

# ATF2 – at the crossroad of nuclear and cytosolic functions

Eric Lau\* and Ze'ev A. Ronai\*

Signal Transduction Program, Sanford-Burnham Medical Research Institute, 10901 N. Torrey Pines Rd, La Jolla, CA 92130, USA

\*Authors for correspondence: ([elau@sbmri.org](mailto:elau@sbmri.org); [ronai@sbmri.org](mailto:ronai@sbmri.org))

*Journal of Cell Science* 125, 2815–2824  
© 2012. Published by The Company of Biologists Ltd  
doi: 10.1242/jcs.095000

## Summary

An increasing number of transcription factors have been shown to elicit oncogenic and tumor suppressor activities, depending on the tissue and cell context. Activating transcription factor 2 (ATF2; also known as cAMP-dependent transcription factor ATF-2) has oncogenic activities in melanoma and tumor suppressor activities in non-malignant skin tumors and breast cancer. Recent work has shown that the opposing functions of ATF2 are associated with its subcellular localization. In the nucleus, ATF2 contributes to global transcription and the DNA damage response, in addition to specific transcriptional activities that are related to cell development, proliferation and death. ATF2 can also translocate to the cytosol, primarily following exposure to severe genotoxic stress, where it impairs mitochondrial membrane potential and promotes mitochondrial-based cell death. Notably, phosphorylation of ATF2 by the epsilon isoform of protein kinase C (PKC $\epsilon$ ) is the master switch that controls its subcellular localization and function. Here, we summarize our current understanding of the regulation and function of ATF2 in both subcellular compartments. This mechanism of control of a non-genetically modified transcription factor represents a novel paradigm for ‘oncogene addiction’.

**Key words:** ATF2, Transcription, DNA damage, Mitochondria, Melanoma, Skin cancer, JNK, p38 MAPK, PKC

## Introduction

The activating transcription factor (ATF; also known as cAMP-dependent transcription factor) and cAMP-response-element-binding (CREB) families of transcription factors comprise 16 members of the activator protein 1 (AP1) transcription factor superfamily. ATF and CREB proteins can homodimerize or heterodimerize with members of the Jun, Fos or Maf transcription factor families to form complexes that regulate diverse cellular functions, such as stress responses, embryonic development, disease development and cell death (Lopez-Bergami et al., 2010). ATF2 requires phosphorylation by Jun N-terminal kinase (JNK), p38 (MAPK14), or extracellular-signal-regulated kinase 1 (ERK1) in order to be transcriptionally active. After its activation following stress and cytokine stimuli, ATF2 contributes to the cellular responses to hypoxic or osmotic stress, DNA damage, viral infection and cell death (Bhoumik et al., 2007; Choi et al., 2009; Merika et al., 1998; Wang et al., 2011). The precise transcriptional output of ATF2 is dictated by its dimerization partners, which are predominantly members of the AP-1 family. The importance of the transcriptional activity of ATF2 has been demonstrated in organismal development of several genetic models (see Box 1).

Although there are no reports of genetic changes in ATF2, altered ATF2 expression and/or activity have been implicated in several pathological conditions, including neurological diseases and cancer (Chen et al., 2008; Pearson et al., 2005; Reimold et al., 1996; Yamada et al., 1997). Intriguingly, ATF2 can elicit oncogenic or tumor suppressor activities depending on the tissue or cell type; earlier work has associated these functions with its nuclear or cytoplasmic localization (Berger et al., 2003; Bhoumik et al., 2008a). Although the mechanisms underlying these

opposing activities are being elucidated, recent studies reveal that ATF2 also has transcription-independent functions in the DNA damage response, chromatin remodeling and mitochondrial membrane organization, thereby highlighting the diverse location-dependent functions of this protein (Bhoumik et al., 2008b; Bhoumik et al., 2005; Cho et al., 2001; Lau et al., 2012). In this Commentary, we summarize our current understanding of the functions of ATF2 and the link between its subcellular localization and oncogenic or tumor suppressor activities.

## Regulation of ATF2

The *ATF2* gene is located on chromosome 2q32 and encodes a 505-amino-acid protein, which is ubiquitously expressed, with more abundant expression in the brain (Kara et al., 1990; Takeda et al., 1991). Although the existence of numerous truncated ATF2 isoforms is predicted on the basis of splice variation (Box 2), only full-length ATF2 has been extensively studied to date. Similar to other AP-1 transcription factors, the ATF2 protein contains a basic leucine zipper (bZIP) domain within its C-terminus (amino acids 350–414) that enables homo- or hetero-dimerization. The bZIP domain contains nuclear localization and export sequences that facilitate trafficking of ATF2 to and from the nucleus; the latter function is regulated by exportin-1 (Liu et al., 2006). ATF2 also contains an N-terminal zinc finger region and a transactivation domain, which regulates its transcriptional activity (Nagadoi et al., 1999) through an intramolecular autoinhibitory interaction (Li and Green, 1996). Phosphorylation of the N-terminal residues Thr69 and Thr71 in response to mitogenic or stress signals is required to relieve this intramolecular interaction, which enables ATF2 dimerization and subsequent transcriptional activity (Gupta et al., 1995; Li and Green, 1996; Livingstone et al., 1995).

**Box 1. Loss of ATF2 function in murine models**

A number of somatic and tissue-specific knockout mouse models have been used to examine the effects of loss of ATF2 function. The targeted disruption of the *Atf2* gene, inducing complete somatic loss of ATF2, results in postnatal lethality that is associated with severe respiratory defects and meconium aspiration syndrome (Ackermann et al., 2011; Maekawa et al., 1999). In this murine model, the reduced levels of PDGFR $\alpha$  protein and cytrophoblast cell populations that are detected in the knockout placenta are attributed to neonatal respiratory distress and lethality. Another murine model, which targets the disruption of the *Atf2* gene by the introduction of a mutation at position +826 relative to the transcription start site, produces similar postnatal lethality. Detailed characterization of mutant pups found that they exhibited severe neurological and skeletal defects, including a 50% loss of Purkinje cell populations in the cerebellar molecular-granular layer, overt skeletal dwarfism and hypochondroplasia (Reimold et al., 1996). These findings demonstrate the crucial role that ATF2 plays in development and highlight its particular functional involvement in placental, neuronal and skeletal tissues. These phenotypes appear to be specific for ATF2, despite the fact that ATF2 requires dimerization with other AP1 transcription factors, such as Jun, for transcriptional activities [note: somatic loss of *Jun* in knockout mice results in distinctly different consequences, including midgestational lethality and specific impaired hepatogenesis (Hilberg et al., 1993; Johnson et al., 1993)]. A transgenic mouse expressing ATF2 where Thr69 or Thr71 (the required phosphorylation sites for transcriptional activity) is replaced by an alanine residue exhibits a similar lethality and cyanotic phenotype to the somatic knockout model (Maekawa et al., 1999), indicating that phosphorylation and transcriptional activation of ATF2 is also crucial for viability and development (Breitwieser et al., 2007).

