. MLL1 deficiency affected the oscillation of the level of IκBα protein.** (**A**) In wild-type and *Mll1*$^{-/-}$ cells, TNFα activates NF-κB pathways to the same level in a luciferase reporter assay. (**B**) A ChIP assay of p65 shows that the recruitment of p65 to the *Nfkbia* (IκBα) (left) and *Sod2* (right) promoters was not reduced in the *Mll1*$^{-/-}$ cell, compared with wild-type and Flag–MLL1-expressing MEFs. (**C**) The oscillation of IκBα was affected in *Mll1*$^{-/-}$ cell. With prolonged TNFα treatment in the wild-type cell, levels of IκBα had decreased by 30 minutes, but had recovered at 4 hours and had decreased again at 12 hours. In *Mll1*$^{-/-}$ cell, the level of IκBα was very similar at the different time points. The right-hand panel shows a quantification of western blot.

### The cytoplasmic MLL1 complex translocates into nucleus after TNFα treatment

To investigate the role of the MLL1 complex in TNFα-mediated NF-κB signaling, we first studied the localization of MLL1 and RBBP5 upon TNFα treatment. The 3F-MLL1-expressing HCT116 cell line was treated with 10 ng/ml TNFα for 30 minutes before being fractionated to give cytosol and nuclear extracts. The results of immune blotting showed that p65 was translocated into the nuclei after TNFα treatment as expected. The protein levels of 3F-MLL1 in the cytosol also decreased upon TNFα treatment. MLL1 might be translocated from cytosol into nucleus (Fig. 4E). We did not see a significant increase in 3F-MLL1 in the nuclear fraction, which might be owing to the large amount of MLL1 protein in the nucleus before TNFα treatment (Fig. 4E). We also tried immunofluorescent staining experiment with anti-Flag antibody, but we could not see MLL1 signal owing to the low expression level. The localization of RBBP5 was also examined by western blotting and immunofluorescent staining. The pattern was similar to that in MEF cell (Fig. 4A) and only a very tiny change was observed in the amount of this protein that was present in both the cytosol and nuclear fractions. Since RBBP5 is a common subunit of all six H3K4 methyltransferases, a change in the distribution of the MLL1 complex might not affect the distribution of RBBP5 greatly in the cell.

### MLL1 is associated with p65

The above studies suggest that there is a correlation between MLL1 localization and TNFα-stimulated signaling transduction. Thus, we further explored the interaction between p65 and MLL1 complex in immunoprecipitation studies. Anti-Flag antibody pulled down 3F-MLL1, as well as p65, in the cytoplasm fraction, which suggests that MLL1 is associated with NF-κB in the cytoplasm (Fig. 4E). After TNFα treatment, MLL1 disappeared from the cytoplasm but a large amount of p65 still remained. However, anti-Flag antibody did not bring down detectable p65 protein, which serves as good control (Fig. 4E). We did not observe obvious interaction in the nuclear fraction. This might be because the high concentration of NaCl (420 mM) used in the fractionation procedure broke the interaction.

### MLL1 binds to the promoters of NF-κB target genes before activation

Because MLL1 regulates the expression of NF-κB target genes but does not affect the activation of NF-κB, it might function

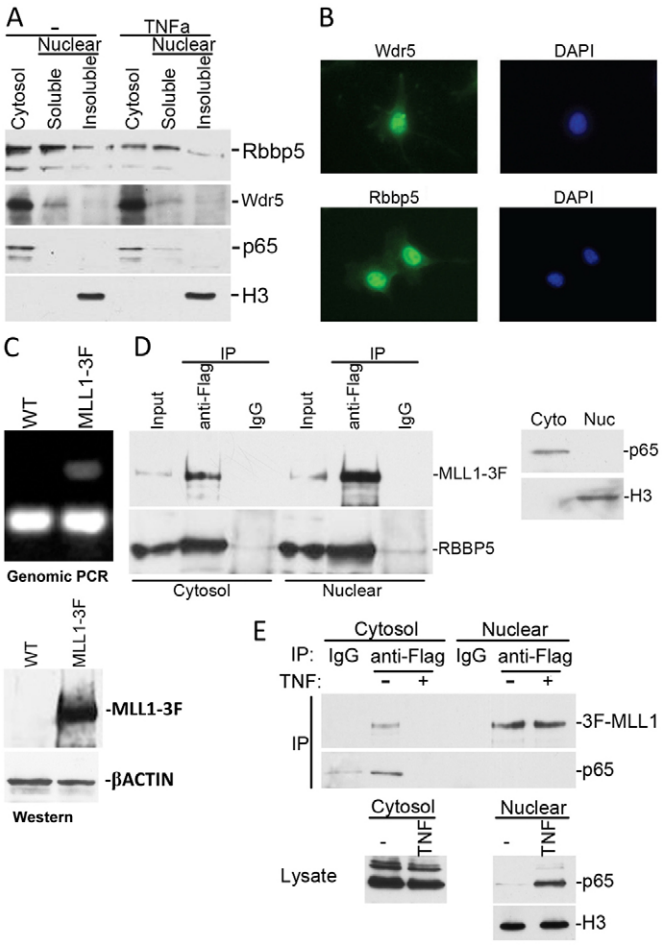


**Fig. 4. MLL1 translocates into the nucleus upon TNFα treatment.** (**A**) MEF cell was fractionated into cytoplasmic, and soluble and insoluble nuclear fractions. RBBP5 and WDR5 were found in both the cytoplasm and nucleus. (**B**) Immunofluorescent staining shows that WDR5 and RBBP5 in MEF cell are localized in both the cytoplasm and nucleus. (**C**) PCR of genomic DNA (top) and anti-Flag western blotting (bottom) of the 3F-MLL1-expressing HCT116 cell. (**D**) After fractionation, the cytoplasm and nuclear fractions of the 3F-MLL1-expressing HCT116 cell were used for anti-Flag immunoprecipitation (IP). 3F-MLL1 brought down RBBP5 in both fractions. Western blots of p65 and H3 are shown as the control for fractionation. (**E**) 3F-MLL1 in the cytoplasm disappeared after TNFα treatment. Immunoprecipitation of 3F-MLL1 brought down p65 in the cytoplasm fraction. Western blots of H3 and p65 are shown as the loading control.

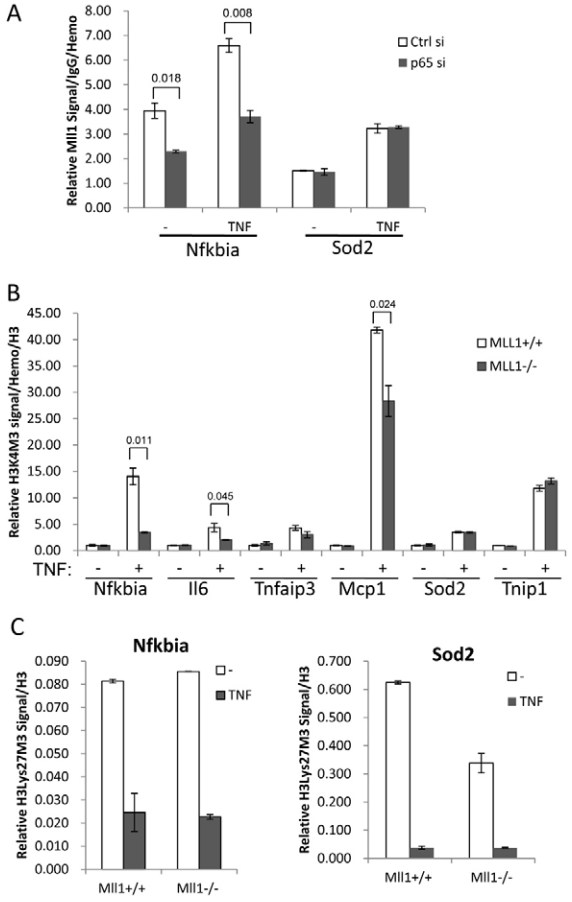


**Fig. 5. MLL1 regulates the increased H3K4 trimethylation on the *Nfkbia* (IκBα) promoter induced by TNFα.** (**A**) p65 was knocked down in the F-Mll1 MEF cell line by siRNA. A ChIP assay was performed to study the amount of F-Mll1 on chromatin. MLL1 bound to the promoters of *Nfkbia* and *Sod2* in the untreated cell. After knocking down p65, the bound F-Mll1 on the *Nfkbia* promoter was reduced in comparison with that in the control. (**B**) A ChIP assay indicated that, in wild-type cells, TNFα induced the increase of H3K4 trimethylation on the promoters of *Mll1*-dependent genes [*Nfkbia* (IκBα), *Il6*, *Tnfaip3* (A20) and *Mcp1*]. In the *Mll1*$^{-/-}$ cell, the basal level of H3K4 trimethylation was the same, but the induction of methylation was impaired. The H3K4 trimethylation on Mll1-independent genes (*Sod2* and *TNIP1*) promoter was still elevated in the absence of MLL1. (**C**) H3K27 trimethylation of *Nfkbia* and *Sod2* promoters decreased with TNFα treatment in wild type and *Mll1*$^{-/-}$ MEF cells. The *P* value of significantly different results is indicated above the corresponding columns.

after NF-κB binds to the chromatin. In addition, it is possible that MLL1 functions differently on the promoters of *Nfkbia* (encoding IκBα) and *Sod2*. We first studied whether MLL1 binds to the promoters of *Nfkbia* and *Sod2* in MEF cell lines by using a CHIP assay. The results showed that MLL1 binds to both of the promoters before treatment (Fig. 5A). Although the signal on the *Sod2* promoter was quite low, we observed it above background in most of the experiments. This result is consistent with the genome-wide chromatin association study of MLL1 reported previously (Guenther et al., 2005). The trimethylation of H3K4 on the promoters of multiple genes were also studied in wild-type and *Mll1*$^{-/-}$ cells. All of the promoters were had H3K4 trimethylation, which did not show a significant reduction in *Mll1*$^{-/-}$ cells compared that of with the wild type (Fig. 5B). This is also consistent with our previous report (Wang et al., 2009). Considering that the mRNA of the two genes did not reduce upon *Mll1* deficiency, it seems that MLL1 just pre-binds the promoters and has no function without stimulation.

## p65 is indispensable for MLL1 recruitment to NF-κB target genes

Because MLL1 pre-binds the promoters of genes downstream of NF-κB, we questioned whether the cytoplasmic MLL1 is still required for the gene activation. We performed an MLL1 CHIP assay to study MLL1 occupancy on promoters after TNFα treatment. MEF cells were treated with TNFα and cells were harvested 30 minutes later. The result showed that the amount of MLL1 bound to both the *Nfkbia* (encoding IκBα) and *Sod2*

promoters increased substantially (Fig. 5A). When p65 was knocked down by siRNA, the amount of MLL1 bound to the *Nfkbia* promoter substantially reduced (Fig. 5A). However, there was no obvious difference in the amount of MLL1 on the *Sod2* promoter with or without p65 (Fig. 5A). These results suggest that the translocation of MLL1 to the *Nfkbia* promoter is dependent on p65, but that other factors might mediate MLL1 translocation to the *Sod2* promoter.

### MLL1 mediates the induced H3K4 methylation on the *Nfkbia* promoter

MLL1 is a histone H3K4 methyltransferase and, hence, we analyzed the levels of histone H3K4 trimethylation on promoters. In wild-type cells, the H3K4 trimethylation on the *Nfkbia* promoter increased dramatically upon TNFα treatment. In *Mll1*$^{-/-}$ cells, the basal level of H3K4 trimethylation at this promoter was the same as that of wild-type cells, but after TNFα treatment, the increase in H3K4 trimethylation was much less than that of wild-type cells (Fig. 5B). Other MLL1-dependent genes also showed similar results (Fig. 5B). This suggests that MLL1 is not required for the basal level of H3K4 trimethylation on the *Nfkbia* promoter, but is necessary for the trimethylation induced by TNFα. In the case of the *Sod2* and *Tnip1* promoters, the H3K4 trimethylation still increased in *Mll1*$^{-/-}$ cells upon TNFα treatment (Fig. 5B), which suggests other enzymes might regulate their H3K4 trimethylation levels.

H3K27 trimethylation was also analyzed on the *Nfkbia* and *Sod2* promoters. When treated with TNFα, the amount of the H3K27 trimethylation reduced dramatically on both promoters, which suggests that MLL1 functions independently of the regulation of H3K27 trimethylation on these sites (Fig. 5C). We also analyzed H3K9 dimethylation on these promoters and no obvious signals were detected with or without TNFα. This suggests that H3K9 dimethylation might not be involved in the regulation of *Nfkbia* and *Sod2* expression.

### The H3K4 methyltransferases synergistically regulate the activation of the NF-κB signaling pathway

Given that the H3K4 trimethylation on the *Sod2* promoter did not change in *Mll1*$^{-/-}$ cells, we were aware that there might be other H3K4 methyltransferases involved in the process. The closest homologs of *Mll1* include the five genes *Setd1a*, *Setd1b*, *Mll2* (also called Wbp7), *Mll3* and *Mll4* (also called Alr). It is possible that one or several of these five genes is responsible for the H3K4 trimethylation on *Sod2* promoter. We analyzed the bound RBBP5 and WDR5 proteins on the promoters. RBBP5 and WDR5 are two subunits that are common to all of the six methyltransferase complexes. RBBP5 was recruited to both *Nfkbia* and *Sod2* promoters upon TNFα treatment in wild-type cells. In *Mll1*$^{-/-}$ cells, RBBP5 was still recruited to the promoters but the amount was greatly reduced (Fig. 6A). WDR5 behaved very similarly to RBBP5 in the above cell lines (supplementary material Fig. S7). This suggests that some other methyltransferases might also be involved.

### SETD1A and SETD1B regulate the expression of *Nfkbia* and *Sod2*

We investigated the functions of *Mll2*, *Setd1A* and *Setd1B* in NF-κB signaling by using RNA interference. Small interfering RNAs (siRNAs) were transfected into MEFs and, 72 hours after transfection, cells were treated with TNFα before harvesting.

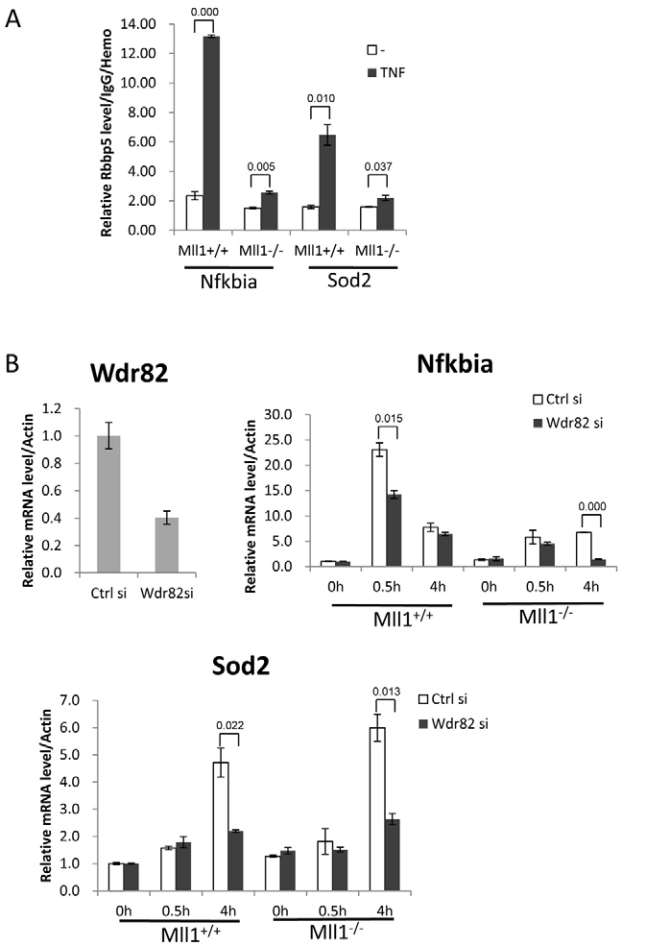


**Fig. 6. SETD1A regulates the activation of genes downstream of NF-κB.** (**A**) ChIP results showing that the increased amount of RBBP5 on *Nfkbia* (IκBα) and *Sod2* promoters was less in *Mll1*$^{-/-}$ cell than in wild-type cells. However, this level still increased slightly upon TNFα treatment. (**B**) *Wdr82* was knocked down by siRNA in wild-type MEFs (top left), which mimics deficiency of *Setd1a*. The basal mRNA levels of *Nfkbia* (top right) and *Sod2* (bottom) were not changed upon *Wdr82* deficiency. However, the elevation of their mRNA after TNFα stimulation was significantly impaired. The *P* value of significantly different results is indicated above the corresponding columns.

*Mll2* deficiency did not affect the basal level or activation of genes downstream of NF-κB (supplementary material Fig. S8). Because *Wdr82* deficiency is known to lead to a reduction of SETD1A protein, knockdown *Wdr82* will mimic the effect of SETD1A and/or SETD1B reduction (Wu et al., 2008). siRNA against *Wdr82* was transfected into MEFs, and similar experiments to those described above were performed. The knockdown of *Wdr82* did not affect the basal level of NF-κB target gene expression; however, both the *Nfkbia* and *Sod2* genes showed impaired expression upon treatment with TNFα (Fig. 6B). By using specific siRNAs against the methyltransferases, we also confirmed that SETD1A and SETD1B were involved in the transcriptional activation of *Nfkbia* and *Sod2* (supplementary material Fig. S9). These data suggest that SETD1A and SETD1B, but not MLL2, also regulate the activation of genes downstream of NF-κB.

## Discussion

The NF-κB signaling pathway can be activated by numerous upstream signals. Usually, the activated gene expression patterns

vary depending on the signals and cell lines, but the mechanisms involved are not clear. Epigenetics has emerged as a key player that is involved in regulation of gene transcription and cell identity. Different combination of chromatin modifications and their enzymes might be crucial in 'tuning' gene expression.

MLL1 and SETD1A are two well-studied histone H3K4 methyltransferases in mammals. The role of MLL1 in leukemogenesis has been extensively studied; however, its functions in other physiological events require more work. Previously, MLL1 has been reported to be associated with CLOCK and to regulate the oscillation of circadian gene expression. We found that MLL1 is associated with p65, the transactivation subunit of NF-κB. When the NF-κB pathway is activated, MLL1 is translocated onto the promoters of NF-κB target genes in a p65-dependent manner. Moreover, MLL1 deficiency also causes the change in the pattern of IκBα oscillation. Interestingly, MLL1 only regulates a subgroup of genes downstream of NF-κB. SETD1A and SETD1B also seem to be important in the regulation of gene transcription. These methyltransferases might act synergistically in gene regulation and it is possible that all the six members behave in a similar manner. The different combination of H3K4 methyltransferases might be another regulatory step in selective transcriptional regulation.

Surprisingly, none of the H3K4 methyltransferases tested in this study regulated the basal expression of *Nfkbia* and *Sod2*. Therefore, further experiments are required to determine whether any other H3K4 tri-methyltransferases, such as MLL5, are required for the basal level expression of *Nfkbia* and *Sod2*. Another possibility is that the regulatory step of H3K4 trimethylation is not necessary for some genes. Set1 is the only H3K4 methyltransferase in *S. cerevisiae*; however, the Δset1 strain is still viable under certain conditions. This means many genes are still transcribed without H3K4 methylation. It is possible that although H3K4 trimethylation is always accompanied with active gene transcription, it is dispensable for some genes under certain circumstances.

Most of the previous studies on MLL1 focused on its role in the nucleus, such as in histone modification and transcriptional regulation. We found that MLL1 exists both in the cytoplasm and nucleus. Moreover, MLL1 is still associated with RBBP5 in the cytoplasm, which suggests that the active catalytic complex might exist in both fractions. Many methyltransferases have been reported to be able to modify multiple subunits. We performed an in vitro histone methyltransferase (HMT) assay with $^{3}$H-labeled S-adenosylmethionine (SAM) and purified proteins. Although we did not detect a catalytic activity of MLL1 against p65, it is still possible that MLL1 might have other substrates, both inside and outside of the nucleus.

Previous studies reported that MLL1 binds to a large number of gene promoters, but that the methylation status and gene expression profile was be affected too much by its absence. If this is the case, then why does MLL1 bind to these regions? We found that MLL1 binds to the promoter of *Nfkbia* and does not affect its expression and methylation status before activation. However, upon activation, the amount of MLL1 on the *Nfkbia* promoter increased immediately, as did the level of H3K4 trimethylation. The behavior of MLL1 is very much like the poised RNA polymerase II (RNA pol II). It has been reported that RNA pol II is associated with some silenced genes. However, when the transcription program is initiated, the amount of RNA pol II on the promoter increases dramatically and leads to rapid transcription of the gene. We hypothesized that the poised Mll1 pre-binds chromatin and will methylate H3 immediately upon gene activation, which facilitates a quick response to signal transduction. A previous report categorized TNFα-induced genes into three groups (Zhou et al., 2003). The first group elevates rapidly and decreases fast, such as *Il6* and *Cxcl1*; the second elevates rapidly and has sustained upregulation, such as *Nfkbia* and *Tnfaip3* (A20); the third elevates slowly, such as *Sod2*. The rapid elevated genes were all *Mll1*-dependent genes in our experiments, which supports our hypothesis.

## Materials and Methods

### Cell lines and antibodies

MEF wild type, Mll1 knockout and F-MLL1 cell lines were a gift from Jay L. Hess (University of Pennsylvania). HL-7702 cell line was purchased from the Cell Bank of Chinese Science Academy. The antibodies against Flag (Sigma), trimethylated H3K4 (Millipore), trimethylated H3K27 (Millipore), H3 (Abcam), NF-κB p65 (Abcam), WDR5 (Bethyl) and RBBP5 (Bethyl) were purchased from indicated companies. The siRNAs against p65 (5′-GCGACAAGGTGCAGAAAGA-3′), Wdr82 (5′-AGAGAACCCUGUACAGUAA-3′), Mll1 (5′-GGACAAGAGTAG-AGAGAGA-3′) and Mll2 (5′-AGGAGAAGGAAGAGGCAAA-3′) were synthesized by Genepharma. The PCR primers are available in the supplementary material Table S1.

### Cell fractionation

Cells were harvested and spun down in cold PBS. Approximately 5 volumes of buffer A (10 mM Hepes pH 7.9, 1.5 mM $MgCl_2$, 10 mM KCl, 0.5 mM DTT, plus proteinase inhibitors; compared with the volume of the of cell pellet) was added to the cells, which were then incubated on ice for 15 minutes. Cells were spun down and the supernatant was discarded. Another 2 volumes of buffer A was added to the pellet and the resuspended cells were homogenized with a homogenizer (Wheaton). The mixture was then centrifuged at 25,000 ***g*** and the supernatant was taken as the cytoplasm fraction. The pellet was resuspended in buffer C (20 mM Hepes pH 7.9, 25% glycerol, 1.5 mM $MgCl_2$, 0.2 mM EDTA, 0.5 mM DTT, plus proteinase inhibitors) and a solution containing 5 M NaCl was dropped into the suspension followed by immediate homogenization. The final NaCl concentration was 0.42 M. The mixture was incubated on ice for 30 minutes and ultracentrifuged at 40,000 ***g*** for 1 hour. The resulting supernatant was taken as the soluble fraction of the nucleus and the pellet was the insoluble fraction of nucleus.

### Immunofluorescent staining

Cells were cultured on coverslips and fixed with frozen methanol after washing twice in PBS. The coverslips were then washed three times with PBS and blocked in PBS with 1% BSA for 10 minutes. The coverslips were hybridized with primary and second antibodies for 1 hour, respectively. Then the coverslips were mounted with prolong anti-fade kit (Invitrogen) and observed using fluorescent microscopy.

### Immunoprecipitation

The cells were harvested and lysed in NP40 lysis buffer (50 mM Tris-HCl pH 7.4, 150 mM NaCl, 0.5% NP40) or high-salt lysis buffer (20 mM Hepes pH 7.4, 10% glycerol, 0.35 M NaCl, 1 mM $MgCl_2$, 0.5% Triton X-100, 1 mM DTT) with proteinase inhibitors. The supernatant was then incubated with Protein G beads (GE Healthcare) and the desired antibody at 4℃ for 4 hours. The beads were spun down and washed three times with lysis buffer. The final drop of wash buffer was vacuumed out and SDS loading buffer was added to the beads, which were then used for western blotting.

### Luciferase reporter assay

HEK293T cells (approximately $1\times10^5$) were seeded on 24-well plates and transfected by calcium phosphate precipitation. The reporter plasmid (pRL-TK or pRL-SV40 *Renilla* luciferase) was added to each transfection to normalize for transfection efficiency. A dual-specific luciferase assay kit (Promega) was used for the luciferase assays. Assays were repeated at least three times. Data shown are means±s.d. for one representative experiment.

### ChIP assay

The ChIP assay was performed as previously described (Wu et al., 2008). Briefly, $\sim1\times10^7$ cells were fixed with 1% formaldehyde and quenched by glycine. The cells were washed three times with PBS and then harvested in ChIP lysis buffer (50 mM Tris-HCl pH 8.0, 1% SDS, 5 mM EDTA). DNA was sonicated to 400–600 bp before extensive centrifugation. Four volumes of ChIP dilution buffer (20 mM Tris-HCl, pH 8.0, 150 mM NaCl, 2 mM EDTA, 1% Triton X-100) was added to the supernatant. The resulted lysate was then incubated with Protein G beads and antibodies at 4℃ overnight. The beads were washed five times, and

DNA was eluted using the Chip elution buffer (0.1 M $NaHCO_3$, 1% SDS, 30 μg/ml proteinase K). The elution was incubated at 65℃ overnight, and DNA was extracted with a DNA purification kit (Sangon). The purified DNA was assayed by quantitative PCR with Biorad MyIQ. Assays were repeated at least three times. Data shown are means±s.d. for representative experiments.

#### Reverse transcription and quantitative PCR

Cells were scraped down and collected by centrifugation. Total RNA was extracted using an RNA extraction kit (Yuanpinghao) according to the manufacturer's manual. Approximately 1 μg of total RNA was used for reverse transcription with a first-strand cDNA synthesis kit (Toyobo). The amount of mRNA was assayed by quantitative PCR. β-actin was used to normalize the amount of each sample. Assays were repeated at least three times. Data shown are means±s.d. for one representative experiment.

#### ELISA

Experiments were carried out with an IL6 ELISA kit (Boster), according to the manufacturer's procedure. Assays were repeated at least three times. Data shown are means±s.d. for representative experiments.

#### Next generation sequencing and data analysis

The cells were treated with TNFα for 4 hours before collection. Total RNA was extracted and reverse transcribed. Then, the cDNA were analyzed by Sinogenomax CO. The raw reads containing low-quality data were cleaned by removing those contain either a base of N or overhalf qualities below 20. Then, the resulting clean reads were mapped to the mouse mRNA sequences with TopHat software. The RPKM value, which is the normalized number of reads of each mRNA, was calculated and used as the expression level. Genes expressed differently between every two samples were analyzed by the DESeq R package using a cutoff of $P<0.01$. To study the relationship of the differentially expressed genes, the values of selected genes were submitted for cluster analysis by using Cluster3.0 and the heatmap was presented using Java Treeview.

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We thank J. Hess (University of Pennsylvania) for wild-type, *Mll1*$^{-/-}$ and F-Mll1 MEF cell lines, and our colleagues for discussions. Author contributions: Xiang Wang and Kun Zhu performed most of the experiments. Shangze Li, Runlei Du and Xiangdong Zhang made the 3F-MLL1 cell line. Anyuan Guo and Yifang Liao analyzed the data from the next-generation sequencing. Hong-bing Shu provided many reagents and contributed to writing the manuscript. Min Wu and Lianyun Li directed the project, conducted the experiments and wrote the manuscript.

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http://jcs.biologists.org/lookup/suppl/doi:10.1242/jcs.103531/-/DC1

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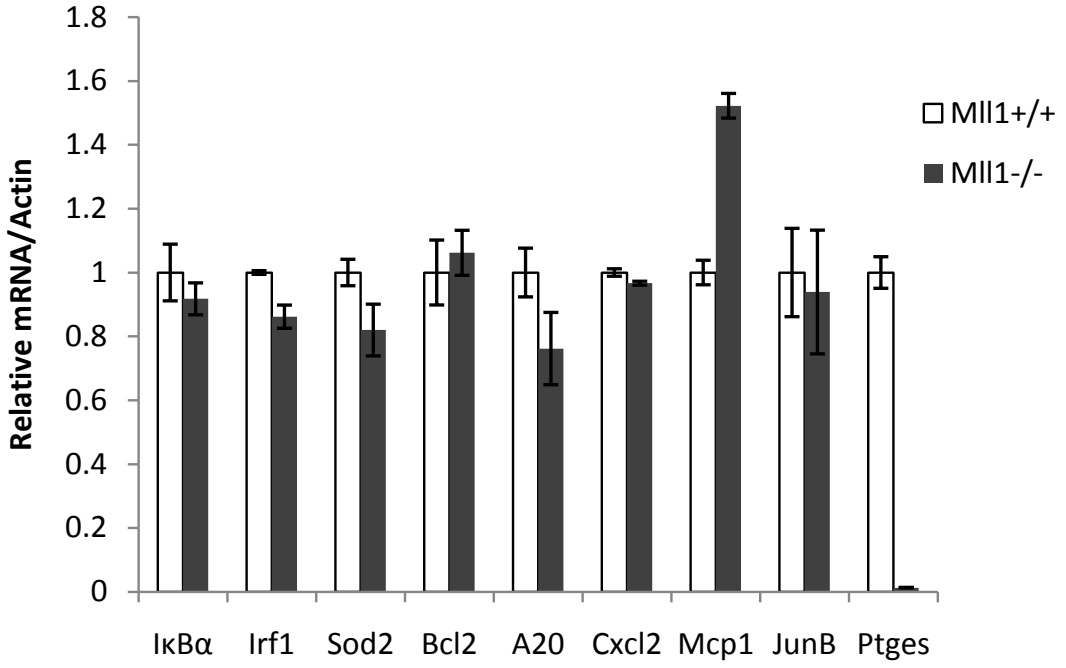
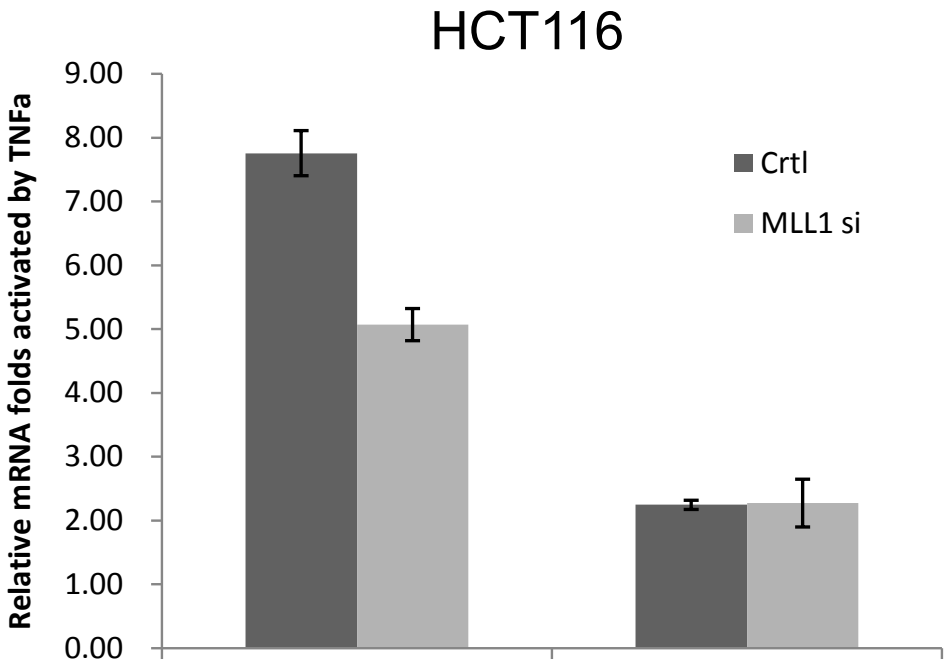
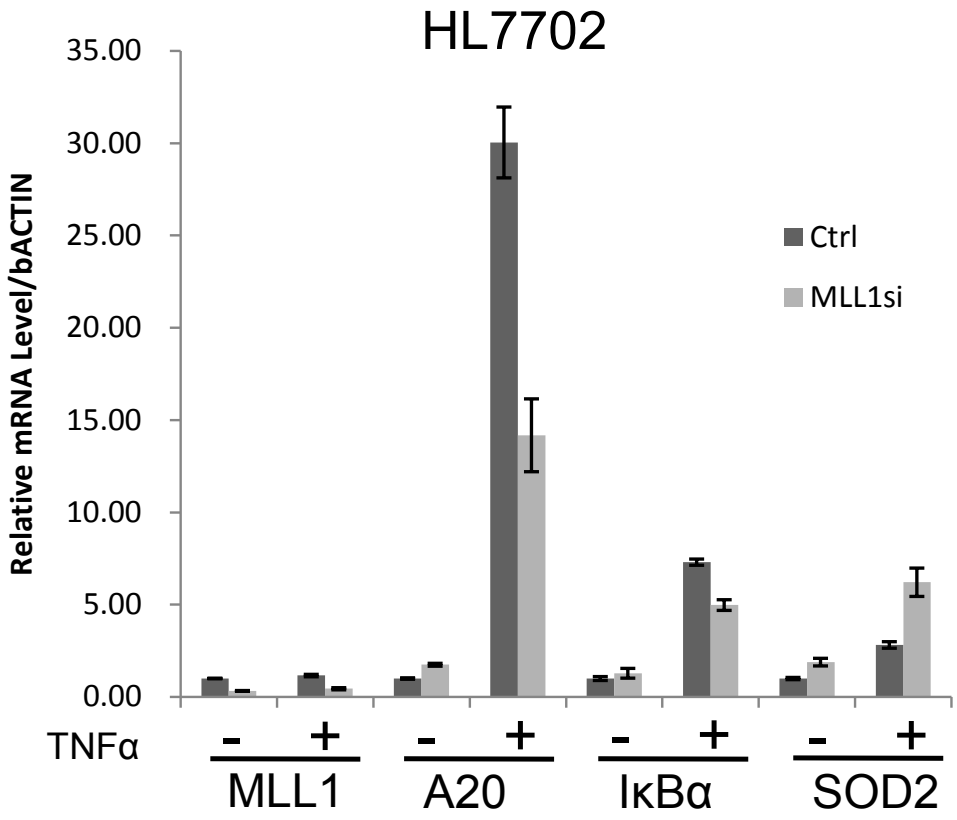



**Sup. Fig. 1 The basal mRNA level of NF-κB targeting genes in wide type and *Mll1*$^{-/-}$ cells.** The wide type and *Mll1*$^{-/-}$ cell were harvested and RT-PCR was performed to analyze the expression of indicated genes. Totally 40 reported NF-κB targeting genes were assayed (only part of data were presented). Among them, the expression of Ptges was significantly reduced.

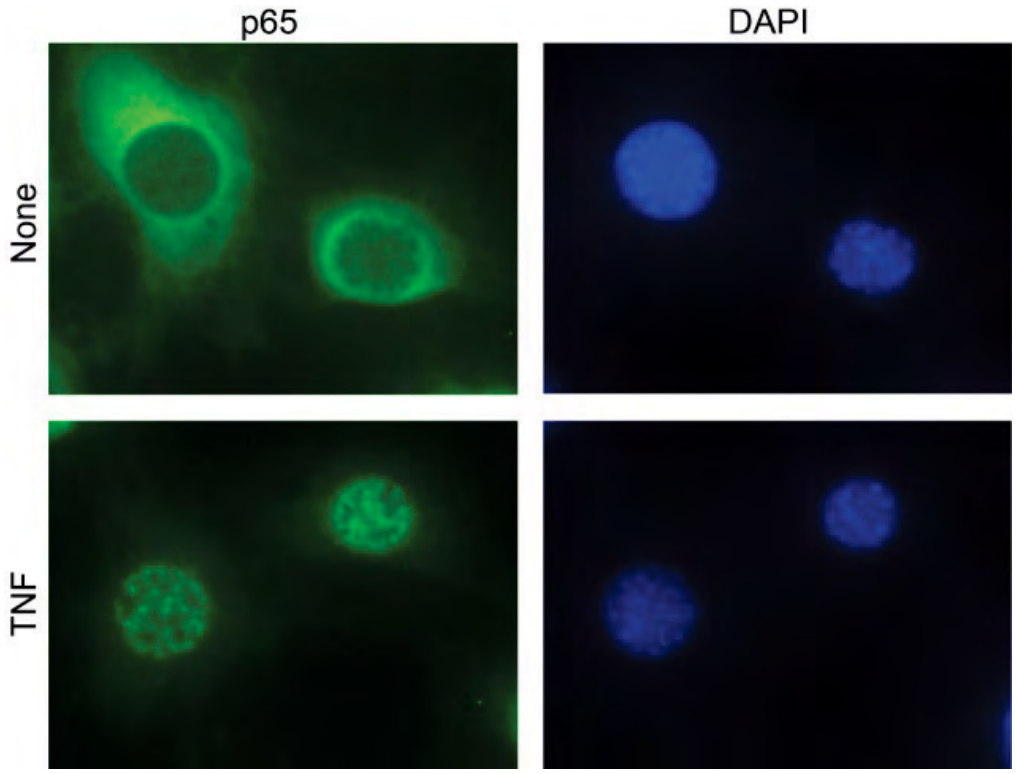



**Sup. Fig. 2 MLL1 regulated the activation of IκBα in HCT116 cell.** HCT116 cell was transient transfected with MLL1 siRNA and treated by TNFα 72hr after transfection. The elevated levels of IκBα and SOD2 mRNA were monitored by real time PCR.