Tissue-specific ablation of *Atf2* has illustrated the requirements for ATF2 in individual tissue types. Neuronal-specific deletion of *Atf2*, mediated by nestin-driven Cre, results in embryonic cranial motor neuron degeneration, specifically in the hypoglossal, abducens and facial nuclei regions (Ackermann et al., 2011). In terms of disease models, work from our laboratory has demonstrated that the melanocyte-specific expression of a transcriptionally inactive ATF2, mediated by tyrosinase-driven Cre, is sufficient to block melanoma development in the *Nras<sup>(Q61K)</sup>*::Ink4A<sup>-/-</sup> (Ink4A is also known as *Cdkn2a*) murine melanoma model (Shah et al., 2010). By contrast, expression of transcriptionally inactive ATF2 in the keratinocytes of the DMBA-TPA-induced [7,12-dimethylbenz(a)anthracene and 12-O-tetradecanoylphorbol-13-acetate, respectively] murine skin cancer model increases the number and size of skin papilloma, as well as their formation rate (Bhoumik et al., 2008a). Expression of transcriptionally inactive ATF2 in mammary tissues bearing a mutant p53 also accelerates tumor development (Maekawa et al., 2007).

**Post-translational regulation of ATF2**

A number of upstream kinases activate ATF2 by direct phosphorylation, including mitogen-activated protein kinases (MAPKs), such as ERK1, and stress-activated protein kinases (SAPKs) (Fig. 1). Correspondingly, the two major kinases that phosphorylate ATF2 on Thr69 and Thr71 are the SAPKs JNK and p38 (Gupta et al., 1995; Livingstone et al., 1995; van Dam et al., 1995). A role for the MAPK ERK in Thr71 phosphorylation of ATF2 has also been proposed (Ouwens et al., 2002). Phosphorylation of ATF2 by these kinases occurs within minutes of the stress stimulus, rendering ATF2 an ‘early response’ protein. Later on in the stress response, ATF2 can be phosphorylated on Ser121 by several protein kinase C (PKC) isoforms (including  $\alpha$ ,  $\beta$ I,  $\beta$ II and  $\gamma$ ) (Yamasaki et al., 2009), which promotes cooperation

between ATF2 and Jun, activating transcription. Recently, our laboratory reported that PKC $\epsilon$  phosphorylates ATF2 on Thr52, which promotes its nuclear retention and transcriptional activity (Lau et al., 2012). ATF2 is also phosphorylated by ataxia-telangiectasia mutated (ATM) kinase (Fig. 1), which mediates its transcription-independent role in the DNA damage response (Bhoumik et al., 2005).

In addition to being phosphorylated, ATF2 is also acetylated on Lys357 and Lys374 by p300/CREB-binding protein (CBP, also known as CREBBP), which contributes to its transcriptional activity (Karanam et al., 2007). Binding of ATF2 suppresses the acetyltransferase activity of the transcriptional coactivator p300/CBP. Notably, the relationship between acetylation and phosphorylation of ATF2, in the context of its transcriptional activities, has yet to be elucidated.

**Regulation of ATF2 transcription**

Little is known of the transcriptional control of *ATF2*. The putative minimal *ATF2* promoter is composed of one cyclic AMP response element (CRE) and three Sp1 elements located between positions –50 and +90 relative to the transcription start site (Nagase et al., 1990). To date, these elements have been associated with the activities of E2F4 transcription factor and biliverdin IX $\alpha$  reductase (Cam et al., 2004; Kravets et al., 2004). Further scanning of the promoter using the ECR Browser (<http://ecrbrowser.dcode.org/>) reveals the presence of conserved regulatory elements that are potentially recognized by transcription factors, such as AP2 $\alpha$ , AP4, the Sox family members 1, 5 and 9, androgen receptor, and transcriptional coactivator CCAT/enhancer-binding protein (C/EBP), which suggests that *ATF2* transcription is likely to be regulated by diverse signaling pathways and to be dependent on cellular context. ATF2 protein expression increases as cells transit from G1 through the S phase of the cell cycle (Shimizu et al., 1998). Dynamic temporal and spatial regulation of ATF2 expression has been demonstrated during blastulation and gastrulation of *Xenopus laevis* (Villareal and Richter, 1995). Transcription of *ATF2* is also induced by viral proteins, as has been shown for the Epstein–Barr viral nuclear antigen 1 (EBNA1) (O’Neil et al., 2008). EBNA1 binds to the *ATF2* promoter and induces transcription as part of a pro-angiogenic transcription program in nasopharyngeal carcinoma cells.

The stability of *ATF2* mRNA transcripts is also regulated. Binding of the cytoplasmic RNA-binding protein HuR to the 3'-untranslated region (UTR) stabilizes *ATF2* mRNA, whereas intracellular polyamines destabilize *ATF2* mRNA (Xiao et al., 2007). *ATF2* transcript levels are also negatively regulated by the microRNA miR-26b in lung cancer cells, and this suppression is relieved by ionizing radiation (Arora et al., 2011). Alternative splicing has also been predicted to result in over a dozen of *ATF2* splice forms (Box 2).

**Regulation of ATF2 protein stability**

The stability of ATF2 protein is regulated by ubiquitylation and proteasomal degradation. Previous work from our laboratory has demonstrated that N-terminal phosphorylation and heterodimerization of ATF2 reduces its transcriptional activity by promoting ubiquitylation-dependent degradation (Fuchs and Ronai, 1999). Binding of JNK to ATF2 under non-stressed conditions serves to limit the availability of ATF2 by promoting its degradation under conditions in which it is not required (Fuchs et al., 1997). However, the E3 ubiquitin ligases that are involved in

## Box 2. ATF2 splice isoforms

Alternative promoter usage or mRNA splicing is predicted to produce over a dozen splice isoforms of human ATF2, which vary predominantly in exons 1, 3, 4 and 9 (Alternate Splicing Gallery, <http://statgen.ncsu.edu/asg>; and e!Ensemble, <http://www.ensembl.org>). Isoforms lacking N-terminal exons, specifically exon 3 and 4, do not incorporate the known phosphoregulatory sites Thr52, Thr69 or Thr71, and therefore are likely not to be subjected to the known upstream phosphorylation by MAPKs and SAPKs, or PKC $\epsilon$ . It remains to be determined whether these isoforms are transcriptionally dead or preferentially localized to the cytoplasm or mitochondria, because they lack these activating phosphoregulatory sites, or whether they are constitutively active, as they are also likely to have lost their intramolecular autoinhibitory interaction. The functional effect of loss of exon 9 is also not known. Lack of reagents that are able to specifically distinguish among the isoforms currently hampers their direct characterization in normal growth, development, as well as in pathological cases.

Although full-length ATF2 has been the most extensively studied ATF2 form, three murine splice orthologs (CRE-BP1, CRE-BP2 and CRE-BP3) and one human isoform (ATF2-sm) have also been characterized. Work in murine T cells studies has revealed that CRE-BP1 and CRE-BP3 are nearly identical, except for an eight hydrophobic amino acid substitution in CRE-BP3 that replaces the first 15 amino acids of CRE-BP1 (Georgopoulos et al., 1992). In contrast, CRE-BP2 exhibits a 98-amino-acid N-terminal internal deletion. The splice variation of these three murine isoforms occurs predominantly in the N- and extreme C-termini, whereas the bZIP domain is conserved, suggesting that the transcription factor function of the variants is conserved but that their regulation might differ as a result of the loss of various regulatory elements at the termini (Georgopoulos et al., 1992; Kara et al., 1990). Consistently, in murine T cells, the splice variants exhibit variable transcriptional activity; CRE-BP3 and CRE-BP1 have either only weak or no transcriptional activity, respectively, whereas CRE-BP2 exhibits strong transcriptional activity.

The human ATF2 splice isoform ATF2-sm lacks the entire bZIP domain and retains only the first and the two last exons of full-length ATF2. However, despite its lack of the bZIP domain, ATF2-sm still exhibits transcriptional activity (Bailey et al., 2002). ATF2-sm is specifically expressed in endometrial tissue and its protein levels fluctuate dynamically throughout pregnancy and labor (Bailey et al., 2002). This differential expression pattern suggests that ATF2 splice variants might elicit tissue- and temporal-specific functions, which is consistent with the finding that ATF2-sm transcriptionally regulates genes that are distinct from those regulated by full-length ATF2 (Bailey and Europe-Finner, 2005).

the ubiquitylation and degradation of ATF2 have not yet been identified. The SUMO-conjugating enzyme Ubc9 has been shown to interact with ATF2 and to affect ATF2 stability (Firestein and Feuerstein, 1998), although ATF2 SUMOylation has not been formally shown.

## Nuclear functions of ATF2

### Transcriptional roles of ATF2

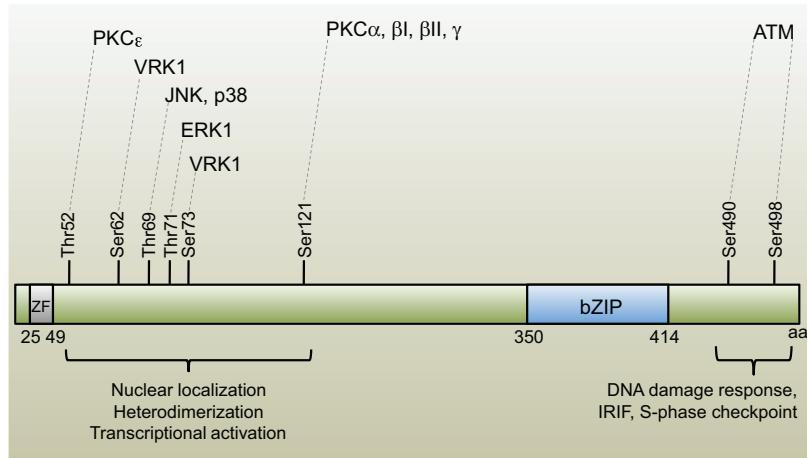
ATF2 homodimers display poor transcriptional activity, and thus heterodimerization of ATF2 is essential for its transcriptional function. Depending on the heterodimeric partner, ATF2 binds to different response elements on target genes and elicits distinct transcriptional programs. For example, ATF2–CREB or ATF2–Jun complexes predominantly exhibit DNA-binding specificity for the

eight-base CRE 5'-TGACGTCA-3' (Hai et al., 1989). ATF2 also binds to other promoter sequences on its target genes, including the interferon (IFN)- $\gamma$  promoter (i.e. 5'-AAAACCTTGTGAAAT-ACGTAATCCT-3'), the stress-response elements (StREs; 5'-T/CCTGAGTC-3') and UV response elements (URE; 5'-TGACAACA-3') (Gong et al., 2002; Lopez-Bergami et al., 2010; Ronai et al., 1998; van Dam and Castellazzi, 2001). Binding of ATF2–AP-1 dimers to DNA alters the local structure of DNA and facilitates the recruitment and directional orientation of other regulatory transcriptional complexes, which either enhance (i.e. enhanceosomes) or repress (i.e. repressosomes) transcription. Such a coordinated transcriptional regulation is illustrated by the ATF2–Jun-mediated enhanceosome assembly at the promoter of IFN- $\beta$  (*IFNB1*) (Falvo et al., 2000; Falvo et al., 1995). Conversely, binding of ATF2 to the histone acetyltransferase TIP49b effectively suppresses its transcriptional activity (Cho et al., 2001). ATF2–JunB dimers bind to the *SOX10* promoter and suppress its transcription, with concomitant silencing of microphthalmia-associated transcription factor (*MITF*) transcription in melanocytes and melanoma cells (Shah et al., 2010). In Table 1, we have categorized the known transcriptional targets of ATF2 into functional groups, along with the respective AP1 family binding partner, case-specific stimuli and cell types (see also the UCSD Signaling Gateway Molecule Pages for ATF2; <http://www.signaling-gateway.org/molecule/query?afcsid=A000347>).

ATF2 can also affect transcription of target genes in trans through its interaction with other transcription factors. In hypoxia, for example, ATF2 binds and stabilizes hypoxia-inducible factor 1 $\alpha$  (HIF1 $\alpha$ ), thereby promoting its transcriptional activity (Choi et al., 2009). ATF2–MafA dimers provide another example of transactivation; together they contribute to the induction of insulin transcription in concert with the binding of Pdx1 and B cell E box transactivator 2 (Beta2, also known as TCF3) to adjacent A-box elements on the insulin promoter (Han et al., 2011).

The transcriptional function of ATF2 is also modulated by its interaction with transcriptional coactivators or corepressors. For example, p300/CBP and C/EBP $\alpha$  bind to the bZIP domain of ATF2, disrupting its intrinsic autoinhibition and augmenting its transcriptional activity (Duyndam et al., 1999; Shuman et al., 1997). This mechanism is exploited by pathogens as a means to activate transcription. For example, the viral proteins E1A and Epstein–Barr viral nuclear antigen-2 (EBNA2) enhance ATF2 transcriptional output by promoting its heterodimerization with either CREB or Jun (Abdel-Hafiz et al., 1993; Haghmeyer et al., 1995). Other viral transactivators, such as Epstein–Barr BZLF1 and BRLF1, enhance ATF2 transcriptional activities indirectly through their effect on the ATF2-phosphorylating kinases JNK or p38, whereas human vaccinia-related kinase 1 (VRK1) activates and stabilizes ATF2 through direct phosphorylation of Ser62 and Thr73 (Sevilla et al., 2004).

ATF2 also affects more global transcriptional programs through its association with histone modifying enzymes. For instance, the fission yeast ATF2 homologs, Atf1 and Pcr1, are essential for accurate histone H3 or H4 deacetylation and Swi6-mediated heterochromatin assembly in *Schizosaccharomyces pombe*, and loss of Atf1 or Pcr1 results in loss of heterochromatin silencing (Jia et al., 2004; Kim et al., 2004). During amino acid deprivation, the recruitment of ATF2 to the amino acid response element (AARE; 5'-ATTGCATCA-3') is required for subsequent acetylation of histones H4 and H2B (Bruhat et al., 2007). ATF2 recruitment of the repressive



**Fig. 1. Schematic of phosphorylation of ATF2.** Shown here is a schematic illustration of the basic structure of ATF2 together with its phosphoacceptor sites for the respective kinases (known to date), as well as the functional consequences of phosphorylation. ZF and bZIP indicate the zinc finger and basic leucine zipper domain, respectively. IRIF indicates ionizing-radiation-induced foci.

macroH2A histone variant to the IL8 promoter silences IL8 transcription in B cells (Agelopoulos and Thanos, 2006). Interestingly, ATF2 has been shown to affect global heterochromatin organization in *Drosophila*, and disruption of the ATF2–chromatin interaction in response to stress results in heritable heterochromatin defects that are maintained in subsequent generations (Seong et al., 2011). Thus, ATF2 not only controls the transcription of its specific target genes through direct binding to DNA promoter elements, but also has a key regulatory role in chromatin restructuring through its interaction with chromatin-modifying proteins.