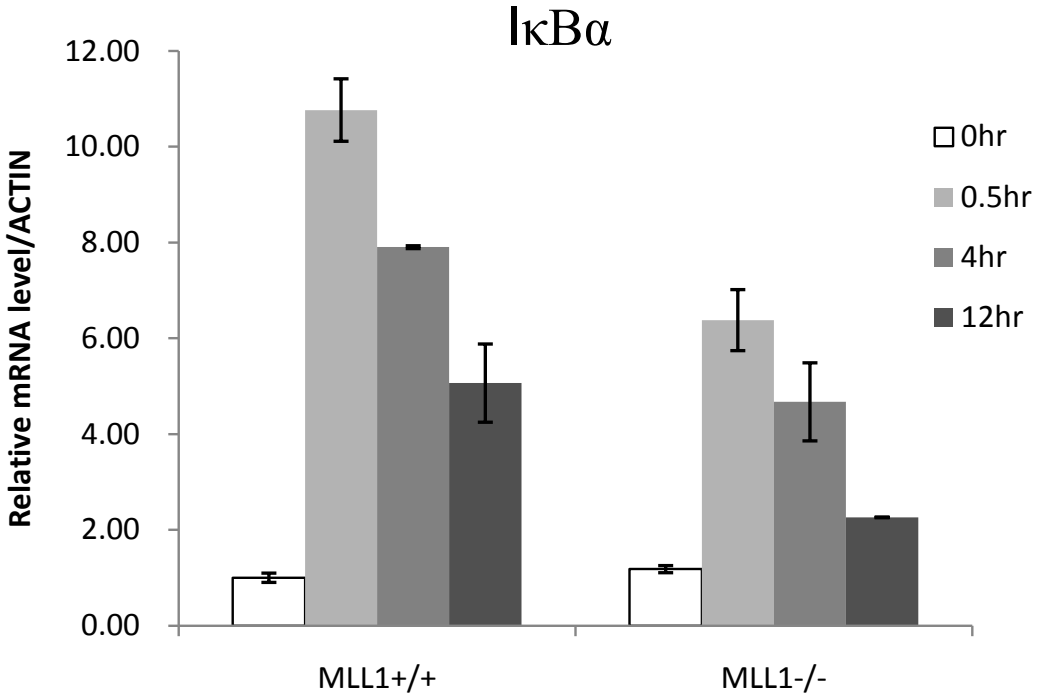



**Sup. Fig. 3 MLL1 regulated the activation of NFKB downstream genes in HL7702 cell.**

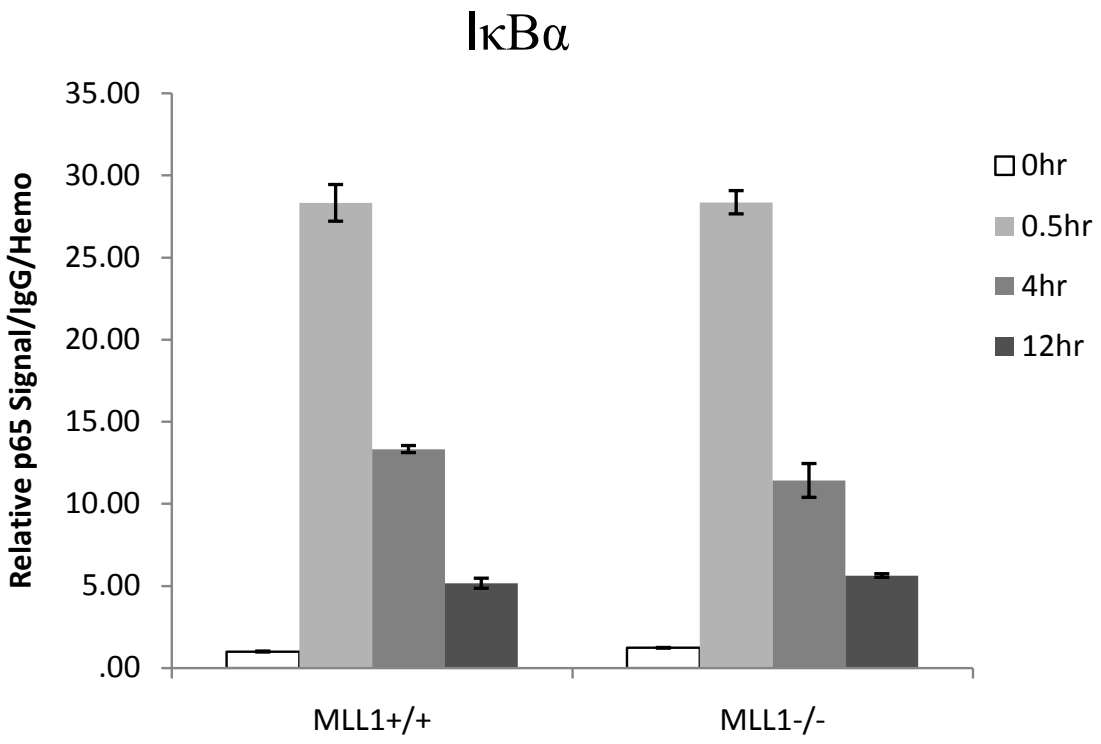
Immortalized liver cell HL7702 was transient transfected with MLL1 siRNA and treated by TNFα 72hr after transfection. The elevated mRNA levels of indicated genes were assayed by real time PCR.



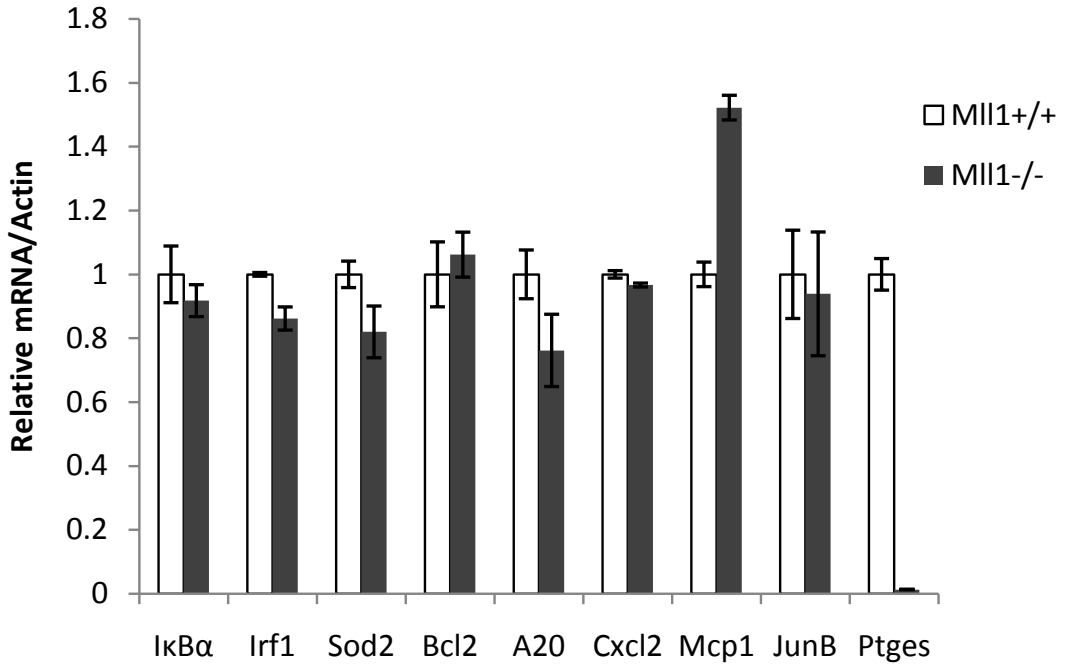

**Sup. Fig. 4 NF-κB was translcated into nuclear in *Mll1*$^{-/-}$ cell.** Immunofluorescent staining experiment was performed to study the localization of p65 in *Mll1*$^{-/-}$ cell. p65 is localized in the cytoplasm (upper) and translocated into nuclear (lower) after TNFα treatment, which is no difference from wide type cell.




**Sup. Fig. 5 The *IκBα* mRNA level at different time points after TNFα treatment.** *Mll1*$^{+/+}$ and *Mll1*$^{-/-}$ cells were treat with TNF and harvested at 0hr, 0.5hr, 4hr and 12hr. The *IκBα* mRNA levels of were analyzed.

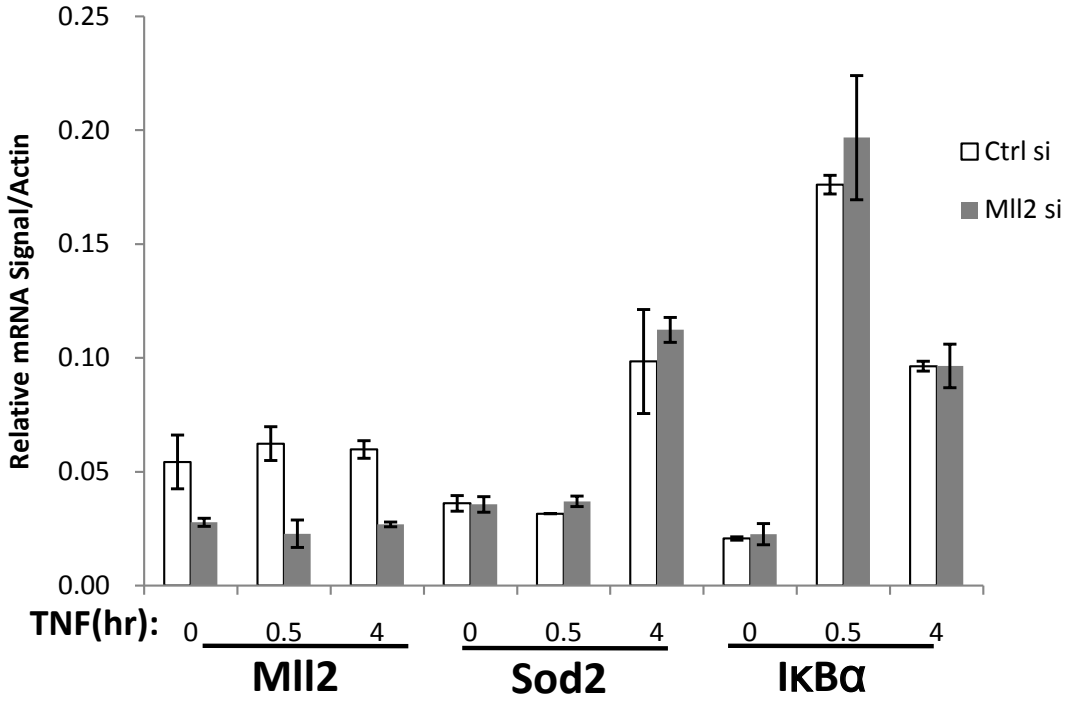



**Sup. Fig. 6 The bound p65 amount on *IκBα* promoter at different time points after TNFα treatment.** *Mll1*$^{+/+}$ and *Mll1*$^{-/-}$ cells were treat with TNF and harvested at 0hr, 0.5hr, 4hr and 12hr. The amount of p65 protein on *IκBα* promoter was analyzed by CHIP assay.



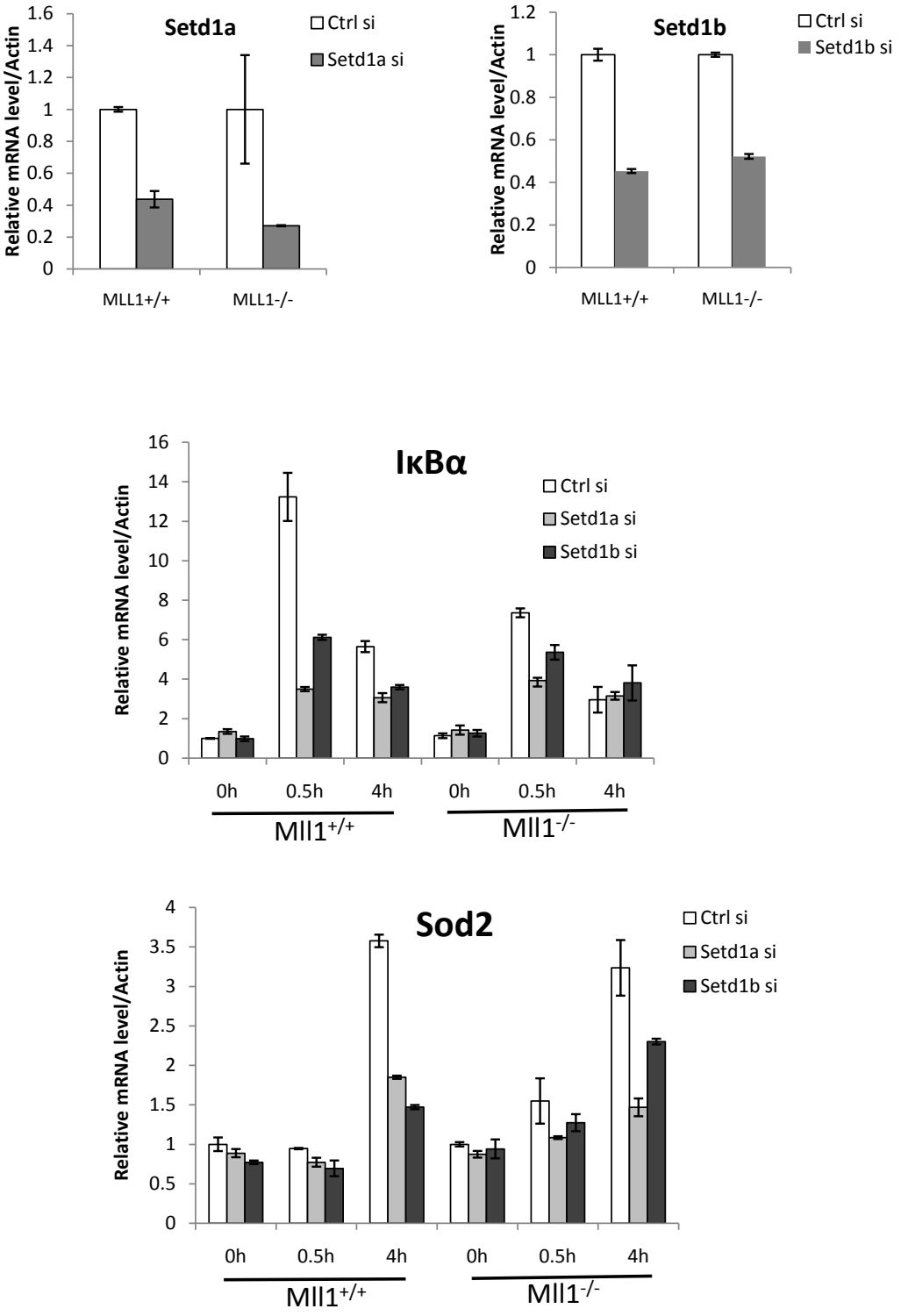

**Sup. Fig. 7 The amount of Wdr5 on IκBα increased upon TNFα treatment in *Mll1*$^{-/-}$ cell.**

ChIP assay was performed to analyze the amount of Wdr5 on IκBα promoter. Wdr5 bound IκBα promoter in wide type MEF and increased upon TNFα treatment. The bound Wdr5 decreased in *Mll1*$^{-/-}$ cell, but still increased after treatment.




**Sup. Fig. 8 Mll2/HRX2 did not regulate the expression of *IκBα* and *Sod2* in MEF cell.**

Mll2 was knocked down by siRNA in MEF cell and the mRNA levels of indicated genes were assayed by quantitative PCR following reverse transcription.




**Sup. Fig. 9 Setd1a and Setd1b regulated the expression of the expression of *IκBα* and *Sod2* in MEF cell.** *Setd1a* and *Setd1b* were knocked down in *Mll1*$^{+/+}$ and *Mll1*$^{-/-}$ cells by siRNA respectively. The up panels showed the knockdown effect assayed by real time PCR. The middle and bottom showed that the expression of both *IκBα* (middle) and *Sod2* (bottom) were impaired with Setd1a or Setd1b deficiency.

**Supplementary Table 1**

**The sequences of primers used in the study**

| Primers for RT PCR | | |
|---|---|---|
| Gene | Forward primer | Reverse Primer |
| mb-Actin | aggtcatcactattggcaac | agaggtctttacggatgtca |
| mWdr82 | CTCTAGCAGCGATGATGACT | GGTCCACACCGTACTTCTTA |
| mMll1 | ATGGGGAATGATGACAAGT | GGTGACAGGCTTAATTGGT |
| mMll2 | AGCACAGTGATGGAGCTG | AGCTGGTACAGAAGAGCAAG |
| mMll3 | CAAGCCTTATTTGATTCCAC | GTTCTTCCATTTGGCATATT |
| mMll4 | CATGGTGCCTGAAGATGT | TCTCTGATGCTGATGACGTA |
| mSet1A | GTCATGGGCAACATCATT | TGAGGAGTGTAAGAGCCATT |
| mp65 | ATGGCTACTATGAGGCTGAC | GTCTCGCTTCTTCACACACT |
| mB94 | ATACCTACTTGCTGCTGCTC | GACACCTTGAAGCTCCTGT |
| mPGES | TACAGGAGTGACCCAGATGT | CGAGGAAGAGGAAAGGATAG |
| mikBa | TCCTCAACTTCCAGAACAAC | GGGTATTTCCTCGAAAGTCT |
| mSOD2 | ACACCATTTTCTGGACAAAC | CAAAGTCACGCTTGATAGC |
| mMCP1 | CTGGAGCATCCACGTGTT | CATCTTGCTGGTGAATGAG |
| mIAP1 | ATAGAACACGCCAAATGGT | GCTTGAATCTCATCAACAAAC |
| mCox2 | GTACCCGGACTGGATTCTAT | GGCTTCAGCAGTAATTTGAT |
| mJunB | CAGCTACTTTTCGGGTCAG | GATCAAGCGCTCCAGTTC |
| mC-myc | tagtgctgcatgaggagac | caccacatcaatttcttcct |
| mIL6 | cacatgttctctgggaaatc | catcgttgttcatacaatcag |
| mTap1 | ACTCCTGCTTATCTTGGATG | CTTGGGGCTCTCATACAG |
| mTAPBP | TCTACCTGGCTACGGTACAC | GTGCTGGTGTTAGAGACACTC |
| mTraf1 | ATGAGAGGAGAATACGATGC | GGTTGTTCTGGTCAAGTAGC |
| mTraf2 | ACCGCTACTGCTCCTTCT | TACAGGCCTTCATAGACACA |
| mTraf3 | AAGCATCATCAAAGACAAGG | ATTCCGACAGTAGACCTGAA |
| mGch1 | TAGTGATTGAAGCGACACAC | TGGTGCTAGTGACAGTCTTG |
| mGfpt2 | CCGAGGTTATGATGTTGACT | GGTGACGACAGTCTTGTGAT |
| mKlrc2 | GCTGAACTGAAGAAGCAGAT | TTGGACAATGAGGACAAG |
| mIcam1 | CACGCTACCTCTGCTCCT | GGATGGATGGATACCTGAG |
| mIl27ra | TTCTGCTGTCGCTGATGT | GACCGACGCTGTAGCACT |
| mNFkB1 | CTGAGTCCTGCTCCTTCTAA | CTGTGTAGCCCATCTGTTG |
| mNFkB2 | TGGACACATACAGGAAGACC | CAATAGACCCACCAAGTCC |
| mcRel | AGAACTGTGGAAGTGTCAGG | GTCATTCAACACAAAACGAA |
| mTrim16 | GAACTCAAGTGTCTGCCATT | TGTCACAGGCATATTGAAGA |
| mTnip1 | CTGTCACCACCGACATCT | GTAGCAGGATGTACCTGGAC |
| mCyb5 | GTCTAATTCCAGTTGGTGGA | AAGTCAATCTTCTGCCATGT |