#### Non-transcriptional functions in the nucleus

ATF2 also exhibits nuclear functions that are distinct from its transcriptional activity, including its involvement in chromatin restructuring and the DNA damage response. Our earlier studies showed that ATM phosphorylates ATF2 on Ser490 and Ser498 in response to DNA damage, which promotes its colocalization with components of the MRE11–RAD50–NBS1 (MRN) complex in ionizing radiation-induced foci (IRIF) (Bhoumik et al., 2005). Mutation of human ATF2 Ser490 or 498 to alanine abrogates this phosphorylation event and perturbs IRIF formation and subsequent DNA repair. ATF2 phosphorylation by ATM also contributes to the intra-S phase checkpoint, which enables proper repair of damaged DNA (Bhoumik et al., 2005). ATF2 knock-in mice, in which the sites in mouse ATF2 that correspond to amino acids 490 and 498 were mutated to alanines, exhibit genomic instability reflected in greater susceptibility to develop tumors and greater sensitivity to ionizing radiation (Li et al., 2010). In this context, ATF2 interaction with the histone acetyltransferase TIP60 constitutes a positive feed-back loop mechanism through which ATF2 promotes ATM activities. Genotoxic stress attenuates the interaction between TIP60 and ATF2, which stabilizes TIP60 and promotes the subsequent acetylation and activation of ATM (Bhoumik et al., 2008b).

#### Functions of ATF2 in the cytoplasm

##### Cytoplasmic accumulation of ATF2

Although it has been known for some time that ATF2 can also be found in the cytoplasm (Berger et al., 2003), its specific function there remains unclear. Exportin-1 facilitates the nuclear export

of ATF2, although the precise mechanisms that control the nucleocytoplasmic trafficking of ATF2 are unknown (Liu et al., 2006). Notably, a cytoplasmic splice isoform of ATF7, ATF7-4, was recently found to inhibit the phosphorylation and activation of both ATF7 and ATF2 (Diring et al., 2011).

Localization of ATF2 to the cytoplasm has been observed under conditions of cellular stress and in disease states (Berger et al., 2003; Deng et al., 2011). Cytoplasmic accumulation of ATF2 has been detected in the degenerating hippocampal regions and cortical neurons of patients with neurodegenerative diseases such as Alzheimer's, Parkinson's and Huntington's disease (Pearson et al., 2005; Yamada et al., 1997). Consistent with these observations, *in vivo* and *in vitro* studies have shown that neuronal injury by nerve fiber transection or doxorubicin treatment is accompanied with loss of nuclear ATF2 (Martin-Villalba et al., 1998). ATF2 also accumulates in the cytoplasm of prostate cancer cells after treatment with ionizing irradiation (Deng et al., 2008). Furthermore, melanoma cell death is observed after forced expression of N-terminal ATF2 peptides that induce cytoplasmic accumulation and thereby reduce the transcriptional activity of endogenous ATF2 (Bhoumik et al., 2004). Collectively, these observations point to stress- or damage-induced cytosolic localization of ATF2, which is associated with cell death.

Analyses of tumor microarrays have revealed the principal differences between melanoma and non-malignant skin cancers. Whereas the nuclear enrichment of ATF2 correlates with poor prognosis in melanoma, cytoplasmic ATF2 is associated with a more favorable clinical outcome (Berger et al., 2003). Notably, cytosolic localization of ATF2 is also seen in non-malignant skin tumors, e.g. squamous and basal cell carcinomas (SCCs and BCCs, respectively) (Bhoumik et al., 2008a). Hence, the nuclear accumulation of ATF2 appears to be associated with its oncogenic activities, because this localization is observed in melanoma (Shah et al., 2010), whereas the cytosolic localization, as are observed in non-malignant skin tumors (Bhoumik et al., 2008a), is associated with its tumor suppressor activities. Consistent with this, the cytoplasmic accumulation of ATF2 that is observed in prostate cancer cells following ionizing irradiation has been associated with a transient latency of tumor proliferation and a more ‘differentiated’ state (Deng et al., 2008).