| | | |
|---|---|---|
| mPsmb9 | ACGGAAGAAGTCCACACC | GAATCAGAGCCCACCAC |
| mCxcl2 | ACGGAAGAACCAAAGAGAA | AAATAAGTGAACTCTCAGACAGC |
| mTNFa | TACTGAACTTCGGGGTGAT | GCCATAGAACTGATGAGAGG |
| mBID | CCTTCAACCAAGGAAGAATA | CGAGATGTCTGGCAATGT |
| mCtgf | GTGTGTGACGAGCCCAAG | GCCAAATGTGTCTTCCAGT |
| hb-Actin | GATCCACATCTGCTGGAAG | CAGCACAATGAAGATCAAGA |
| hWdr82 | CTCCATCGTGCTCTATGACT | GATGAGGTCCACACCATATT |
| hMLL1 | cgggaaaagtattacgacag | cacacgagtgattgatgaag |
| hMll2 | TGTGCTCTATGCCAACATTA | TTCTCCAGAGCTTCATGATT |
| hMLL3 | gtttggagtatcgacagcat | tatccagaaagaccattgct |
| hMll4 | GACTGGAAAGCAGAAGTCTC | AGCCACACGTTCTCTAAATC |
| hSetd1A | acagtgacctgctgaaactc | acgtattcgatgaccatctc |
| hSetd1b | acagtgacctgctcaagttc | acgtactcgatgaccatctc |
| hp65 | CTGGAGCAGGCTATCAGTC | ACAGCATTCAGGTCGTAGTC |
| hB94 | ACCTACATGCTGCTGCTC | CCATACCCTGCAGCTCAC |
| hIkBa | GTCCTTGGGTGCTGATGT | GAGAATAGCCCTGGTAGGTAA |
| hSOD2 | GCACGCTTACTACCTTCAGT | CTCCCAGTTGATTACATTCC |
| hIl6 | AACCTGAACCTTCCAAAGAT | ACTCCAAAAGACCAGTGATG |
| hcIAP1 | GCCATCTAGTGTTCCAGTTC | AGCATTTGACATCATCATTG |
| hcIAP2 | TCAAGTTCAAGCCAGTTACC | GACTCTGCATTTTCATCTCC |
| hCox2 | CCAGACAAGCAGGCTAATAC | TGATAGCCACTCAAGTGTTG |
| hJunB | CGACGACTCATACACAGCTA | TCGGTTTCAGGAGTTTGTAG |
| hTap1 | GTGGTCCTCTCCTCTCTTG | TGAGCCATCTTGTAGAATCC |
| hTAPBP | GTCCCTGTCTCTGCTCCT | CTCCACGAACCAACACTC |
| hTraf1 | CCACCTCTATCCACCAGAG | CAGGGTCTGCTGAAGCTC |
| hTraf2 | CAAGATTGAAGCCCTGAGTA | ATCTCCAAGACCTTCTGCTC |
| hTraf3 | GGAGAGCGTGGACAAGAG | CACACTCAGCATCTGGTCAT |
| hGch1 | CTACCAGGAGACCATCTCAG | TATGTCCTTCACAATCACCA |
| hGfpt2 | ACAAGCTCTCCACAGAACAG | CCTCTTCATCCGTGTCTTAC |
| hKlrc2 | TATGACTGCCAAGGTTTACTG | ATCAGGACAATGCAAATGAT |
| hIcam1 | GTGACCATCTACAGCTTTCC | TCACACTTCACTGTCACCTC |
| hIl27ra | CTCTCACCAACCTCTCTTTG | ACCAGTAGCTCCGTGCTC |
| hNFkB1 | TGGTATCAGACGCCATCTA | GCTGTCCTGTCCATTCTTAC |
| hNFkB2 | AATTGAACTCCTCCATTGTG | CCTCTCTGCTTAGGCTGTT |
| hcRel | TTCTGACCAGGAAGTTAGTGA | TTTGCTTTATTGCCGTAAGT |
| hTrim16 | ACACCATAGTCTCCCTGGAT | GATGGCATTTTCATTCAACT |
| hTnip1 | AATGCAAGGGATAAAGATGT | TTGTCCTTCACTAGCTCCTC |
| hCyb5 | ACAAGGTGTACGATTTGACC | GTTCTCAGTAGCGTCACCTC |
| hPsmb9 | ATCGAGAGGACTTGTCTGC | GGTTCCATATACCTGACCT |
| hCxcl2 | CAAGAACATCCAAAGTGTGA | CCATTCTTGAGTGTGGCTAT |

| | | |
|---|---|---|
| hCtgf | GAGTGGGTGTGTGACGAG | CGTGTCTTCCAGTCGGTA |
| | | |
| Primers for ChIP | | |
| Name | Forward | Reverse |
| mHemob | CTTTGGGCATCTAGCTTTTA | AATCCTTGCAAGAAACAAAA |
| mIkBapro | GAGGACTTTCCAGCCACTCA | GCTCGTCCTCCACTGAGAAG |
| mSOD2proF | AGTCTCAGGGGCAACAAAGA | GCCCCTCTGACCCAGTTAAT |
| mIl6pro | gggatgtctgtagctcattc | gcagagaggaacttcatagc |
| mTnip1pro | CCTGCAGAAGCTCAGAAA | ACGAGGTGATCTGAAGATGT |
| mA20pro | catggatgtgacgtggaa | ccggagaaactcctaggtc |
| mMcp1pro | ccacagtttctctcttccac | atcaccctggataagtgatg |

Supplementray Table 2 Differential expressed genes of MEF wide type cell with or without TNFα

| ID | ACCESSION NUMBEI | NAME | TNF | Ctrl | FOLDCHANGI |
|---|---|---|---|---|---|
| 17260 | NM_001170537.1 | myocyte enhancer factor 2C | 0.0000 | 0.0449 | 0.0000 |
| 73887 | XR_106601.1 | RIKEN cDNA 4930417022 gene | 0.0000 | 0.2437 | 0.0000 |
| 73887 | XR_106411.1 | RIKEN cDNA 4930417022 gene | 0.0000 | 0.2437 | 0.0000 |
| 100504427 | XR_104672.1 | predicted gene 13404 | 0.0182 | 0.2388 | 0.0762 |
| 100504427 | XR_107364.1 | predicted gene 13404 | 0.0183 | 0.2211 | 0.0826 |
| 78445 | XR_106969.1 | RIKEN cDNA C330013E15 gene | 0.1018 | 0.7192 | 0.1416 |
| 78445 | XR_105710.1 | RIKEN cDNA C330013E15 gene | 0.1018 | 0.7192 | 0.1416 |
| 442801 | NM_177566.3 | Rho guanine nucleotide exchange factor (GEF) 15 | 0.0255 | 0.1455 | 0.1749 |
| 69903 | NM_028544.1 | Ras interacting protein 1 | 0.0564 | 0.2390 | 0.2360 |
| 100342 | NM_175307.6 | family with sequence similarity 46, member B | 0.1406 | 0.5044 | 0.2788 |
| 56379 | NM_019659.3 | potassium inwardly-rectifying channel, subfamily J, member 1 | 0.0931 | 0.3286 | 0.2832 |
| 56379 | NM_001168354.1 | potassium inwardly-rectifying channel, subfamily J, member 1 | 0.0930 | 0.3284 | 0.2832 |
| 11606 | NM_007428.3 | angiotensinogen (serpin peptidase inhibitor, clade A, member 8) | 0.1926 | 0.6801 | 0.2832 |
| 14747 | NM_008153.3 | chemokine-like receptor 1 | 0.8669 | 2.5226 | 0.3437 |
| 22403 | NM_016873.2 | WNT1 inducible signaling pathway protein 2 | 0.4007 | 1.0714 | 0.3740 |
| 11754 | NM_009675.2 | amine oxidase, copper containing 3 | 0.1870 | 0.4676 | 0.3999 |
| 100503611 | XM_003084596.1 | - | 0.6688 | 1.4808 | 0.4516 |
| 100039781 | NM_027511.1 | histidine rich carboxyl terminus 1 | 2.1003 | 4.5465 | 0.4620 |
| 64929 | NM_022886.2 | sciellin | 0.6556 | 1.2876 | 0.5092 |
| 22417 | NM_009523.1 | wingless-related MMTV integration site 4 | 2.9543 | 5.6667 | 0.5213 |
| 56745 | NM_019959.2 | C1q and tumor necrosis factor related protein 1 | 1.6079 | 3.0580 | 0.5258 |
| 100042198 | XR_104937.1 | predicted gene 3716 | 0.9085 | 1.7203 | 0.5281 |
| 100042198 | XR_107688.1 | predicted gene 3716 | 1.0012 | 1.8815 | 0.5321 |
| 15902 | NM_010496.3 | inhibitor of DNA binding 2 | 12.2842 | 22.8301 | 0.5381 |
| 105844 | NM_130859.2 | caspase recruitment domain family, member 10 | 1.7540 | 3.2205 | 0.5446 |
| 70788 | NM_027551.2 | kelch-like 30 (Drosophila) | 2.9826 | 5.4573 | 0.5465 |
| 23882 | NM_011817.2 | growth arrest and DNA-damage-inducible 45 gamma | 12.7631 | 23.2863 | 0.5481 |
| 68169 | NM_172399.3 | RIKEN cDNA A930038C07 gene | 3.8765 | 7.0064 | 0.5533 |

| | | | | | |
|---|---|---|---|---|---|
| 14181 | NM_008009.3 | fibroblast growth factor binding protein 1 | 3.7718 | 6.8084 | 0.5540 |
| 329540 | NM_001001986.2 | RIKEN cDNA 8430427H17 gene | 1.1553 | 2.0751 | 0.5567 |
| 13653 | NM_007913.5 | early growth response 1 | 1.1868 | 2.1249 | 0.5585 |
| 12159 | NM_007554.2 | bone morphogenetic protein 4 | 4.9474 | 8.7537 | 0.5652 |
| 71093 | NM_153778.3 | atonal homolog 8 (Drosophila) | 4.1587 | 7.3353 | 0.5669 |
| 17130 | NM_008542.3 | MAD homolog 6 (Drosophila) | 2.3821 | 4.1757 | 0.5705 |
| 329540 | NM_001134300.2 | RIKEN cDNA 8430427H17 gene | 1.0585 | 1.8549 | 0.5706 |
| 68404 | NM_153529.1 | neuritin 1 | 9.8921 | 17.1447 | 0.5770 |
| 76969 | NM_023850.2 | carbohydrate (keratan sulfate Gal-6) sulfotransferase 1 | 10.1686 | 17.5478 | 0.5795 |
| 231861 | NM_001122730.1 | trinucleotide repeat containing 18 | 3.2867 | 5.5961 | 0.5873 |
| 223650 | NM_144848.2 | epiplakin 1 | 0.6346 | 1.0706 | 0.5928 |
| 231861 | NM_178242.2 | trinucleotide repeat containing 18 | 2.4112 | 4.0547 | 0.5947 |
| 271221 | NM_198642.2 | RIKEN cDNA 5031414D18 gene | 3.7752 | 6.2986 | 0.5994 |
| 74760 | NM_144538.2 | RAB3A interacting protein (rabin3)-like 1 | 5.1150 | 8.3631 | 0.6116 |
| 380912 | NM_199029.2 | zinc finger protein 395 | 2.6201 | 4.2724 | 0.6133 |
| 14200 | NM_010212.3 | four and a half LIM domains 2 | 13.6753 | 22.2197 | 0.6155 |
| 15426 | NM_010466.2 | homeobox C8 | 6.8197 | 11.0521 | 0.6171 |
| 77889 | NM_029999.4 | limb-bud and heart | 3.1456 | 5.0193 | 0.6267 |
| 19252 | NM_013642.3 | dual specificity phosphatase 1 | 15.8758 | 25.1264 | 0.6318 |
| 70445 | NM_054042.2 | CD248 antigen, endosialin | 11.5292 | 18.1946 | 0.6337 |
| 21825 | NM_011580.3 | thrombospondin 1 | 51.2370 | 80.6369 | 0.6354 |
| 16582 | NM_010631.2 | kinesin family member C3 | 4.3592 | 6.7345 | 0.6473 |
| 16582 | NM_001145831.1 | kinesin family member C3 | 4.1775 | 6.4013 | 0.6526 |
| 16582 | NM_001145832.1 | kinesin family member C3 | 4.7334 | 7.1883 | 0.6585 |
| 170676 | NM_001040611.1 | paternally expressed 10 | 3.8115 | 5.7253 | 0.6657 |
| 170676 | NM_130877.2 | paternally expressed 10 | 3.8115 | 5.7253 | 0.6657 |
| 67306 | NM_173181.3 | family with sequence similarity 164, member A | 24.2472 | 36.0316 | 0.6729 |
| 104445 | NM_027219.3 | CDC42 effector protein (Rho GTPase binding) 1 | 18.9825 | 27.8494 | 0.6816 |
| 53881 | NM_017391.3 | solute carrier family 5 (inositol transporters), member 3 | 13.5437 | 19.4589 | 0.6960 |
| 18596 | NM_001146268.1 | platelet derived growth factor receptor, beta polypeptide | 13.0414 | 18.5416 | 0.7034 |

| | | | | | |
|---|---|---|---|---|---|
| 18596 | NM_008809.2 | platelet derived growth factor receptor, beta polypeptide | 13.0684 | 18.5585 | 0.7042 |
| 57265 | NM_020510.2 | frizzled homolog 2 (Drosophila) | 11.0146 | 15.6363 | 0.7044 |
| 94242 | NM_001168333.1 | tubulointerstitial nephritis antigen-like 1 | 43.7188 | 61.8658 | 0.7067 |
| 14313 | NM_008046.2 | follistatin | 26.5054 | 37.4681 | 0.7074 |
| 94242 | NM_023476.3 | tubulointerstitial nephritis antigen-like 1 | 40.5717 | 57.2028 | 0.7093 |
| 20410 | NM_011366.2 | sorbin and SH3 domain containing 3 | 18.2764 | 25.7422 | 0.7100 |
| 20346 | NM_009152.3 | sema domain, immunoglobulin domain (Ig), short basic domain, secr | 11.6199 | 16.1153 | 0.7210 |
| 11826 | NM_007472.2 | aquaporin 1 | 78.5188 | 108.0738 | 0.7265 |
| 100503984 | XR_107221.1 | - | 704.9197 | 524.9652 | 1.3428 |
| 75788 | NM_001038627.1 | SMAD specific E3 ubiquitin protein ligase 1 | 30.0263 | 22.2618 | 1.3488 |
| 75788 | NM_029438.3 | SMAD specific E3 ubiquitin protein ligase 1 | 29.9830 | 22.2181 | 1.3495 |
| 100503946 | XR_107210.1 | - | 736.1257 | 543.3139 | 1.3549 |
| 15364 | NM_010441.2 | high mobility group AT-hook 2 | 151.6343 | 110.8795 | 1.3676 |
| 83946 | NM_001081216.1 | pleckstrin homology domain interacting protein | 11.8800 | 8.6521 | 1.3731 |
| 328949 | NM_001085373.1 | mutated in colorectal cancers | 10.4393 | 7.5425 | 1.3841 |
| 328949 | NM_001085374.1 | mutated in colorectal cancers | 10.6870 | 7.7204 | 1.3843 |
| 19791 | NR_003278.1 | 18S ribosomal RNA | 499.2789 | 360.4836 | 1.3850 |
| 17118 | NM_008538.2 | myristoylated alanine rich protein kinase C substrate | 27.3839 | 19.6516 | 1.3935 |
| 67073 | NM_025951.2 | phosphatidylinositol 4-kinase type 2 beta | 21.1863 | 15.2003 | 1.3938 |
| 218454 | NM_172589.2 | lipoma HMGIC fusion partner-like 2 | 26.8897 | 19.2346 | 1.3980 |
| 67073 | NM_028744.2 | phosphatidylinositol 4-kinase type 2 beta | 20.6771 | 14.7820 | 1.3988 |
| 215449 | NM_024457.2 | RAS related protein 1b | 314.0320 | 224.2397 | 1.4004 |
| 16880 | NM_013584.2 | leukemia inhibitory factor receptor | 10.2795 | 7.3299 | 1.4024 |
| 18828 | NM_008880.2 | phospholipid scramblase 2 | 56.8543 | 40.5030 | 1.4037 |
| 26921 | NM_008696.2 | mitogen-activated protein kinase kinase kinase kinase 4 | 39.3240 | 27.9976 | 1.4046 |
| 20348 | NM_013657.5 | sema domain, immunoglobulin domain (Ig), short basic domain, secr | 60.1780 | 42.8094 | 1.4057 |
| 12977 | NM_001113530.1 | colony stimulating factor 1 (macrophage) | 124.2404 | 87.9714 | 1.4123 |
| 226525 | NM_177644.5 | RAS protein activator like 2 | 4.7036 | 3.3242 | 1.4150 |
| 16476 | NM_010591.2 | Jun oncogene | 19.2680 | 13.5904 | 1.4178 |
| 12977 | NM_007778.4 | colony stimulating factor 1 (macrophage) | 159.7792 | 112.5273 | 1.4199 |