**Table 1. Transcriptional targets of ATF2**

	AP1 binding partner	Cell type	Stimulus	Transcriptional regulation	Target gene (encoded protein)	References
Cell cycle	ATF2, JunD	Rat chondrosarcoma cells, MEFs	Serum	TI	<i>Ccnal</i> (cyclin A1)	(Shimizu et al., 1998)
	BRCA1, Oct-1, Neurofibromin-1	MEFs	Anisomycin, hypoxia	TI	<i>Gadd45a</i> (Gadd45 $\alpha$ )	(Maekawa et al., 2008; Maekawa et al., 2007)
	BRCA1, Oct-1, Neurofibromin-1	MEFs	Anisomycin, hypoxia	TI	<i>SerpinsB</i> (maspin)	(Maekawa et al., 2008; Maekawa et al., 2007)
	CREB1	Murine chondrocytes	TGF $\beta$ , PTHrP	TI	<i>Ccndl</i> (cyclin D1)	(Beier et al., 2001; Beier et al., 1999)
	JunD	Intestinal epithelial cells	Polyamines	TR	<i>Cdk4</i> (Cdk4)	(Xiao et al., 2010)
	n/a	Murine chondrocytes	n/a	TI	<i>Rb1</i> (Rb)	(Vale-Cruz et al., 2008)
Immune and inflammatory	Jun	Endothelial (HUVEC)	UV	TI	<i>SELE</i> (Elam1)	(Read et al., 1997)
	CREB1	Myelogenous leukemia (K562)	Sodium butyrate, trichostatin A	TI	<i>HBCG2</i> (G $\gamma$ -globin)	(Kodeboyina et al., 2010)
	Jun	T-cells (Jurkat)	Ionomycin, PMA	TI	<i>IFNG</i> (interferon- $\gamma$ )	(Penix et al., 1996)
	Jun	Murine macrophage (RAW264.7)	LPS	TI	<i>Il23A</i> (interleukin-23)	(Al-Salleh and Petro, 2008; Liu et al., 2009)
	Jun	Human primary lung and foreskin fibroblasts	Interleukin-1 $\beta$	TI	<i>IL8</i> (interleukin-8 $\beta$ )	(Markovics et al., 2011)
	n/a	Osteoblasts	PDGF	TI	<i>IL6</i> (interleukin-6)	(Franchimont et al., 1999)
Cell death	Jun	Transformed human embryonic kidney (293T)	Oxidative stress (H <sub>2</sub> O <sub>2</sub> )	TI	<i>ACHE</i> (acetylcholinesterase)	(Zhang et al., 2008)
	Jun	Endothelial (HUVECs)	Growth factors (VEGF, EGF)	TI	<i>BCL2L1</i> (Bcl-XL)	(Salameh et al., 2010)
	Jun	Rat cerebellar granule neurons (CGN), murine immortalized gonadotrope cell line (oT3-1)	K <sup>+</sup> withdrawal	TI	<i>Hrk</i> (DP5)	(Ma et al., 2007; Towers et al., 2009)
	JDP2	HeLa, HEPG2, MEFs	Amino acid deprivation	TR	<i>DDIT3</i> (CHOP)	(Averous et al., 2004)
AP1	Jun	Embryonal carcinoma (F9), rat cerebellar granule neurons, monkey kidney epithelial (COS1), human cervical carcinoma (HeLa, SKOV3), NIH3T3, hepatocellular carcinoma (HepG2, HuH7)	UV, MNNG, MMS, K <sup>+</sup> withdrawal, E1A expression, amino acid deprivation	TI	<i>JUN</i> (Jun)	(Fu et al., 2011; Kawasaki et al., 1998; Yamasaki et al., 2009)
	JDP2	Embryonal carcinoma (F9)	Basal, before RA-induced differentiation	TR	<i>JUN</i> (Jun)	(Jin et al., 2002)
	Jun	Normal fibroblasts, HeLa, HEK293, MEF, Rat cerebellar granule neurons (CGN)	IR, amino acids, potassium, gonadotropin-releasing hormone (GnRH), tufenamic acid (TA)	TI	<i>ATF3</i> (ATF3)	(Chaveroux et al., 2009; Fu et al., 2011; Kool et al., 2003; Lee et al., 2010; Mayer et al., 2008)
DUSPs	Jun	Embryonic liver, sympathetic neurons	p39 feedback signaling, NGF withdrawal	TI	<i>DUSP1</i> (MKP1)	(Breitwieser et al., 2007; Kristiansen et al., 2010)
	n/a	Murine fetal hepatocytes	Anisomycin	TI	<i>Dusp8</i> (HB5)	(Breitwieser et al., 2007)
	n/a	Murine fetal hepatocytes	Anisomycin	TI	<i>Dusp5</i> (HVH3)	(Breitwieser et al., 2007)
	n/a	Murine fetal hepatocytes	Anisomycin	TI	<i>Dusp10</i> (MKP5)	(Breitwieser et al., 2007)
Other	Jun	Murine embryonic stem cells	FGF2	TI	<i>Hes1</i> (HES1)	(Sanalkumar et al., 2010)
	Jun	Rat aortic endothelial cells	Thrombin	TI	<i>Arg1</i> (arginase)	(Zhu et al., 2010)
	Jun	Rat osteosarcoma (ROS17/2.8, ROS25), primary murine calvarial osteoblast (MCC)	n/a	TI	<i>Col24A1</i> (COL24A)	(Matsuo et al., 2006)
	Jun	Murine lymphocytic leukemia cells (L1210)	Doxorubicin	TI	<i>Prkcd</i> (PKC $\delta$ )	(Min et al., 2008)
	Jun, JunD, ATF2	NIH3T3, HEPG2	TPA, FGF2	TI	<i>PLAU</i> (uPA)	(Cirillo et al., 1999; D'Orazio et al., 1997)
	JunB	Murine endothelial and endothelioma cells	CoCl <sub>2</sub> , hypoxia	TI	<i>Cbf<math>\beta</math></i> (CBF- $\beta$ )	(Licht et al., 2006)
	n/a	Murine macrophage (RAW264.7)	LPS	TI	<i>Socs3</i> (SOCS3)	(Hirose et al., 2009)
	MafA, Pdx1, Beta2	Rat insulinoma cells (INS-1), $\beta$ -cell-derived cell lines (MIN6), HeLa	Forskolin, UV	TI	<i>IRS1</i> (insulin)	(Han et al., 2011; Hay et al., 2007)
	n/a	Choriocarcinoma cells (Jar), CHO	Hypoxia	TI	<i>Pdgfra</i> (PDGFR $\alpha$ )	(Maekawa et al., 1999)
	n/a	Lung epithelial cells	Rb expression	TI	<i>TGFB2</i> (TGF $\beta$ 2)	(Kim et al., 1992)
	n/a	Myoblasts (C2C12)	Exercise	TI	<i>Ppargc1a</i> (PGC1 $\alpha$ )	(Akimoto et al., 2005)
	n/a	Vascular smooth muscle cells	TGF $\beta$	TI	<i>CSRP2</i> (CRP2)	(Lin et al., 2008)
	n/a	Retinal pigment epithelial cells	Valproic acid	TI	<i>ST3Gal5</i> (ST3Gal5)	(Song et al., 2011)
	NF-YA	Jurkat cells	UV	TI	<i>RHOB</i> (RhoB)	(Ahn et al., 2011; Fritz and Kaina, 2001)
	n/a	Brown adipocytes	Norepinephrine	TI	<i>Fgf21</i> (FGF21)	(Hondares et al., 2011)
	n/a	Rat adrenal medulla-derived cells (PC12)	Nicotine	TI	<i>Th</i> (tyrosine hydroxylase)	(Gueorguiev et al., 2006; Suzuki et al., 2002)
	NFAT, Jun	Dendritic cells, monocytic leukemia cells (THP1)	TLR2 ligation	TI	<i>TNF</i> (TNF $\alpha$ )	(Altmayr et al., 2010; Kumawat et al., 2010; Lawrence et al., 2011)
	n/a	Adrenocortical carcinoma cells (H295R)	Angiotensin II, K <sup>+</sup>	TI	<i>CYP11B2</i> (aldosterone synthase)	(Nogueira and Rainey, 2010)
	n/a	Murine macrophages (RAW)	cAMP	TI	<i>Entpd1</i> (ectonucleoside triphosphate diphosphohydrolase 1)	(Liao et al., 2010)
	n/a	Mouse As4.1 cells	TNF $\alpha$ , MG132	TR	<i>Ren1</i> (renin)	(Desch et al., 2011)

Known transcriptional targets of ATF2 are displayed by functional groups as follows: cell cycle, immune and inflammatory, cell death, AP1, dual-specificity phosphatases (DUSPs) and others. Each target gene is listed with associated AP1 partner, cell-type and stimuli, if known. The nature of transcriptional regulation by ATF2 for each of these targets is indicated as transcriptional induction (TI, green), or transcriptional repression (TR, pink).

### ATF2 localization at the mitochondria following genotoxic stress

The finding that ATF2 is localized in the cytoplasm in non-malignant skin tumors prompted us to investigate the possibility that ATF2 harbors a cytosolic function. In SCC cells, genotoxic stress induces a fraction of nuclear ATF2 to translocate to the cytoplasm within ~8–24 hours, where it localizes at the mitochondrial outer membrane (Lau et al., 2012). This nuclear export coincides with reduced transcriptional activity of ATF2. We used mass spectrometry to analyze ATF2-associated proteins within the cytoplasm, and identified a cluster of mitochondrial proteins that included hexokinase 1 (HK1) and voltage-dependent anion channel 1 (VDAC1) (Lau et al., 2012). Complexes of HK1 and VDAC1 have been associated with mitochondrial membrane pore permeability, and disruption of these complexes is often observed in response to cellular stress that induces apoptosis, including genotoxic stimuli (Abu-Hamad et al., 2008; Shoshan-Barmatz et al., 2009). These disruptions result in impaired mitochondrial membrane potential with concomitant leakage from the mitochondria – hallmarks of mitochondrial-dependent cell death. We have shown that ATF2 is part of the HK1–VDAC1 complex both by immunostaining and biochemical analysis, and mobilization of ATF2 to mitochondria results in decreased HK1 binding to VDAC1 (Lau et al., 2012). ATF2 recruitment to the mitochondria is also associated with reduced membrane potential, activation of the pro-apoptotic Bcl-2 family protein BAX, leakage of cytochrome *c* and sensitization of cells to genotoxic-stress-induced cell death. Collectively, our recent studies reveal a new function for cytoplasmic ATF2 in promoting mitochondrial-based cell death following exposure to genotoxic stress (Lau et al., 2012).

The nuclear localization and mitochondrial function of ATF2 are dependent on PKC $\epsilon$ . The nuclear export of ATF2, which enables its localization and function at the mitochondria, has been observed following genotoxic stimuli in both non-malignant (keratinocytes, melanocytes and fibroblasts) and malignant (BCC and early-phase melanoma) cells (Lau et al., 2012). Significantly, an exclusion of ATF2 from the nucleus is not observed in the more aggressive melanoma cells, which prevents ATF2 from functioning at the mitochondria in these cells (Lau et al., 2012). The control of ATF2 nuclear export is lost in progressively malignant melanoma cells. In particular, we found that PKC $\epsilon$ -mediated phosphorylation of ATF2 on Thr52 is required for its nuclear localization and must be attenuated to allow its nuclear export and localization to the mitochondria. Phosphorylation of ATF2 on Thr52 is reduced following genotoxic stress in most cells tested. However, this is not the case in melanomas, in which the expression and activity of PKC $\epsilon$  are markedly higher and ATF2 phosphorylation on Thr52 is thus maintained (Lau et al., 2012). It is plausible that the mechanism identified in melanoma will be of relevance to a number of other tumors that have a high level of PKC $\epsilon$ .

### Interplay between cytosolic and nuclear ATF2 – a paradigm for oncogene addiction

‘Oncogene addiction’ is a phenomenon whereby key cancer cell phenotypes are driven by an activated oncogene. Turning off the oncogenic signal often results in cell death, illustrating the addiction. To date, oncogenic addiction has been largely associated with genomic mutations that commit signaling pathways towards maintaining or further promoting

transformed phenotypes (i.e. metastasis). Once the oncogenic pressure is relieved (by targeted inhibition of the gene or pathway), the transformed phenotype is partially or fully alleviated. Although the mechanism underlying the upregulation of PKC $\epsilon$  in melanoma is not yet known, it is probable that it is linked to mutation(s) currently being discovered as part of the effort to map the melanoma genome (Dutton-Regester and Hayward, 2012; Walia et al., 2012). In the case of ATF2, PKC $\epsilon$  functions as the addicting signal to maintain nuclear localization of ATF2 and thus prevents its pro-apoptotic function at the mitochondria. Thus, as long as PKC $\epsilon$  activity is sustained, ATF2 will exhibit oncogenic functions within the nucleus. ATF2 addiction to PKC $\epsilon$  therefore establishes a new paradigm for oncogenic addiction, which is likely to be relevant to other transcription factors that are able to elicit both oncogenic and tumor suppressor activities.

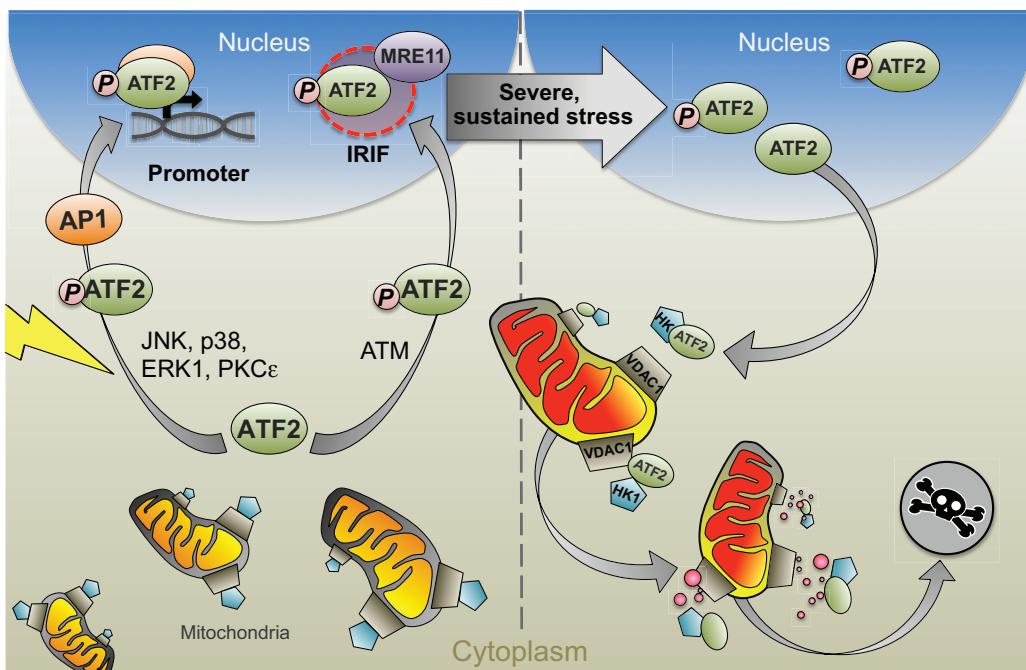
### Future perspectives

A growing number of transcription-dependent and -independent functions have been described for ATF2, while attesting to its capacity to regulate diverse and often opposing functions, a number of questions remain to be addressed.

Understanding how post-translational regulation of ATF2 influences its choice of transcriptional partners will provide great insight into the cell-type-specific transcriptional activities of ATF2. There is growing evidence of a role for ATF2 in global transcription through its effect on histone modifications and imprinted transcriptional signatures, which points to the importance of ATF2 in establishing general transcriptional programs in addition to its specific activity in concert with its AP1 family binding partners. The proportion of nuclear ATF2 that is dedicated to each of the three distinct functions – specific transcription, global transcription and DNA repair – still needs to be determined. Additionally, it will be equally important to assess whether certain conditions, such as cell type or growth conditions, promote or potentiate one function of ATF2 over another.

The recently discovered role of ATF2 in the cytoplasm is likely to be only the tip of an unexplored iceberg. Although the phosphorylation of ATF2 by PKC $\epsilon$  is a key determinant of its subcellular localization and function, the precise mechanism underlying its nuclear export and localization at the mitochondria has yet to be determined. Similarly, it will be important to determine which ATF2 domains are required for its mitochondrial function and their possible relationship to the Bcl-2 family protein signaling that is associated with mitochondrial-based death programs. Finally, given that the cytoplasmic localization of ATF2 has been reported under diverse cellular conditions, it seems unlikely that the function of ATF2 at the mitochondria is its sole activity in the cytoplasm.