| | | | | | |
|---|---|---|---|---|---|
| 14182 | NM_001079909.1 | fibroblast growth factor receptor 1 | 20.2126 | 14.2323 | 1.4202 |
| 14182 | NM_010206.2 | fibroblast growth factor receptor 1 | 19.9201 | 13.9416 | 1.4288 |
| 24136 | NM_015753.3 | zinc finger E-box binding homeobox 2 | 6.3854 | 4.4639 | 1.4304 |
| 14182 | NM_001079908.1 | fibroblast growth factor receptor 1 | 19.8939 | 13.9006 | 1.4312 |
| 13486 | NM_026106.4 | down-regulator of transcription 1 | 29.4534 | 20.5493 | 1.4333 |
| 208846 | NM_172464.2 | dishevelled associated activator of morphogenesis 1 | 7.5518 | 5.2661 | 1.4341 |
| 12977 | NM_001113529.1 | colony stimulating factor 1 (macrophage) | 163.4552 | 113.8839 | 1.4353 |
| 208846 | NM_026102.2 | dishevelled associated activator of morphogenesis 1 | 7.4237 | 5.1657 | 1.4371 |
| 17936 | NM_008667.3 | Ngfi-A binding protein 1 | 18.9093 | 13.1578 | 1.4371 |
| 78388 | NM_080638.3 | major vault protein | 18.0370 | 12.4491 | 1.4489 |
| 20912 | NM_011504.1 | syntaxin binding protein 3A | 13.6674 | 9.4132 | 1.4520 |
| 140780 | NM_080708.1 | BMP2 inducible kinase | 6.9804 | 4.8030 | 1.4533 |
| 54216 | NM_001122758.1 | protocadherin 7 | 11.4650 | 7.8501 | 1.4605 |
| 21664 | NM_009344.3 | pleckstrin homology-like domain, family A, member 1 | 32.8883 | 22.4914 | 1.4623 |
| 12457 | NM_009834.2 | CCR4 carbon catabolite repression 4-like (S. cerevisiae) | 9.8646 | 6.7216 | 1.4676 |
| 22762 | NM_011766.5 | zinc finger protein, multitype 2 | 17.5195 | 11.8835 | 1.4743 |
| 20971 | NM_011521.2 | syndecan 4 | 59.1218 | 39.9927 | 1.4783 |
| 30953 | NM_001113419.1 | schwannomin interacting protein 1 | 11.1351 | 7.5303 | 1.4787 |
| 268396 | NM_177364.3 | SH3 and PX domains 2B | 12.3986 | 8.3803 | 1.4795 |
| 15979 | NM_010511.2 | interferon gamma receptor 1 | 44.6664 | 30.1706 | 1.4805 |
| 16195 | NM_010560.3 | interleukin 6 signal transducer | 62.4263 | 42.1626 | 1.4806 |
| 30953 | NM_001113421.1 | schwannomin interacting protein 1 | 11.9842 | 8.0936 | 1.4807 |
| 14042 | NM_010162.2 | exostoses (multiple) 1 | 51.4466 | 34.5395 | 1.4895 |
| 16423 | NM_010581.3 | CD47 antigen (Rh-related antigen, integrin-associated signal tran | 49.6476 | 33.2580 | 1.4928 |
| 380711 | NM_001015046.2 | RAP1 GTPase activating protein 2 | 6.7583 | 4.5178 | 1.4959 |
| 18412 | NM_011018.2 | sequestosome 1 | 389.4593 | 260.1461 | 1.4971 |
| 23872 | NM_011809.3 | E26 avian leukemia oncogene 2, 3' domain | 33.3136 | 22.1853 | 1.5016 |
| 21928 | NM_009396.2 | tumor necrosis factor, alpha-induced protein 2 | 28.1665 | 18.7552 | 1.5018 |
| 20496 | NM_009194.3 | solute carrier family 12, member 2 | 53.6863 | 35.5881 | 1.5085 |
| 30953 | NM_001113420.1 | schwannomin interacting protein 1 | 15.3918 | 10.1965 | 1.5095 |

| | | | | | |
|---|---|---|---|---|---|
| 30953 | NM_013928.5 | schwannomin interacting protein 1 | 14.5393 | 9.6318 | 1.5095 |
| 54216 | NM_018764.2 | protocadherin 7 | 21.5416 | 14.2519 | 1.5115 |
| 16362 | NM_001159396.1 | interferon regulatory factor 1 | 16.5818 | 10.9424 | 1.5154 |
| 18933 | NM_001025570.1 | paired related homeobox 1 | 10.5276 | 6.9171 | 1.5220 |
| 268515 | NM_198423.3 | BAH domain and coiled-coil containing 1 | 4.7554 | 3.1148 | 1.5267 |
| 71409 | NM_172409.2 | formin-like 2 | 8.1921 | 5.3624 | 1.5277 |
| 110521 | NM_007772.2 | human immunodeficiency virus type I enhancer binding protein 1 | 3.0667 | 1.9942 | 1.5379 |
| 52552 | NM_001081009.1 | poly (ADP-ribose) polymerase family, member 8 | 13.5426 | 8.7941 | 1.5400 |
| 18481 | NM_008778.2 | p21 protein (Cdc42/Rac)-activated kinase 3 | 7.0763 | 4.5827 | 1.5441 |
| 170737 | NM_133206.3 | zinc and ring finger 1 | 6.7605 | 4.3767 | 1.5447 |
| 16362 | NM_008390.2 | interferon regulatory factor 1 | 17.1987 | 11.0824 | 1.5519 |
| 102626 | NM_178907.3 | mitogen-activated protein kinase-activated protein kinase 3 | 9.9259 | 6.3906 | 1.5532 |
| 99382 | NM_178890.3 | ankyrin repeat and BTB (POZ) domain containing 2 | 5.5385 | 3.5475 | 1.5612 |
| 433022 | NM_001134480.1 | phosphatidylinositol-specific phospholipase C, X domain containin | 2.1635 | 1.3833 | 1.5640 |
| 98376 | NM_178883.5 | golgin, RAB6-interacting | 10.4566 | 6.6407 | 1.5746 |
| 100463512 | NM_001190732.1 | - | 113.7580 | 72.2355 | 1.5748 |
| 18933 | NM_175686.3 | paired related homeobox 1 | 22.8892 | 14.5037 | 1.5782 |
| 52118 | NM_027514.2 | poliovirus receptor | 18.4506 | 11.6816 | 1.5795 |
| 21356 | NM_001025313.1 | TAP binding protein | 24.8124 | 15.6451 | 1.5859 |
| 12608 | NM_009883.3 | CCAAT/enhancer binding protein (C/EBP), beta | 30.1458 | 19.0011 | 1.5865 |
| 21356 | NM_009318.2 | TAP binding protein | 24.8915 | 15.6753 | 1.5879 |
| 18933 | NM_011127.2 | paired related homeobox 1 | 22.7663 | 14.3271 | 1.5890 |
| 14538 | NM_133219.1 | glucosaminyl (N-acetyl) transferase 2, I-branching enzyme | 3.2357 | 2.0359 | 1.5893 |
| 67338 | NM_001164569.1 | ring finger and FYVE like domain containing protein | 10.5859 | 6.6496 | 1.5920 |
| 170737 | NM_001168622.1 | zinc and ring finger 1 | 6.1730 | 3.8729 | 1.5939 |
| 16177 | NM_008362.2 | interleukin 1 receptor, type I | 2.8510 | 1.7883 | 1.5942 |
| 12837 | NM_007739.2 | collagen, type VIII, alpha 1 | 32.0221 | 20.0786 | 1.5948 |
| 67338 | NM_001164570.1 | ring finger and FYVE like domain containing protein | 10.7568 | 6.7268 | 1.5991 |
| 67338 | NM_001007465.3 | ring finger and FYVE like domain containing protein | 11.0411 | 6.9021 | 1.5997 |
| 16177 | NM_001123382.1 | interleukin 1 receptor, type I | 2.8175 | 1.7552 | 1.6053 |

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|---|---|---|---|---|---|
| 67338 | NM_026097.3 | ring finger and FYVE like domain containing protein | 10.6633 | 6.6350 | 1.6071 |
| 12192 | NM_007564.5 | zinc finger protein 36, C3H type-like 1 | 13.5355 | 8.4117 | 1.6091 |
| 20620 | NM_152804.2 | polo-like kinase 2 (Drosophila) | 226.8847 | 140.7800 | 1.6116 |
| 67338 | NM_001164571.1 | ring finger and FYVE like domain containing protein | 10.9996 | 6.8126 | 1.6146 |
| 15980 | NM_008338.3 | interferon gamma receptor 2 | 48.4175 | 29.8441 | 1.6223 |
| 18033 | NM_008689.2 | nuclear factor of kappa light polypeptide gene enhancer in B-cell | 34.4185 | 21.1595 | 1.6266 |
| 58244 | NM_021433.3 | syntaxin 6 | 21.9780 | 13.5074 | 1.6271 |
| 231549 | NM_178701.3 | leucine rich repeat containing 8D | 12.1910 | 7.4796 | 1.6299 |
| 231549 | NM_001122768.1 | leucine rich repeat containing 8D | 12.1168 | 7.4340 | 1.6299 |
| 75234 | NM_029219.1 | ring finger protein 19B | 20.7091 | 12.7049 | 1.6300 |
| 74194 | NM_028810.2 | Rho family GTPase 3 | 29.4216 | 17.9490 | 1.6392 |
| 192657 | NM_138953.2 | elongation factor RNA polymerase II 2 | 22.6277 | 13.6865 | 1.6533 |
| 22031 | NM_001048206.1 | TNF receptor-associated factor 3 | 10.4963 | 6.3396 | 1.6557 |
| 20352 | NM_013659.4 | sema domain, immunoglobulin domain (Ig), transmembrane domain (TM | 6.6758 | 4.0122 | 1.6639 |
| 14573 | NM_010275.2 | glial cell line derived neurotrophic factor | 5.8571 | 3.5149 | 1.6663 |
| 22031 | NM_011632.2 | TNF receptor-associated factor 3 | 10.5627 | 6.3387 | 1.6664 |
| 16362 | NM_001159393.1 | interferon regulatory factor 1 | 10.8842 | 6.5247 | 1.6682 |
| 236285 | NM_173414.3 | LanC lantibiotic synthetase component C-like 3 (bacterial) | 6.3554 | 3.8088 | 1.6686 |
| 75296 | NM_201230.4 | Fgfr1 oncogene partner | 13.8136 | 8.2592 | 1.6725 |
| 114774 | NM_054056.2 | PRKC, apoptosis, WT1, regulator | 17.2460 | 10.2983 | 1.6746 |
| 19288 | NM_008987.3 | pentraxin related gene | 48.8220 | 29.0910 | 1.6783 |
| 320924 | NM_178793.4 | collagen and calcium binding EGF domains 1 | 11.1861 | 6.6199 | 1.6898 |
| 16155 | NM_008349.5 | interleukin 10 receptor, beta | 17.5100 | 10.3314 | 1.6948 |
| 19225 | NM_011198.3 | prostaglandin-endoperoxide synthase 2 | 27.0702 | 15.9376 | 1.6985 |
| 19734 | NM_011267.3 | regulator of G-protein signaling 16 | 7.4345 | 4.3718 | 1.7005 |
| 75599 | NM_029357.3 | protocadherin 1 | 3.0870 | 1.8115 | 1.7041 |
| 387609 | NM_199449.2 | zinc fingers and homeoboxes 2 | 3.1821 | 1.8640 | 1.7072 |
| 672511 | XM_001476651.2 | ring finger protein 213 | 5.8450 | 3.4128 | 1.7127 |
| 672511 | XM_001477846.2 | ring finger protein 213 | 5.8450 | 3.4128 | 1.7127 |
| 100504142 | XR_106553.1 | predicted gene, 20084 | 240.3367 | 140.3107 | 1.7129 |

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|---|---|---|---|---|---|
| 100504142 | XR_105374.1 | predicted gene, 20084 | 240.3367 | 140.3107 | 1.7129 |
| 380855 | NM_001013769.1 | regulator of sex limited protein 1 | 4.7169 | 2.7497 | 1.7154 |
| 260315 | NM_001081035.1 | neuron navigator 3 | 0.9002 | 0.5237 | 1.7191 |
| 100504290 | XR_105381.1 | predicted gene, 20152 | 21.0056 | 12.0925 | 1.7371 |
| 100504290 | XR_106558.1 | predicted gene, 20152 | 21.1812 | 12.1505 | 1.7432 |
| 100125931 | NR_030676.1 | RIKEN cDNA A130049A11 gene | 3.6301 | 2.0793 | 1.7458 |
| 72747 | NM_028341.4 | tetratricopeptide repeat domain 39C | 7.9645 | 4.5361 | 1.7558 |
| 15273 | NM_010437.2 | human immunodeficiency virus type I enhancer binding protein 2 | 5.4886 | 3.1134 | 1.7629 |
| 408065 | NM_001001186.3 | zinc finger protein 456 | 1.9103 | 1.0698 | 1.7856 |
| 229675 | NM_172684.2 | rosbin, round spermatid basic protein 1 | 5.7704 | 3.1845 | 1.8120 |
| 20308 | NM_011338.2 | chemokine (C-C motif) ligand 9 | 17.2538 | 9.4835 | 1.8193 |
| 26399 | NM_011943.2 | mitogen-activated protein kinase kinase 6 | 7.2214 | 3.9488 | 1.8287 |
| 53970 | NM_017395.2 | regulatory factor X, 5 (influences HLA class II expression) | 2.0734 | 1.1278 | 1.8385 |
| 16477 | NM_008416.2 | Jun-B oncogene | 10.6419 | 5.7279 | 1.8579 |
| 319622 | NM_001033380.3 | inositol 1,4,5-triphosphate receptor interacting protein-like 2 | 44.3796 | 23.7390 | 1.8695 |
| 73683 | NM_001111111.1 | autophagy related 16 like 2 (S. cerevisiae) | 2.2595 | 1.2060 | 1.8736 |
| 231830 | NM_174850.3 | MICAL-like 2 | 28.4579 | 15.1649 | 1.8766 |
| 20656 | NM_013671.3 | superoxide dismutase 2, mitochondrial | 28.3965 | 15.0895 | 1.8819 |
| 13874 | NM_007950.2 | epiregulin | 17.2754 | 9.1729 | 1.8833 |
| 108767 | NM_001033225.2 | proline-rich nuclear receptor coactivator 1 | 9.7834 | 5.1865 | 1.8863 |
| 223881 | NM_172612.3 | Rho family GTPase 1 | 63.4554 | 33.5264 | 1.8927 |
| 75985 | NM_029494.2 | RAB30, member RAS oncogene family | 7.7293 | 4.0790 | 1.8949 |
| 671535 | NM_001163576.1 | poly (ADP-ribose) polymerase family, member 10 | 5.1870 | 2.7172 | 1.9090 |
| 18174 | NM_008732.2 | solute carrier family 11 (proton-coupled divalent metal ion trans | 28.1269 | 14.7291 | 1.9096 |
| 671535 | NM_001163575.1 | poly (ADP-ribose) polymerase family, member 10 | 5.3393 | 2.7918 | 1.9125 |
| 64292 | NM_022415.3 | prostaglandin E synthase | 6.7331 | 3.4511 | 1.9510 |
| 67844 | NM_026405.3 | RAB32, member RAS oncogene family | 67.8149 | 34.7469 | 1.9517 |
| 12125 | NM_009754.3 | BCL2-like 11 (apoptosis facilitator) | 4.2829 | 2.1795 | 1.9651 |
| 100503984 | XR_104558.1 | - | 24.2867 | 12.2887 | 1.9763 |
| 100503984 | XR_104553.1 | - | 25.6072 | 12.9568 | 1.9763 |

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|---|---|---|---|---|---|
| 100503984 | XR_104554.1 | - | 24.1888 | 12.2392 | 1.9763 |
| 100503984 | XR_104561.1 | - | 25.5255 | 12.9155 | 1.9763 |
| 100503984 | XR_104562.1 | - | 27.3260 | 13.8265 | 1.9763 |
| 100503984 | XR_104560.1 | - | 24.7879 | 12.5423 | 1.9763 |
| 100503984 | XR_104557.1 | - | 25.0726 | 12.6863 | 1.9763 |
| 100503984 | XR_104555.1 | - | 24.7369 | 12.5165 | 1.9763 |
| 100503984 | XR_104563.1 | - | 28.2008 | 14.2479 | 1.9793 |
| 100503984 | XR_104559.1 | - | 24.3228 | 12.2887 | 1.9793 |
| 100503984 | XR_104556.1 | - | 24.0312 | 12.1414 | 1.9793 |
| 230073 | NM_172689.3 | DEAD (Asp-Glu-Ala-Asp) box polypeptide 58 | 1.7282 | 0.8609 | 2.0074 |
| 12125 | NM_207681.2 | BCL2-like 11 (apoptosis facilitator) | 4.3432 | 2.1615 | 2.0094 |
| 74732 | NM_001163590.1 | syntaxin 11 | 3.1775 | 1.5791 | 2.0123 |
| 270118 | NM_001013813.3 | mastermind like 2 (Drosophila) | 2.6256 | 1.2998 | 2.0200 |
| 74732 | NM_001163591.1 | syntaxin 11 | 3.3312 | 1.6469 | 2.0227 |
| 319909 | NM_001126490.1 | isthmin 1 homolog (zebrafish) | 1.1413 | 0.5635 | 2.0253 |
| 12125 | NM_207680.2 | BCL2-like 11 (apoptosis facilitator) | 4.2339 | 2.0894 | 2.0264 |
| 212168 | NM_172503.3 | zinc finger, SWIM domain containing 4 | 4.6611 | 2.2975 | 2.0287 |
| 108797 | NM_175366.3 | mex3 homolog B (C. elegans) | 6.2886 | 3.0933 | 2.0330 |
| 70701 | NM_001081205.1 | NIPA-like domain containing 1 | 0.9605 | 0.4717 | 2.0363 |
| 17082 | NM_001025602.2 | interleukin 1 receptor-like 1 | 31.0010 | 15.1780 | 2.0425 |
| 67916 | NM_080555.2 | phosphatidic acid phosphatase type 2B | 17.1256 | 8.3487 | 2.0513 |
| 74732 | NM_029075.1 | syntaxin 11 | 3.1328 | 1.5202 | 2.0607 |
| 100503392 | XR_107188.1 | - | 3.8623 | 1.8678 | 2.0679 |
| 100503392 | XR_105978.1 | - | 3.8623 | 1.8678 | 2.0679 |
| 22038 | NM_011636.2 | phospholipid scramblase 1 | 44.7919 | 21.5776 | 2.0758 |
| 100502974 | XR_107727.1 | predicted gene, 19481 | 4.4408 | 2.1310 | 2.0839 |
| 18174 | NM_001146161.1 | solute carrier family 11 (proton-coupled divalent metal ion trans | 32.4984 | 15.5207 | 2.0939 |
| 16878 | NM_001039537.1 | leukemia inhibitory factor | 6.5125 | 3.0480 | 2.1366 |
| 17082 | NM_010743.2 | interleukin 1 receptor-like 1 | 53.3054 | 24.9395 | 2.1374 |
| 16878 | NM_008501.2 | leukemia inhibitory factor | 6.2228 | 2.9103 | 2.1382 |