ATF2 possesses several functions and properties that might serve as a paradigm for other transcription factors (Fig. 2). First, ATF2 is one of several transcription factors, including Notch,  $\beta$ -catenin and Myc, that have been identified to elicit either oncogenic or tumor suppressor functions (Koch and Radtke, 2007; Larsson and Henriksson, 2010). In the past, this characteristic has been primarily explained on the basis of tissue and/or cell type specificity, or genetic alterations that conferred oncogenic activities [e.g. Notch mutation (Koch and Radtke, 2007)]. However, the example of ATF2 raises the possibility that post-translational modifications and



**Fig. 2. Divergent nuclear and cytosolic functions of ATF2.** ATF2 is regulated by multiple upstream kinases in response to acute stress (shown on the left), including DNA damage and cytokine stimuli (yellow lightning bolt). During acute stress (~0.5–7 hours, DNA damage or cytokine stimulation), JNK, p38 or ERK1 are known to phosphorylate ATF2, facilitating its dimerization with other AP1 transcription factors and its translocation to the nucleus, where it can engage in transcriptional activities at target gene promoters. PKC $\epsilon$  phosphorylation of ATF2 on Thr52 serves as another regulatory layer controlling its nuclear localization and transcriptional activity. Upon DNA damage, ATF2 is phosphorylated by ATM, which stimulates its function in DNA damage response at ionizing-radiation-induced foci (IRIF), where it recruits the DNA repair proteins MRE11, RAD50 and NBS1. Sustained nuclear localization of ATF2 functions together with lack of its export into the cytoplasm. In response to severe and/or sustained stress (shown on the right), including genotoxic stress chemicals, UV irradiation and ionizing radiation that culminate in cell death, a portion of nuclear ATF2 is exported from the nucleus and accumulates in the cytoplasm. There, ATF2 interacts with and perturbs HK1- and VDAC1-containing complexes at the mitochondrial outer membrane, thereby impairing mitochondrial membrane potential, inducing mitochondrial leakage (e.g. cytochrome *c* leakage, which is shown on the right as pink circles exiting from mitochondria through VDAC1), and promoting cell death.

non-transcriptional functions also have a role in tilting the balance between these opposing functions. A second important concept is the recognition that a single phosphorylation event, such as that of Thr52 in the example of ATF2, might suffice to alter the subcellular localization and primary function of a transcription factor. The control of ATF2 localization by PKC $\epsilon$  is also likely to be relevant for other transcription factors and regulatory proteins that elicit diverse activities in distinct subcellular localizations. The third notion is that this regulation can be modified in cancer and other diseases and could thus direct or limit its specific function(s).

Understanding the regulation and function of ATF2 might also prompt the re-evaluation of many transcription factors that, until now, have been unexplored or considered uninteresting. The loss of the cytosolic function of ATF2 in melanomas that express high levels of PKC $\epsilon$  offers just a glimpse into the rich, yet to be explored, role of ATF2 and of many transcription factors that might be subjected to similar regulatory cues.

It is generally agreed that targeting transcription factors is likely to be one of the more specific means to alter a select phenotype(s) associated with a given disease. However, transcription factors are also some of the most challenging therapeutic targets and are often considered ‘undruggable’. An understanding of the mechanisms that alter their subcellular localization, and thus activities, could provide a platform for

identifying small molecules that affect upstream signaling or control their subcellular localization. In the case of melanoma, small molecules that promote the nuclear export of ATF2 would be expected to restore its tumor suppressor function and thus to sensitize the cancer to genotoxic agents.

#### Acknowledgements

We thank the members of the Ronai laboratory for advice and our collaborators, Anindita Bhoumik, Meera Shah, Harriet Kluger, Immo Scheffler and Trey Ideker.

#### Funding

The work of our laboratory is supported by the National Cancer Institute (NCI) [grant numbers CA099961, CA117927, CA051995 to Z.R.J.]. E.L. is supported in part by an ACS Postdoctoral Fellowship, Illinois Division [grant number 117090-PF-09-112-01-GMC]; and an NCI T32 training grant [grant number T32-CA121949]. Deposited in PMC for release after 12 months.

#### References

- Abdel-Hafiz, H. A., Chen, C. Y., Marcell, T., Kroll, D. J. and Hoeffler, J. P. (1993). Structural determinants outside of the leucine zipper influence the interactions of CREB and ATF-2: interaction of CREB with ATF-2 blocks E1a-ATF-2 complex formation. *Oncogene* **8**, 1161–1174.
- Abu-Hamad, S., Zaid, H., Israelson, A., Nahon, E. and Shoshan-Barmatz, V. (2008). Hexokinase-I protection against apoptotic cell death is mediated via interaction with the voltage-dependent anion channel-1: mapping the site of binding. *J. Biol. Chem.* **283**, 13482–13490.