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|---|---|---|---|---|---|
| 100503392 | XR_107187.1 | - | 4.1181 | 1.9161 | 2.1492 |
| 100503392 | XR_105977.1 | - | 4.1181 | 1.9161 | 2.1492 |
| 57875 | NM_020581.2 | angiopoietin-like 4 | 1.9028 | 0.8847 | 2.1509 |
| 100503984 | XR_104572.1 | - | 3.1527 | 1.4563 | 2.1648 |
| 100503984 | XR_104565.1 | - | 3.1695 | 1.4641 | 2.1648 |
| 192656 | NM_138952.3 | receptor (TNFRSF)-interacting serine-threonine kinase 2 | 45.2043 | 20.8356 | 2.1696 |
| 209086 | NM_010156.3 | sterile alpha motif domain containing 9-like | 14.2532 | 6.5460 | 2.1774 |
| 100503984 | XR_104570.1 | - | 12.4206 | 5.6963 | 2.1805 |
| 100503984 | XR_104569.1 | - | 12.3266 | 5.6532 | 2.1805 |
| 100503984 | XR_104567.1 | - | 11.8513 | 5.3866 | 2.2001 |
| 11796 | NM_007464.3 | baculoviral IAP repeat-containing 3 | 3.6884 | 1.6753 | 2.2016 |
| 100503984 | XR_104568.1 | - | 12.2280 | 5.5361 | 2.2088 |
| 100503984 | XR_104566.1 | - | 12.1348 | 5.4939 | 2.2088 |
| 326623 | NM_177371.3 | tumor necrosis factor (ligand) superfamily, member 15 | 0.7176 | 0.3218 | 2.2300 |
| 270118 | NM_173776.3 | mastermind like 2 (Drosophila) | 3.0188 | 1.3528 | 2.2315 |
| 50908 | NM_001097617.1 | complement component 1, s subcomponent | 1.7196 | 0.7684 | 2.2380 |
| 239650 | NM_177716.3 | expressed sequence AI836003 | 2.8046 | 1.2457 | 2.2514 |
| 50908 | NM_144938.2 | complement component 1, s subcomponent | 1.6859 | 0.7465 | 2.2584 |
| 15937 | NM_133662.2 | immediate early response 3 | 34.3661 | 15.1534 | 2.2679 |
| 100503551 | XR_107722.1 | predicted gene 15817 | 2.1234 | 0.9284 | 2.2872 |
| 100503551 | XR_106291.1 | predicted gene 15817 | 2.1234 | 0.9284 | 2.2872 |
| 70737 | NM_001037711.2 | cingulin | 1.3052 | 0.5654 | 2.3084 |
| 16206 | NM_008377.2 | leucine-rich repeats and immunoglobulin-like domains 1 | 25.1269 | 10.8787 | 2.3097 |
| 170677 | NM_130878.2 | cadherin-related family member 1 | 0.4505 | 0.1901 | 2.3701 |
| 20312 | NM_009142.3 | chemokine (C-X3-C motif) ligand 1 | 0.7390 | 0.3097 | 2.3860 |
| 319236 | NM_001146007.1 | tripartite motif-containing 12C | 0.5071 | 0.2124 | 2.3877 |
| 12521 | NM_001136055.1 | CD82 antigen | 2.6123 | 1.0928 | 2.3903 |
| 12521 | NM_007656.4 | CD82 antigen | 2.4983 | 1.0321 | 2.4206 |
| 20821 | NM_001082552.1 | tripartite motif-containing 21 | 1.5322 | 0.6264 | 2.4462 |
| 215113 | NM_173388.1 | solute carrier family 43, member 2 | 2.7445 | 1.1175 | 2.4559 |

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|---|---|---|---|---|---|
| 18034 | NM_019408.3 | nuclear factor of kappa light polypeptide gene enhancer in B-cell | 58.9402 | 23.9000 | 2.4661 |
| 18034 | NM_001177370.1 | nuclear factor of kappa light polypeptide gene enhancer in B-cell | 62.8664 | 25.4739 | 2.4679 |
| 12609 | NM_007679.4 | CCAAT/enhancer binding protein (C/EBP), delta | 4.0962 | 1.6596 | 2.4683 |
| 20821 | NM_009277.3 | tripartite motif-containing 21 | 1.5457 | 0.6238 | 2.4778 |
| 18034 | NM_001177369.1 | nuclear factor of kappa light polypeptide gene enhancer in B-cell | 62.2524 | 25.1053 | 2.4797 |
| 230738 | NM_153159.2 | zinc finger CCCH type containing 12A | 15.0109 | 6.0299 | 2.4894 |
| 71683 | NM_001048207.1 | glycophorin C | 15.8227 | 6.3333 | 2.4983 |
| 21929 | NM_001166402.1 | tumor necrosis factor, alpha-induced protein 3 | 13.3463 | 5.3201 | 2.5087 |
| 21929 | NM_009397.3 | tumor necrosis factor, alpha-induced protein 3 | 13.1228 | 5.2182 | 2.5148 |
| 100048759 | XM_003086792.1 | - | 5.9885 | 2.3270 | 2.5735 |
| 434438 | NM_001135198.1 | coiled-coil domain containing 36 | 0.5216 | 0.2005 | 2.6017 |
| 12266 | NM_009778.2 | complement component 3 | 5.8334 | 2.2281 | 2.6180 |
| 18812 | NM_011118.2 | prolactin family 2, subfamily c, member 3 | 33.4373 | 12.7137 | 2.6300 |
| 17533 | NM_008625.2 | mannose receptor, C type 1 | 1.5246 | 0.5760 | 2.6469 |
| 107849 | NM_181852.1 | prolactin family 2, subfamily c, member 5 | 14.0089 | 5.2485 | 2.6691 |
| 20568 | NM_011414.3 | secretory leukocyte peptidase inhibitor | 4.1181 | 1.5329 | 2.6864 |
| 18811 | NM_031191.1 | prolactin family 2, subfamily c, member 2 | 36.9197 | 13.7408 | 2.6869 |
| 19260 | NM_008979.1 | protein tyrosine phosphatase, non-receptor type 22 (lymphoid) | 2.8108 | 1.0421 | 2.6973 |
| 71816 | NM_027934.2 | ring finger protein 180 | 0.4627 | 0.1715 | 2.6980 |
| 80859 | NM_001159395.1 | nuclear factor of kappa light polypeptide gene enhancer in B-cell | 6.1356 | 2.2726 | 2.6998 |
| 80859 | NM_030612.3 | nuclear factor of kappa light polypeptide gene enhancer in B-cell | 5.6188 | 2.0768 | 2.7055 |
| 18208 | NM_008744.2 | netrin 1 | 4.8428 | 1.7853 | 2.7125 |
| 80859 | NM_001159394.1 | nuclear factor of kappa light polypeptide gene enhancer in B-cell | 5.8570 | 2.1589 | 2.7130 |
| 666317 | NM_001045532.1 | Prolactin family 2, subfamily c, member 1 | 5.0628 | 1.8389 | 2.7531 |
| 57783 | NM_021327.2 | TNFAIP3 interacting protein 1 | 30.0159 | 10.7610 | 2.7893 |
| 545551 | NR_033629.1 | cDNA sequence BC021767 | 1.0428 | 0.3723 | 2.8010 |
| 630663 | XM_904245.4 | predicted gene 7040 | 9.9369 | 3.4792 | 2.8561 |
| 11988 | NM_007514.3 | solute carrier family 7 (cationic amino acid transporter, y+ syst | 0.2404 | 0.0840 | 2.8632 |
| 11988 | NM_001044740.1 | solute carrier family 7 (cationic amino acid transporter, y+ syst | 0.2411 | 0.0842 | 2.8632 |
| 20556 | NM_011408.1 | schlafen 2 | 2.7381 | 0.9423 | 2.9058 |

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|---|---|---|---|---|---|
| 16997 | NM_013589.3 | latent transforming growth factor beta binding protein 2 | 0.2106 | 0.0708 | 2.9733 |
| 630663 | XM_001473551.2 | predicted gene 7040 | 13.9888 | 4.6690 | 2.9961 |
| 16149 | NM_001042605.1 | CD74 antigen (invariant polypeptide of major histocompatibility c | 1.3238 | 0.4284 | 3.0899 |
| 16149 | NM_010545.3 | CD74 antigen (invariant polypeptide of major histocompatibility c | 1.4713 | 0.4657 | 3.1592 |
| 19698 | NM_009046.2 | avian reticuloendotheliosis viral (v-rel) oncogene related B | 14.9871 | 4.7315 | 3.1675 |
| 233552 | NM_201352.2 | glycerophosphodiester phosphodiesterase domain containing 5 | 1.9709 | 0.6096 | 3.2333 |
| 12051 | NM_033601.3 | B-cell leukemia/lymphoma 3 | 3.6036 | 1.0416 | 3.4595 |
| 21822 | NM_011579.3 | T-cell specific GTPase 1 | 0.3563 | 0.1027 | 3.4689 |
| 14239 | NM_010226.2 | forkhead box S1 | 0.9542 | 0.2751 | 3.4689 |
| 20306 | NM_013654.3 | chemokine (C-C motif) ligand 7 | 342.8538 | 98.8195 | 3.4695 |
| 56489 | NM_019777.3 | inhibitor of kappaB kinase epsilon | 6.0930 | 1.7114 | 3.5602 |
| 20296 | NM_011333.3 | chemokine (C-C motif) ligand 2 | ######### | 433.7946 | 3.7885 |
| 100039796 | NM_001145164.1 | T-cell specific GTPase 2 | 0.3427 | 0.0896 | 3.8229 |
| 21942 | NM_001077508.1 | tumor necrosis factor receptor superfamily, member 9 | 0.6437 | 0.1624 | 3.9645 |
| 14102 | NM_007987.2 | Fas (TNF receptor superfamily member 6) | 9.7176 | 2.4512 | 3.9645 |
| 626578 | NM_001039646.2 | guanylate-binding protein 10 | 0.3242 | 0.0818 | 3.9645 |
| 18035 | NM_010907.2 | nuclear factor of kappa light polypeptide gene enhancer in B-cell | 66.4125 | 16.4009 | 4.0493 |
| 16193 | NM_031168.1 | interleukin 6 | 4.9981 | 1.2276 | 4.0716 |
| 18606 | NM_001136077.1 | ectonucleotide pyrophosphatase/phosphodiesterase 2 | 0.9115 | 0.2233 | 4.0811 |
| 56619 | NM_019948.2 | C-type lectin domain family 4, member e | 0.7095 | 0.1718 | 4.1296 |
| 320207 | NM_177320.2 | phosphoinositide-3-kinase, regulatory subunit 5, p101 | 1.8842 | 0.4464 | 4.2214 |
| 21942 | NM_011612.2 | tumor necrosis factor receptor superfamily, member 9 | 0.6532 | 0.1521 | 4.2948 |
| 238393 | NM_001033335.3 | serine (or cysteine) peptidase inhibitor, clade A, member 3F | 0.4199 | 0.0978 | 4.2948 |
| 18606 | NM_015744.2 | ectonucleotide pyrophosphatase/phosphodiesterase 2 | 1.0805 | 0.2447 | 4.4150 |
| 102502 | NM_001033210.3 | plastin 1 (I-isoform) | 0.6961 | 0.1561 | 4.4600 |
| 238393 | NM_001168294.1 | serine (or cysteine) peptidase inhibitor, clade A, member 3F | 0.4282 | 0.0960 | 4.4600 |
| 238393 | NM_001168295.1 | serine (or cysteine) peptidase inhibitor, clade A, member 3F | 0.4726 | 0.1060 | 4.4600 |
| 100702 | NM_194336.2 | guanylate binding protein 6 | 0.4128 | 0.0916 | 4.5051 |
| 14102 | NM_001146708.1 | Fas (TNF receptor superfamily member 6) | 3.5421 | 0.7798 | 4.5426 |
| 18788 | NM_011111.4 | serine (or cysteine) peptidase inhibitor, clade B, member 2 | 1.0686 | 0.2336 | 4.5744 |

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|---|---|---|---|---|---|
| 21942 | NM_001077509.1 | tumor necrosis factor receptor superfamily, member 9 | 0.7267 | 0.1535 | 4.7353 |
| 12363 | NM_007609.2 | caspase 4, apoptosis-related cysteine peptidase | 12.0475 | 2.5167 | 4.7871 |
| 18788 | NM_001174170.1 | serine (or cysteine) peptidase inhibitor, clade B, member 2 | 1.0608 | 0.2177 | 4.8730 |
| 214854 | NM_153408.2 | neuralized homolog 3 homolog (Drosophila) | 7.3203 | 1.4660 | 4.9933 |
| 14468 | NM_010259.2 | guanylate binding protein 1 | 0.2915 | 0.0512 | 5.6989 |
| 547253 | NM_001039530.3 | poly (ADP-ribose) polymerase family, member 14 | 0.1528 | 0.0249 | 6.1449 |
| 18037 | NM_008690.3 | nuclear factor of kappa light polypeptide gene enhancer in B-cell | 6.8181 | 1.1019 | 6.1878 |
| 17384 | NM_019471.2 | matrix metallopeptidase 10 | 1.4331 | 0.2305 | 6.2170 |
| 14469 | NM_010260.1 | guanylate binding protein 2 | 1.6490 | 0.2627 | 6.2771 |
| 22029 | NM_009421.3 | TNF receptor-associated factor 1 | 10.6692 | 1.6442 | 6.4890 |
| 630294 | NM_001177467.1 | predicted gene 7030 | 0.7952 | 0.1203 | 6.6074 |
| 240675 | NM_172840.2 | von Willebrand factor A domain containing 2 | 0.1288 | 0.0186 | 6.9378 |
| 100503422 | XM_003085129.1 | predicted gene, 19684 | 0.4659 | 0.0672 | 6.9378 |
| 100503422 | XM_003085162.1 | predicted gene, 19684 | 0.4665 | 0.0672 | 6.9378 |
| 547347 | NM_001034909.3 | predicted gene 6034 | 0.3064 | 0.0442 | 6.9378 |
| 17392 | NM_010809.1 | matrix metallopeptidase 3 | 0.3270 | 0.0388 | 8.4245 |
| 17386 | NM_008607.2 | matrix metallopeptidase 13 | 1.1358 | 0.1348 | 8.4245 |
| 20715 | NM_009251.1 | serine (or cysteine) peptidase inhibitor, clade A, member 3G | 2.0601 | 0.2310 | 8.9200 |
| 16819 | NM_008491.1 | lipocalin 2 | 18.0602 | 1.9871 | 9.0887 |
| 216799 | NM_145827.3 | NLR family, pyrin domain containing 3 | 0.1689 | 0.0179 | 9.4156 |
| 17395 | NM_013599.2 | matrix metallopeptidase 9 | 0.1347 | 0.0113 | 11.8934 |
| 414084 | NM_001001495.2 | TNFAIP3 interacting protein 3 | 3.2149 | 0.2488 | 12.9226 |
| 15945 | NM_021274.1 | chemokine (C-X-C motif) ligand 10 | 5.3800 | 0.4071 | 13.2149 |
| 20311 | NM_009141.2 | chemokine (C-X-C motif) ligand 5 | 337.7799 | 24.9941 | 13.5144 |
| 22329 | NM_011693.3 | vascular cell adhesion molecule 1 | 21.2693 | 1.3054 | 16.2930 |
| 14825 | NM_008176.3 | chemokine (C-X-C motif) ligand 1 | 319.9473 | 18.5556 | 17.2426 |
| 12981 | NM_009969.4 | colony stimulating factor 2 (granulocyte-macrophage) | 0.6228 | 0.0349 | 17.8401 |
| 408066 | XR_001629.2 | cDNA sequence BC067074 | 0.1007 | 0.0044 | 22.7956 |
| 16165 | NM_008356.3 | interleukin 13 receptor, alpha 2 | 0.5735 | 0.0231 | 24.7779 |
| 20297 | NM_016960.2 | chemokine (C-C motif) ligand 20 | 56.3419 | 1.6931 | 33.2767 |

| | | | | | |
|---|---|---|---|---|---|
| 20210 | NM_011315.3 | serum amyloid A 3 | 4.6446 | 0.1358 | 34.1934 |
| 20297 | NM_001159738.1 | chemokine (C-C motif) ligand 20 | 55.8253 | 1.6142 | 34.5847 |
| 71132 | NM_001042418.1 | calcium-binding tyrosine-(Y)-phosphorylation regulated (fibroushe | 0.1741 | 0.0000 | Inf |
| 14728 | NM_013532.2 | leukocyte immunoglobulin-like receptor, subfamily B, member 4 | 0.2769 | 0.0000 | Inf |
| 20310 | NM_009140.2 | chemokine (C-X-C motif) ligand 2 | 0.4951 | 0.0000 | Inf |
| 13982 | NM_007956.4 | estrogen receptor 1 (alpha) | 0.0662 | 0.0000 | Inf |
| 18126 | NM_010927.3 | nitric oxide synthase 2, inducible | 1.2452 | 0.0000 | Inf |
| 16365 | NM_008392.1 | immunoresponsive gene 1 | 0.1381 | 0.0000 | Inf |
| 15894 | NM_010493.2 | intercellular adhesion molecule 1 | 0.1407 | 0.0000 | Inf |
| 408066 | XR_035217.2 | cDNA sequence BC067074 | 0.0759 | 0.0000 | Inf |
| 100503281 | XR_108224.1 | - | 0.4655 | 0.0000 | Inf |

Supplementary Table 3 Differential expressed genes of MLL1-/- MEF cell with or without TNFα

| ID | ACCESSION NUMBER | NAME | TNF | Ctrl | FOLDCHANGE |
|---|---|---|---|---|---|
| 12695 | NM_001005787.1 | InaD-like (Drosophila) | 0.0000 | 0.1546 | 0.0000 |
| 100045736 | XM_001474842.2 | - | 0.0722 | 1.2501 | 0.0578 |
| 100039589 | XM_003084688.1 | predicted gene 2329 | 0.0722 | 1.1112 | 0.0650 |
| 380698 | NM_199152.2 | obscurin, cytoskeletal calmodulin and titin-interacting RhoGEF | 0.0023 | 0.0260 | 0.0867 |
| 245607 | NM_001163016.1 | G protein-coupled receptor associated sorting protein 2 | 0.0274 | 0.2769 | 0.0991 |
| 245607 | NM_001163017.1 | G protein-coupled receptor associated sorting protein 2 | 0.0275 | 0.2780 | 0.0991 |
| 245607 | NM_001163015.1 | G protein-coupled receptor associated sorting protein 2 | 0.0272 | 0.2742 | 0.0991 |
| 100503347 | XM_003086491.1 | predicted gene, 19648 | 0.0400 | 0.2308 | 0.1734 |
| 19784 | NR_004439.1 | ribonuclease P RNA-like 2 | 0.2223 | 1.2111 | 0.1836 |
| 24131 | NM_011918.4 | LIM domain binding 3 | 0.2466 | 0.6916 | 0.3566 |
| 24131 | NM_001039072.2 | LIM domain binding 3 | 0.2533 | 0.7001 | 0.3618 |
| 24131 | NM_001039071.2 | LIM domain binding 3 | 0.2561 | 0.7079 | 0.3618 |
| 24131 | NM_001039074.2 | LIM domain binding 3 | 0.2509 | 0.6936 | 0.3618 |
| 24131 | NM_001039073.2 | LIM domain binding 3 | 0.2624 | 0.7148 | 0.3671 |
| 19017 | NR_027710.1 | peroxisome proliferative activated receptor, gamma, coactivator 1 alpha | 0.1675 | 0.4523 | 0.3702 |
| 19017 | NM_008904.2 | peroxisome proliferative activated receptor, gamma, coactivator 1 alpha | 0.1683 | 0.4545 | 0.3702 |
| 11754 | NM_009675.2 | amine oxidase, copper containing 3 | 0.2003 | 0.5324 | 0.3762 |
| 100047224 | XM_003086950.1 | - | 1.6493 | 4.3521 | 0.3790 |
| 195727 | NM_001081052.1 | Nance-Horan syndrome (human) | 0.3465 | 0.7773 | 0.4458 |
| 223650 | NM_144848.2 | epiplakin 1 | 0.2347 | 0.5250 | 0.4471 |
| 668066 | XM_001004338.2 | predicted gene 14418 | 1.5995 | 3.4546 | 0.4630 |
| 243385 | NM_183183.2 | GPRIN family member 3 | 1.6040 | 3.3894 | 0.4732 |
| 244867 | NM_175535.3 | Rho GTPase activating protein 20 | 1.5055 | 3.0903 | 0.4872 |
| 625703 | XM_904090.4 | - | 1.7629 | 3.5234 | 0.5003 |
| 13838 | NM_007936.3 | Eph receptor A4 | 1.0641 | 2.1247 | 0.5008 |

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|---|---|---|---|---|---|
| 231861 | NM_178242.2 | trinucleotide repeat containing 18 | 3.0532 | 6.0066 | 0.5083 |
| 242481 | NM_172868.2 | paralemmin 2 | 1.5201 | 2.9836 | 0.5095 |
| 240427 | NM_053099.2 | SET binding protein 1 | 0.7680 | 1.4917 | 0.5149 |
| 66395 | NM_009643.1 | AHNAK nucleoprotein (desmoyokin) | 96.8238 | 183.5819 | 0.5274 |
| 67393 | NM_133687.2 | CXXC finger 5 | 2.4654 | 4.5681 | 0.5397 |
| 330938 | NM_178118.2 | DIX domain containing 1 | 6.9659 | 12.5231 | 0.5562 |
| 100503159 | XR_108047.1 | - | 6.5701 | 11.6379 | 0.5645 |
| 26408 | NM_008580.4 | mitogen-activated protein kinase kinase kinase 5 | 1.8536 | 3.2225 | 0.5752 |
| 231861 | NM_001122730.1 | trinucleotide repeat containing 18 | 3.9304 | 6.6259 | 0.5932 |
| 17309 | NM_010795.3 | mannoside acetylglucosaminyltransferase 3 | 5.4516 | 9.0626 | 0.6016 |
| 100042862 | XM_003085879.1 | predicted gene 4076 | 234.2826 | 388.2562 | 0.6034 |
| 100042862 | XM_001478943.2 | predicted gene 4076 | 246.8104 | 408.8011 | 0.6037 |
| 11630 | NM_172393.2 | absent in melanoma 1 | 11.4334 | 18.8011 | 0.6081 |
| 214137 | NM_172525.2 | Rho GTPase activating protein 29 | 6.1049 | 9.9728 | 0.6122 |
| 271564 | NM_173028.3 | vacuolar protein sorting 13A (yeast) | 3.3181 | 5.4093 | 0.6134 |
| 68861 | NM_001033145.2 | RIKEN cDNA 1190002N15 gene | 18.2794 | 28.9826 | 0.6307 |
| 77057 | NM_029858.2 | stonin 1 | 13.2659 | 20.9501 | 0.6332 |
| 54127 | NM_016844.2 | ribosomal protein S28 | 718.3538 | 452.7200 | 1.5868 |
| 667682 | XM_991853.3 | predicted gene 8759 | 1085.2008 | 683.1858 | 1.5884 |
| 14455 | NR_002840.2 | growth arrest specific 5 | 65.1405 | 40.7494 | 1.5986 |
| 671641 | XM_001479052.2 | predicted gene 10063 | 1981.0625 | 1234.7892 | 1.6044 |
| 100042561 | XM_003086748.1 | predicted gene 10177 | 175.4771 | 109.3654 | 1.6045 |
| 100042561 | XM_001478520.2 | predicted gene 10177 | 175.4771 | 109.3654 | 1.6045 |
| 100046297 | XM_001477362.2 | - | 703.1160 | 436.4319 | 1.6111 |
| 100043718 | XM_001480721.2 | predicted gene 4604 | 236.1249 | 146.3981 | 1.6129 |
| 14775 | NM_008160.5 | glutathione peroxidase 1 | 92.2788 | 57.2039 | 1.6132 |
| 12859 | NM_009942.2 | cytochrome c oxidase, subunit Vb | 141.0200 | 87.3991 | 1.6135 |
| 54217 | NM_018730.3 | ribosomal protein L36 | 284.0859 | 175.7512 | 1.6164 |
| 30055 | NM_013895.4 | translocase of inner mitochondrial membrane 13 homolog (yeast) | 59.4914 | 36.7882 | 1.6171 |

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|---|---|---|---|---|---|
| 635470 | XM_003086282.1 | predicted gene 14407 | 157.9373 | 97.5871 | 1.6184 |
| 100046079 | XM_001475417.2 | - | 166.5536 | 102.7729 | 1.6206 |
| 27370 | NM_013765.2 | ribosomal protein S26 | 1431.4740 | 881.8388 | 1.6233 |
| 67673 | NM_026305.2 | transcription elongation factor B (SIII), polypeptide 2 | 147.6390 | 90.6721 | 1.6283 |
| 665533 | XM_003086398.1 | predicted gene 13004 | 529.7444 | 324.9924 | 1.6300 |
| 665533 | XM_977600.2 | predicted gene 13004 | 529.7444 | 324.9924 | 1.6300 |
| 546695 | XM_003086080.1 | predicted gene, 16519 | 106.6450 | 65.3828 | 1.6311 |
| 545487 | XM_619852.4 | predicted gene 14439 | 156.3150 | 95.8047 | 1.6316 |
| 16206 | NM_008377.2 | leucine-rich repeats and immunoglobulin-like domains 1 | 49.2302 | 30.1324 | 1.6338 |
| 20335 | NM_011343.3 | SEC61, gamma subunit | 104.4851 | 63.9293 | 1.6344 |
| 19981 | NM_009084.4 | ribosomal protein L37a | 536.2309 | 328.0250 | 1.6347 |
| 18034 | NM_001177370.1 | nuclear factor of kappa light polypeptide gene enhancer in B-cells 2, p49/p100 | 74.7410 | 45.7093 | 1.6351 |
| 15980 | NM_008338.3 | interferon gamma receptor 2 | 35.3064 | 21.5783 | 1.6362 |
| 18034 | NM_001177369.1 | nuclear factor of kappa light polypeptide gene enhancer in B-cells 2, p49/p100 | 73.8610 | 45.0676 | 1.6389 |
| 18034 | NM_019408.3 | nuclear factor of kappa light polypeptide gene enhancer in B-cells 2, p49/p100 | 70.1387 | 42.7890 | 1.6392 |
| 72338 | NM_028203.1 | WD repeat domain 89 | 77.4768 | 47.2237 | 1.6406 |
| 57294 | NM_027015.4 | ribosomal protein S27 | 683.5674 | 415.9998 | 1.6432 |
| 100043813 | NM_001190258.1 | predicted gene 9846 | 676.2565 | 411.5506 | 1.6432 |
| 100048613 | XM_001480380.2 | - | 107.3612 | 65.2260 | 1.6460 |
| 67126 | NM_025983.3 | ATP synthase, H+ transporting, mitochondrial F1 complex, epsilon subunit | 97.9056 | 59.4226 | 1.6476 |
| 12857 | NM_009941.2 | cytochrome c oxidase subunit IV isoform 1 | 312.4543 | 189.3574 | 1.6501 |
| 27425 | NM_013795.5 | ATP synthase, H+ transporting, mitochondrial F0 complex, subunit g | 227.3541 | 137.6219 | 1.6520 |
| 100042348 | XM_001478455.2 | predicted gene 10221 | 234.8841 | 142.1616 | 1.6522 |
| 230075 | NM_001033305.2 | NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 6 | 89.4306 | 54.0857 | 1.6535 |
| 100503897 | XR_107153.1 | predicted gene, 19947 | 161.3130 | 97.2955 | 1.6580 |
| 100503897 | XR_105996.1 | predicted gene, 19947 | 161.3130 | 97.2955 | 1.6580 |

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|---|---|---|---|---|---|
| 69878 | NM_027246.1 | small nuclear ribonucleoprotein polypeptide F | 105.8570 | 63.8354 | 1.6583 |
| 17133 | NM_010755.3 | v-maf musculoaponeurotic fibrosarcoma oncogene family, protein F (avian) | 22.5600 | 13.5280 | 1.6677 |
| 12010 | NM_009735.3 | beta-2 microglobulin | 363.5380 | 217.7566 | 1.6695 |
| 99382 | NM_178890.3 | ankyrin repeat and BTB (POZ) domain containing 2 | 7.1917 | 4.3023 | 1.6716 |
| 12866 | NM_009945.3 | cytochrome c oxidase, subunit VIIa 2 | 156.6245 | 93.5164 | 1.6748 |
| 666642 | XM_985134.3 | predicted pseudogene 8210 | 93.1370 | 55.5507 | 1.6766 |
| 629750 | NR_033523.1 | predicted gene 11517 | 130.3621 | 77.7199 | 1.6773 |
| 13014 | NM_007793.3 | cystatin B | 234.4187 | 139.6702 | 1.6784 |
| 751556 | NR_030451.1 | microRNA 682 | 435.4102 | 259.3550 | 1.6788 |
| 100040259 | NM_001111330.1 | predicted pseudogene 16379 | 248.8759 | 147.5966 | 1.6862 |
| 57294 | NR_033727.1 | ribosomal protein S27 | 344.5862 | 204.2557 | 1.6870 |
| 192657 | NM_138953.2 | elongation factor RNA polymerase II 2 | 15.9917 | 9.4558 | 1.6912 |
| 66491 | NM_025593.1 | polymerase (RNA) II (DNA directed) polypeptide L | 17.0794 | 10.0725 | 1.6956 |
| 67945 | NM_018860.4 | ribosomal protein L41 | 2637.6470 | 1554.9638 | 1.6963 |
| 17392 | NM_010809.1 | matrix metallopeptidase 3 | 42.4850 | 24.9785 | 1.7009 |
| 233016 | NM_144923.3 | biliverdin reductase B (flavin reductase (NADPH)) | 32.8141 | 19.2852 | 1.7015 |
| 19944 | NM_009082.2 | ribosomal protein L29 | 110.8143 | 64.9454 | 1.7063 |
| 21929 | NM_001166402.1 | tumor necrosis factor, alpha-induced protein 3 | 9.5689 | 5.5609 | 1.7208 |
| 67184 | NM_023312.2 | NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 13 | 19.4337 | 11.2887 | 1.7215 |
| 20656 | NM_013671.3 | superoxide dismutase 2, mitochondrial | 29.2301 | 16.9286 | 1.7267 |
| 223881 | NM_172612.3 | Rho family GTPase 1 | 87.7922 | 50.8359 | 1.7270 |
| 21929 | NM_009397.3 | tumor necrosis factor, alpha-induced protein 3 | 9.4206 | 5.4543 | 1.7272 |
| 665964 | XM_980604.3 | predicted gene 7866 | 522.4457 | 302.1944 | 1.7288 |
| 22186 | NM_019883.3 | ubiquitin A-52 residue ribosomal protein fusion product 1 | 1030.7802 | 595.3682 | 1.7313 |
| 100039782 | XM_003086738.1 | predicted gene 10709 | 131.6384 | 76.0086 | 1.7319 |
| 665964 | XM_003086743.1 | predicted gene 7866 | 530.0628 | 305.8558 | 1.7330 |
| 11927 | NM_009720.2 | ATX1 (antioxidant protein 1) homolog 1 (yeast) | 63.5819 | 36.6762 | 1.7336 |
| 67916 | NM_080555.2 | phosphatidic acid phosphatase type 2B | 23.7194 | 13.6538 | 1.7372 |
| 17319 | NM_010798.2 | macrophage migration inhibitory factor | 600.4224 | 343.1800 | 1.7496 |

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|---|---|---|---|---|---|
| 230073 | NM_172689.3 | DEAD (Asp-Glu-Ala-Asp) box polypeptide 58 | 9.9966 | 5.7019 | 1.7532 |
| 20422 | NM_009169.2 | split hand/foot malformation (ectrodactyly) type 1 | 189.0396 | 107.7058 | 1.7551 |
| 629957 | XM_003086273.1 | predicted gene 14303 | 507.7795 | 289.1612 | 1.7560 |
| 100504654 | XR_105586.1 | predicted gene 10736 | 1840.2606 | 1046.0660 | 1.7592 |
| 100504654 | XR_105587.1 | predicted gene 10736 | 1911.2104 | 1086.3963 | 1.7592 |
| 100504654 | XR_106826.1 | predicted gene 10736 | 1778.6007 | 1010.8844 | 1.7595 |
| 100504654 | XR_106827.1 | predicted gene 10736 | 1844.7812 | 1048.4987 | 1.7595 |
| 100038969 | XM_001472037.2 | predicted gene 14958 | 1600.4838 | 908.9360 | 1.7608 |
| 626048 | XM_001473380.2 | predicted pseudogene 6646 | 1601.3925 | 908.9360 | 1.7618 |
| 100503567 | XM_003085762.1 | predicted gene 11694 | 209.1386 | 118.6965 | 1.7620 |
| 100503567 | XM_003085509.1 | predicted gene 11694 | 209.1386 | 118.6965 | 1.7620 |
| 434460 | XM_001477611.2 | predicted gene 5623 | 96.9986 | 54.7627 | 1.7713 |
| 434460 | XM_001477346.2 | predicted gene 5623 | 96.9986 | 54.7627 | 1.7713 |
| 20200 | NM_011313.2 | S100 calcium binding protein A6 (calcyclin) | 729.7546 | 411.8745 | 1.7718 |
| 67067 | NM_001164216.1 | reactive oxygen species modulator 1 | 41.9669 | 23.6771 | 1.7725 |
| 12864 | NM_053071.2 | cytochrome c oxidase, subunit VIc | 211.6069 | 119.3407 | 1.7731 |
| 665032 | XM_974069.2 | predicted gene 13841 | 123.4288 | 69.4725 | 1.7767 |
| 665032 | XM_991641.2 | predicted gene 13841 | 123.1820 | 69.3078 | 1.7773 |
| 66379 | NM_183256.3 | RIKEN cDNA 2310016M24 gene | 34.5307 | 19.4212 | 1.7780 |
| 434843 | XM_486761.5 | predicted pseudogene 5642 | 1693.9502 | 952.3672 | 1.7787 |
| 665463 | XM_977110.3 | predicted pseudogene 7643 | 1693.9502 | 952.3672 | 1.7787 |
| 665611 | XM_978135.3 | predicted pseudogene 7711 | 1693.9502 | 952.3672 | 1.7787 |
| 665522 | XM_977540.3 | predicted pseudogene 7671 | 1693.9502 | 952.3672 | 1.7787 |
| 665579 | XM_977918.3 | predicted pseudogene 7698 | 1693.9502 | 952.3672 | 1.7787 |
| 665032 | XM_003085349.1 | predicted gene 13841 | 123.6729 | 69.4848 | 1.7799 |
| 665032 | XM_003086489.1 | predicted gene 13841 | 123.4220 | 69.3181 | 1.7805 |
| 382265 | XM_356374.5 | predicted gene 5167 | 99.8413 | 56.0350 | 1.7818 |
| 100043714 | XM_003086243.1 | predicted pseudogene 10774 | 55.6842 | 31.2394 | 1.7825 |
| 100043714 | XM_001480774.2 | predicted pseudogene 10774 | 55.6842 | 31.2394 | 1.7825 |
| 629957 | XM_894924.4 | predicted gene 14303 | 818.9727 | 458.8247 | 1.7849 |

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|---|---|---|---|---|---|
| 54405 | NM_019443.2 | NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 1 | 40.6538 | 22.7750 | 1.7850 |
| 20198 | NM_011311.2 | S100 calcium binding protein A4 | 2385.4436 | 1331.7804 | 1.7912 |
| 17991 | NM_010885.4 | NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 2 | 116.5165 | 64.9515 | 1.7939 |
| 66142 | NM_025379.2 | cytochrome c oxidase subunit VIIb | 88.5289 | 49.2034 | 1.7992 |
| 100039782 | XM_001473311.2 | predicted gene 10709 | 98.9061 | 54.9447 | 1.8001 |
| 13198 | NM_007837.3 | DNA-damage inducible transcript 3 | 21.3312 | 11.8400 | 1.8016 |
| 11839 | NM_009704.3 | amphiregulin | 13.9534 | 7.7248 | 1.8063 |
| 319238 | XR_107318.1 | RIKEN cDNA 9330123L03 gene | 5.1955 | 2.8542 | 1.8203 |
| 20090 | NM_009093.2 | ribosomal protein S29 | 601.5951 | 330.0521 | 1.8227 |
| 433941 | XM_003086189.1 | predicted gene 5561 | 108.9998 | 59.7879 | 1.8231 |
| 433941 | XM_001478364.2 | predicted gene 5561 | 108.9998 | 59.7879 | 1.8231 |
| 56187 | NM_019519.2 | Rab geranylgeranyl transferase, a subunit | 6.1415 | 3.3628 | 1.8263 |
| 100503055 | XM_003085327.1 | - | 50.2746 | 27.5242 | 1.8266 |
| 100043718 | XM_003086523.1 | predicted gene 4604 | 237.7590 | 130.0606 | 1.8281 |
| 320415 | NM_177157.4 | GTP cyclohydrolase I feedback regulator | 84.2406 | 46.0753 | 1.8283 |
| 11983 | NM_007512.3 | ATPase inhibitory factor 1 | 56.6753 | 30.9422 | 1.8317 |
| 622707 | XM_001475711.2 | predicted gene 6344 | 71.2296 | 38.8333 | 1.8342 |
| 102644 | NM_178644.3 | OAF homolog (Drosophila) | 35.9188 | 19.5807 | 1.8344 |
| 17873 | NM_008655.1 | growth arrest and DNA-damage-inducible 45 beta | 19.2499 | 10.4934 | 1.8345 |
| 66169 | NM_025394.3 | translocase of outer mitochondrial membrane 7 homolog (yeast) | 68.1720 | 36.9712 | 1.8439 |
| 68949 | NM_001081005.1 | RIKEN cDNA 1500012F01 gene | 60.4516 | 32.7572 | 1.8454 |
| 72655 | XM_986352.2 | small nucleolar RNA host gene 5 | 46.3329 | 25.0715 | 1.8480 |
| 217344 | NM_172572.3 | rhomboid 5 homolog 2 (Drosophila) | 4.4054 | 2.3712 | 1.8578 |
| 13197 | NM_007836.1 | growth arrest and DNA-damage-inducible 45 alpha | 9.3944 | 5.0447 | 1.8622 |
| 66915 | NR_028108.1 | myeloma overexpressed 2 | 27.9426 | 15.0044 | 1.8623 |
| 217344 | NM_001167680.1 | rhomboid 5 homolog 2 (Drosophila) | 4.6732 | 2.5079 | 1.8634 |
| 72655 | XM_925560.3 | small nucleolar RNA host gene 5 | 46.0753 | 24.7247 | 1.8635 |
| 12609 | NM_007679.4 | CCAAT/enhancer binding protein (C/EBP), delta | 11.3447 | 6.0813 | 1.8655 |
| 69920 | NM_027259.1 | polymerase (RNA) II (DNA directed) polypeptide I | 22.6379 | 12.1145 | 1.8687 |

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|---|---|---|---|---|---|
| 18036 | NM_010908.4 | nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, beta | 11.1049 | 5.9397 | 1.8696 |
| 20308 | NM_011338.2 | chemokine (C-C motif) ligand 9 | 17.4949 | 9.3368 | 1.8738 |
| 100503653 | XR_104731.1 | predicted gene 14036 | 102.2717 | 54.5805 | 1.8738 |
| 13167 | NM_007830.4 | diazepam binding inhibitor | 152.6526 | 81.3535 | 1.8764 |
| 14790 | NM_013535.1 | gene rich cluster, C10 gene | 20.6090 | 10.9587 | 1.8806 |
| 66915 | NM_001163425.1 | myeloma overexpressed 2 | 47.8378 | 25.2243 | 1.8965 |
| 68040 | NM_024215.2 | zinc finger protein 593 | 5.6453 | 2.9763 | 1.8968 |
| 17384 | NM_019471.2 | matrix metallopeptidase 10 | 36.3866 | 19.1835 | 1.8968 |
| 66481 | NM_025587.2 | ribosomal protein S21 | 735.2156 | 386.8005 | 1.9008 |
| 69895 | NR_028574.1 | small nucleolar RNA host gene 8 | 27.6465 | 14.5265 | 1.9032 |
| 83673 | NR_002896.3 | small nucleolar RNA host gene (non-protein coding) 1 | 128.6195 | 67.4759 | 1.9062 |
| 18049 | NM_013609.2 | nerve growth factor | 16.0144 | 8.3903 | 1.9087 |
| 22272 | NM_025352.2 | ubiquinol-cytochrome c reductase, complex III subunit VII | 90.2122 | 47.2625 | 1.9087 |
| 30059 | NM_013899.2 | translocase of inner mitochondrial membrane 10 homolog (yeast) | 56.7326 | 29.7171 | 1.9091 |
| 100041286 | XR_106636.1 | predicted gene 11974 | 25.8980 | 13.5425 | 1.9123 |
| 100041286 | XR_105435.1 | predicted gene 11974 | 25.8980 | 13.5425 | 1.9123 |
| 74732 | NM_001163590.1 | syntaxin 11 | 7.2620 | 3.7881 | 1.9170 |
| 100504319 | XM_003086228.1 | - | 207.0361 | 107.9865 | 1.9172 |
| 100504319 | XM_003084494.1 | - | 207.0361 | 107.9865 | 1.9172 |
| 100503669 | XM_003086525.1 | - | 83.2977 | 43.3896 | 1.9198 |
| 100503669 | XM_003084644.1 | - | 83.2977 | 43.3896 | 1.9198 |
| 13167 | NM_001037999.2 | diazepam binding inhibitor | 135.1238 | 70.3696 | 1.9202 |
| 74732 | NM_001163591.1 | syntaxin 11 | 7.5787 | 3.9447 | 1.9212 |
| 20568 | NM_011414.3 | secretory leukocyte peptidase inhibitor | 83.3139 | 43.3349 | 1.9226 |
| 80859 | NM_030612.3 | nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, zeta | 3.9502 | 2.0538 | 1.9233 |
| 19698 | NM_009046.2 | avian reticuloendotheliosis viral (v-rel) oncogene related B | 14.7822 | 7.6782 | 1.9252 |
| 100041859 | XM_003086090.1 | predicted gene 3550 | 55.8534 | 28.9648 | 1.9283 |
| 100041859 | XM_001477476.2 | predicted gene 3550 | 55.8534 | 28.9648 | 1.9283 |

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|---|---|---|---|---|---|
| 22038 | NM_011636.2 | phospholipid scramblase 1 | 49.7638 | 25.7935 | 1.9293 |
| 15040 | NM_010398.3 | histocompatibility 2, T region locus 23 | 10.7368 | 5.5581 | 1.9317 |
| 68763 | NR_015536.1 | RIKEN cDNA 1110038B12 gene | 160.2223 | 82.5510 | 1.9409 |
| 18049 | NM_001112698.1 | nerve growth factor | 18.6172 | 9.5834 | 1.9427 |
| 74732 | NM_029075.1 | syntaxin 11 | 7.0690 | 3.6370 | 1.9436 |
| 80859 | NM_001159395.1 | nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, zeta | 4.3422 | 2.2293 | 1.9478 |
| 100503826 | XR_107649.1 | predicted gene 13075 | 22.0599 | 11.3206 | 1.9487 |
| 100503826 | XR_104900.1 | predicted gene 13075 | 22.0599 | 11.3206 | 1.9487 |
| 66141 | NM_025378.2 | interferon induced transmembrane protein 3 | 157.5462 | 80.6882 | 1.9525 |
| 80859 | NM_001159394.1 | nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, zeta | 4.1437 | 2.1155 | 1.9587 |
| 68763 | NR_027943.1 | RIKEN cDNA 1110038B12 gene | 142.2872 | 72.5673 | 1.9608 |
| 12578 | NM_001040654.1 | cyclin-dependent kinase inhibitor 2A | 33.7588 | 17.1650 | 1.9667 |
| 100045766 | XM_001474415.2 | predicted gene 10126 | 123.5835 | 62.6092 | 1.9739 |
| 100045766 | XM_003084933.1 | predicted gene 10126 | 123.5835 | 62.6092 | 1.9739 |
| 434394 | XM_915072.3 | predicted gene 5614 | 78.8342 | 39.9309 | 1.9743 |
| 436081 | XM_001004069.3 | predicted gene 5745 | 26.9668 | 13.5951 | 1.9836 |
| 436081 | XM_488179.5 | predicted gene 5745 | 26.9668 | 13.5951 | 1.9836 |
| 100503585 | XM_003086438.1 | - | 334.0994 | 168.0256 | 1.9884 |
| 100503585 | XM_003084617.1 | - | 334.0994 | 168.0256 | 1.9884 |
| 12578 | NM_009877.2 | cyclin-dependent kinase inhibitor 2A | 34.1776 | 17.0990 | 1.9988 |
| 381155 | XR_035375.1 | RIKEN cDNA 9630014M24 gene | 3.0137 | 1.5066 | 2.0003 |
| 66293 | NR_027819.1 | RIKEN cDNA 1810032008 gene | 8.9850 | 4.4602 | 2.0145 |
| 11435 | NM_007389.4 | cholinergic receptor, nicotinic, alpha polypeptide 1 (muscle) | 1.8119 | 0.8826 | 2.0529 |
| 100504928 | XR_106975.1 | - | 1.9112 | 0.9253 | 2.0655 |
| 230738 | NM_153159.2 | zinc finger CCCH type containing 12A | 6.5553 | 3.1600 | 2.0745 |
| 108153 | NM_001003911.2 | a disintegrin-like and metallopeptidase (reprolysin type) with thrombospondin type 1 motif, 7 | 4.0967 | 1.9739 | 2.0755 |
| 320207 | NM_177320.2 | phosphoinositide-3-kinase, regulatory subunit 5, p101 | 15.2432 | 7.3159 | 2.0836 |
| 19260 | NM_008979.1 | protein tyrosine phosphatase, non-receptor type 22 (lymphoid) | 6.3087 | 2.9870 | 2.1120 |

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|---|---|---|---|---|---|
| 668092 | XM_994269.1 | predicted gene 8973 | 58.7021 | 27.6645 | 2.1219 |
| 15937 | NM_133662.2 | immediate early response 3 | 58.4487 | 27.5021 | 2.1252 |
| 434394 | XM_486208.5 | predicted gene 5614 | 73.9478 | 34.7634 | 2.1272 |
| 76964 | NM_029816.2 | RIKEN cDNA 2610028H24 gene | 3.8487 | 1.8077 | 2.1291 |
| 12916 | NM_001110853.1 | cAMP responsive element modulator | 2.4338 | 1.1359 | 2.1427 |
| 12916 | NM_001110857.1 | cAMP responsive element modulator | 2.2933 | 1.0690 | 2.1453 |
| 72275 | NM_028179.1 | RIKEN cDNA 2200002D01 gene | 25.1042 | 11.6382 | 2.1571 |
| 56695 | NM_025580.2 | paroxysmal nonkinesiogenic dyskinesia | 8.5520 | 3.9558 | 2.1619 |
| 668092 | XM_003085977.1 | predicted gene 8973 | 58.2089 | 26.8741 | 2.1660 |
| 100504742 | XM_003086332.1 | - | 117.6074 | 52.9206 | 2.2223 |
| 18037 | NM_008690.3 | nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, epsilon | 18.0281 | 8.0801 | 2.2312 |
| 12856 | NM_001017429.2 | cytochrome c oxidase, subunit XVII assembly protein homolog (yeast) | 25.4228 | 11.3069 | 2.2484 |
| 66594 | NM_025650.2 | ubiquinol-cytochrome c reductase, complex III subunit XI | 101.8100 | 44.6566 | 2.2798 |
| 57783 | NM_021327.2 | TNFAIP3 interacting protein 1 | 43.2784 | 18.8918 | 2.2909 |
| 18788 | NM_011111.4 | serine (or cysteine) peptidase inhibitor, clade B, member 2 | 5.7035 | 2.4563 | 2.3220 |
| 20361 | NM_011352.2 | sema domain, immunoglobulin domain (Ig), and GPI membrane anchor, (semaphorin) 7A | 3.0227 | 1.3017 | 2.3222 |
| 18788 | NM_001174170.1 | serine (or cysteine) peptidase inhibitor, clade B, member 2 | 5.7580 | 2.4547 | 2.3457 |
| 546663 | XM_915258.4 | predicted pseudogene 5963 | 278.1877 | 118.0584 | 2.3564 |
| 546663 | XM_001002128.3 | predicted pseudogene 5963 | 278.1877 | 118.0584 | 2.3564 |
| 545551 | NR_033629.1 | cDNA sequence BC021767 | 1.5344 | 0.6482 | 2.3673 |
| 100504629 | XM_003086098.1 | predicted gene, 17669 | 12.2776 | 5.1640 | 2.3775 |
| 319689 | XM_003086426.1 | predicted gene, 17739 | 1.6810 | 0.7050 | 2.3844 |
| 319689 | XM_003084614.1 | predicted gene, 17739 | 1.6810 | 0.7050 | 2.3844 |
| 12051 | NM_033601.3 | B-cell leukemia/lymphoma 3 | 4.2058 | 1.7639 | 2.3844 |
| 100503758 | XR_106535.1 | predicted gene, 19876 | 75.6369 | 31.6424 | 2.3904 |
| 100503758 | XR_105417.1 | predicted gene, 19876 | 75.6369 | 31.6424 | 2.3904 |
| 26434 | NM_023043.2 | prion protein dublet | 1.4915 | 0.6234 | 2.3924 |
| 17748 | NM_013602.3 | metallothionein 1 | 125.7142 | 52.4440 | 2.3971 |

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|---|---|---|---|---|---|
| 69221 | NR_030738.1 | RIKEN cDNA 2410006H16 gene | 63.5934 | 26.4643 | 2.4030 |
| 257632 | NM_145857.2 | nucleotide-binding oligomerization domain containing 2 | 1.7822 | 0.7220 | 2.4684 |
| 18035 | NM_010907.2 | nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha | 54.3012 | 21.8327 | 2.4871 |
| 16193 | NM_031168.1 | interleukin 6 | 2.7637 | 1.0995 | 2.5137 |
| 16878 | NM_001039537.1 | leukemia inhibitory factor | 9.2464 | 3.6711 | 2.5187 |
| 233552 | NM_201352.2 | glycerophosphodiester phosphodiesterase domain containing 5 | 3.5449 | 1.4074 | 2.5188 |
| 17395 | NM_013599.2 | matrix metallopeptidase 9 | 1.1058 | 0.4378 | 2.5261 |
| 16878 | NM_008501.2 | leukemia inhibitory factor | 8.9014 | 3.5099 | 2.5361 |
| 110332 | NM_173449.3 | RIKEN cDNA 4921523A10 gene | 1.8618 | 0.7240 | 2.5715 |
| 20306 | NM_013654.3 | chemokine (C-C motif) ligand 7 | 144.0293 | 55.3655 | 2.6014 |
| 69749 | XR_107112.1 | RIKEN cDNA 2410004N09 gene | 15.6704 | 5.9801 | 2.6204 |
| 69749 | XR_105940.1 | RIKEN cDNA 2410004N09 gene | 15.6704 | 5.9801 | 2.6204 |
| 26434 | NM_001126338.1 | prion protein dublet | 1.7468 | 0.6616 | 2.6404 |
| 11796 | NM_007464.3 | baculoviral IAP repeat-containing 3 | 2.7367 | 1.0242 | 2.6721 |
| 17750 | NM_008630.2 | metallothionein 2 | 39.0333 | 14.5985 | 2.6738 |
| 12363 | NM_007609.2 | caspase 4, apoptosis-related cysteine peptidase | 4.9157 | 1.8070 | 2.7204 |
| 56489 | NM_019777.3 | inhibitor of kappaB kinase epsilon | 10.8508 | 3.9800 | 2.7264 |
| 17386 | NM_008607.2 | matrix metallopeptidase 13 | 8.4810 | 3.0902 | 2.7445 |
| 74013 | NM_028713.1 | raftlin family member 2 | 0.7582 | 0.2700 | 2.8084 |
| 14727 | NM_008147.1 | glycoprotein 49 A | 3.6912 | 1.2974 | 2.8451 |
| 20296 | NM_011333.3 | chemokine (C-C motif) ligand 2 | 752.1989 | 255.4061 | 2.9451 |
| 57875 | NM_020581.2 | angiopoietin-like 4 | 1.7842 | 0.5978 | 2.9848 |
| 227659 | NM_001177627.1 | solute carrier family 2 (facilitated glucose transporter), member 6 | 2.6249 | 0.8495 | 3.0899 |
| 76773 | NM_029734.1 | WDYHV motif containing 1 | 8.4159 | 2.7215 | 3.0924 |
| 22329 | NM_011693.3 | vascular cell adhesion molecule 1 | 58.3048 | 18.8018 | 3.1010 |
| 22029 | NM_009421.3 | TNF receptor-associated factor 1 | 17.6218 | 5.5043 | 3.2014 |
| 24088 | NM_011905.3 | toll-like receptor 2 | 4.2713 | 1.3168 | 3.2437 |
| 751530 | NR_030494.1 | - | 48.9708 | 14.9388 | 3.2781 |

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|---|---|---|---|---|---|
| 227659 | NM_172659.2 | solute carrier family 2 (facilitated glucose transporter), member 6 | 2.9099 | 0.8859 | 3.2847 |
| 75614 | XR_105882.1 | RIKEN cDNA 2610019E17 gene | 6.6720 | 2.0256 | 3.2938 |
| 414084 | NM_001001495.2 | TNFAIP3 interacting protein 3 | 6.7889 | 2.0214 | 3.3584 |
| 100217453 | NR_028548.1 | small nucleolar RNA, C/D box 16A | 18.7832 | 5.4721 | 3.4325 |
| 14468 | NM_010259.2 | guanylate binding protein 1 | 1.7816 | 0.5121 | 3.4792 |
| 16149 | NM_010545.3 | CD74 antigen (invariant polypeptide of major histocompatibility complex, class II antigen-associated) | 1.1287 | 0.3215 | 3.5105 |
| 14102 | NM_007987.2 | Fas (TNF receptor superfamily member 6) | 13.0013 | 3.6861 | 3.5271 |
| 14728 | NM_013532.2 | leukocyte immunoglobulin-like receptor, subfamily B, member 4 | 6.6386 | 1.8586 | 3.5719 |
| 16819 | NM_008491.1 | lipocalin 2 | 7.4081 | 2.0432 | 3.6257 |
| 14469 | NM_010260.1 | guanylate binding protein 2 | 2.7460 | 0.6852 | 4.0077 |
| 14528 | NM_008102.3 | GTP cyclohydrolase 1 | 1.8177 | 0.4504 | 4.0358 |
| 103142 | NM_153133.2 | retinol dehydrogenase 9 | 0.4608 | 0.1107 | 4.1606 |
| 100047734 | XM_003086912.1 | - | 2.0998 | 0.4282 | 4.9036 |
| 408066 | XR_035217.2 | cDNA sequence BC067074 | 0.1158 | 0.0223 | 5.2008 |
| 408066 | XR_001629.2 | cDNA sequence BC067074 | 0.1333 | 0.0244 | 5.4608 |
| 15945 | NM_021274.1 | chemokine (C-X-C motif) ligand 10 | 3.9956 | 0.7027 | 5.6862 |
| 24108 | NM_023137.3 | ubiquitin D | 1.2580 | 0.2103 | 5.9809 |
| 20311 | NM_009141.2 | chemokine (C-X-C motif) ligand 5 | 14.5530 | 1.9858 | 7.3284 |
| 14825 | NM_008176.3 | chemokine (C-X-C motif) ligand 1 | 67.9688 | 9.1431 | 7.4339 |
| 20297 | NM_001159738.1 | chemokine (C-C motif) ligand 20 | 2.3793 | 0.2933 | 8.1133 |
| 20297 | NM_016960.2 | chemokine (C-C motif) ligand 20 | 2.4925 | 0.2922 | 8.5293 |
| 80287 | NM_030255.3 | apolipoprotein B mRNA editing enzyme, catalytic polypeptide 3 | 0.7682 | 0.0844 | 9.1014 |
| 80287 | NM_001160415.1 | apolipoprotein B mRNA editing enzyme, catalytic polypeptide 3 | 0.7372 | 0.0810 | 9.1014 |
| 55932 | NM_018734.3 | guanylate binding protein 3 | 0.9028 | 0.0755 | 11.9618 |
| 73474 | NR_027900.2 | small nucleolar RNA host gene (non-protein coding) 9 | 3.6795 | 0.2721 | 13.5221 |
| 434775 | XR_001556.2 | predicted gene 5636 | 0.2217 | 0.0142 | 15.6024 |
| 20210 | NM_011315.3 | serum amyloid A 3 | 2.6337 | 0.0000 | Inf |
| 18606 | NM_001136077.1 | ectonucleotide pyrophosphatase/phosphodiesterase 2 | 0.2264 | 0.0000 | Inf |

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|---|---|---|---|---|---|
| 16069 | NM_152839.3 | immunoglobulin joining chain | 0.2944 | 0.0000 | Inf |
| 630294 | NM_001177467.1 | predicted gene 7030 | 0.4033 | 0.0000 | Inf |
| 399570 | XR_104919.1 | RIKEN cDNA A730085A09 gene | 0.1518 | 0.0000 | Inf |
| 229320 | NM_153385.2 | clarin 1 | 0.3093 | 0.0000 | Inf |
| 229320 | NM_153384.2 | clarin 1 | 0.3005 | 0.0000 | Inf |
| 229320 | NM_153386.2 | clarin 1 | 0.3428 | 0.0000 | Inf |
| 12642 | NM_009890.1 | cholesterol 25-hydroxylase | 0.4174 | 0.0000 | Inf |