- Ackermann, J., Ashton, G., Lyons, S., James, D., Hornung, J. P., Jones, N. and Breitwieser, W. (2011). Loss of ATF2 function leads to cranial motoneuron degeneration during embryonic mouse development. *PLoS ONE* **6**, e19090.
- Agelopoulos, M. and Thanos, D. (2006). Epigenetic determination of a cell-specific gene expression program by ATF-2 and the histone variant macroH2A. *EMBO J.* **25**, 4843-4853.
- Ahn, J., Choi, J. H., Won, M., Kang, C. M., Gyun, M. R., Park, H. M., Kim, C. H. and Chung, K. S. (2011). The activation of p38 MAPK primarily contributes to UV-induced RhoB expression by recruiting the c-Jun and p300 to the distal CCAAT box of the RhoB promoter. *Biochem. Biophys. Res. Commun.* **409**, 211-216.
- Akimoto, T., Pohnert, S. C., Li, P., Zhang, M., Gumbs, C., Rosenberg, P. B., Williams, R. S. and Yan, Z. (2005). Exercise stimulates Pgc-1alpha transcription in skeletal muscle through activation of the p38 MAPK pathway. *J. Biol. Chem.* **280**, 19587-19593.
- Al-Salleh, F. and Petro, T. M. (2008). Promoter analysis reveals critical roles for SMAD-3 and ATF-2 in expression of IL-23 p19 in macrophages. *J. Immunol.* **181**, 4523-4533.
- Altmayr, F., Jusek, G. and Holzmann, B. (2010). The neuropeptide calcitonin gene-related peptide causes repression of tumor necrosis factor-alpha transcription and suppression of ATF-2 promoter recruitment in Toll-like receptor-stimulated dendritic cells. *J. Biol. Chem.* **285**, 3525-3531.
- Arora, H., Qureshi, R., Park, A. K. and Park, W. Y. (2011). Coordinated regulation of ATF2 by miR-26b in  $\gamma$ -irradiated lung cancer cells. *PLoS ONE* **6**, e23802.
- Averous, J., Bruhat, A., Jousse, C., Carraro, V., Thiel, G. and Fafournoux, P. (2004). Induction of CHOP expression by amino acid limitation requires both ATF4 expression and ATF2 phosphorylation. *J. Biol. Chem.* **279**, 5288-5297.
- Bailey, J. and Europe-Finner, G. N. (2005). Identification of human myometrial target genes of the c-Jun NH<sub>2</sub>-terminal kinase (JNK) pathway: the role of activating transcription factor 2 (ATF2) and a novel spliced isoform ATF2-small. *J. Mol. Endocrinol.* **34**, 19-35.
- Bailey, J., Phillips, R. J., Pollard, A. J., Gilmore, K., Robson, S. C. and Europe-Finner, G. N. (2002). Characterization and functional analysis of cAMP response element modulator protein and activating transcription factor 2 (ATF2) isoforms in the human myometrium during pregnancy and labor: identification of a novel ATF2 species with potent transactivation properties. *J. Clin. Endocrinol. Metab.* **87**, 1717-1728.
- Beier, F., Lee, R. J., Taylor, A. C., Pestell, R. G. and LuValle, P. (1999). Identification of the cyclin D1 gene as a target of activating transcription factor 2 in chondrocytes. *Proc. Natl. Acad. Sci. USA* **96**, 1433-1438.
- Beier, F., Ali, Z., Mok, D., Taylor, A. C., Leask, T., Albanese, C., Pestell, R. G. and LuValle, P. (2001). TGFbeta and PTHrP control chondrocyte proliferation by activating cyclin D1 expression. *Mol. Biol. Cell* **12**, 3852-3863.
- Berger, A. J., Kluger, H. M., Li, N., Kielhorn, E., Halabian, R., Ronai, Z. and Rimm, D. L. (2003). Subcellular localization of activating transcription factor 2 in melanoma specimens predicts patient survival. *Cancer Res.* **63**, 8103-8107.
- Bhoumik, A., Jones, N. and Ronai, Z. (2004). Transcriptional switch by activating transcription factor 2-derived peptide sensitizes melanoma cells to apoptosis and inhibits their tumorigenicity. *Proc. Natl. Acad. Sci. USA* **101**, 4222-4227.
- Bhoumik, A., Takahashi, S., Breitweiser, W., Shiloh, Y., Jones, N. and Ronai, Z. (2005). ATM-dependent phosphorylation of ATF2 is required for the DNA damage response. *Mol. Cell* **18**, 577-587.
- Bhoumik, A., Lopez-Bergami, P. and Ronai, Z. (2007). ATF2 on the double – activating transcription factor and DNA damage response protein. *Pigment Cell Res.* **20**, 498-506.
- Bhoumik, A., Fichtman, B., Derossi, C., Breitwieser, W., Kluger, H. M., Davis, S., Subtil, A., Meltzer, P., Krajewski, S., Jones, N. et al. (2008a). Suppressor role of activating transcription factor 2 (ATF2) in skin cancer. *Proc. Natl. Acad. Sci. USA* **105**, 1674-1679.
- Bhoumik, A., Singha, N., O'Connell, M. J. and Ronai, Z. A. (2008b). Regulation of TIP60 by ATF2 modulates ATM activation. *J. Biol. Chem.* **283**, 17605-17614.
- Breitwieser, W., Lyons, S., Flenniken, A. M., Ashton, G., Bruder, G., Willington, M., Lacaud, G., Kouskoff, V. and Jones, N. (2007). Feedback regulation of p38 activity via ATF2 is essential for survival of embryonic liver cells. *Genes Dev.* **21**, 2069-2082.
- Bruhat, A., Chérasse, Y., Maurin, A. C., Breitwieser, W., Parry, L., Deval, C., Jones, N., Jousse, C. and Fafournoux, P. (2007). ATF2 is required for amino acid-regulated transcription by orchestrating specific histone acetylation. *Nucleic Acids Res.* **35**, 1312-1321.
- Cam, H., Balciunaite, E., Blais, A., Spektor, A., Scarpulla, R. C., Young, R., Kluger, Y. and Dynlacht, B. D. (2004). A common set of gene regulatory networks links metabolism and growth inhibition. *Mol. Cell* **16**, 399-411.
- Chaveroux, C., Jousse, C., Cherasse, Y., Maurin, A. C., Parry, L., Carraro, V., Derijard, B., Bruhat, A. and Fafournoux, P. (2009). Identification of a novel amino acid response pathway triggering ATF2 phosphorylation in mammals. *Mol. Cell. Biol.* **29**, 6515-6526.
- Chen, S. Y., Takeuchi, S., Urabe, K., Hayashida, S., Kido, M., Tomoeda, H., Uchi, H., Dainichi, T., Takahara, M., Shibata, S. et al. (2008). Overexpression of phosphorylated-ATF2 and STAT3 in cutaneous angiosarcoma and pyogenic granuloma. *J. Cutan. Pathol.* **35**, 722-730.
- Cho, S. G., Bhoumik, A., Broday, L., Ivanov, V., Rosenstein, B. and Ronai, Z. (2001). TIP49b, a regulator of activating transcription factor 2 response to stress and DNA damage. *Mol. Cell. Biol.* **21**, 8398-8413.
- Choi, J. H., Cho, H. K., Choi, Y. H. and Cheong, J. (2009). Activating transcription factor 2 increases transactivation and protein stability of hypoxia-inducible factor 1alpha in hepatocytes. *Biochem. J.* **424**, 285-296.
- Cirillo, G., Casalino, L., Vallone, D., Caracciolo, A., De Cesare, D. and Verde, P. (1999). Role of distinct mitogen-activated protein kinase pathways and cooperation between Ets-2, ATF-2, and Jun family members in human urokinase-type plasminogen activator gene induction by interleukin-1 and tetradecanoyl phorbol acetate. *Mol. Cell. Biol.* **19**, 6240-6252.
- Dam, H., Wilhelm, D., Herr, I., Steffen, A., Herrlich, P. and Angel, P. (1995). ATF-2 is preferentially activated by stress-activated protein kinases to mediate c-jun induction in response to genotoxic agents. *EMBO J.* **14**, 1798-1811.
- D'Orazio, D., Besser, D., Marksizer, R., Kunz, C., Hume, D. A., Kiefer, B. and Nagamine, Y. (1997). Cooperation of two PEA3/AP1 sites in uPA gene induction by TPA and FGF-2. *Gene* **201**, 179-187.
- Deng, X., Liu, H., Huang, J., Cheng, L., Keller, E. T., Parsons, S. J. and Hu, C. D. (2008). Ionizing radiation induces prostate cancer neuroendocrine differentiation through interplay of CREB and ATF2: implications for disease progression. *Cancer Res.* **68**, 9663-9670.
- Deng, X., Elzey, B. D., Poulsen, J. M., Morrison, W. B., Ko, S. C., Hahn, N. M., Rathiff, T. L. and Hu, C. D. (2011). Ionizing radiation induces neuroendocrine differentiation of prostate cancer cells in vitro, in vivo and in prostate cancer patients. *Am. J. Cancer Res.* **1**, 834-844.
- Desch, M., Hackmayer, G. and Todorov, V. T. (2011). Identification of ATF2 as a transcriptional regulator of renin gene. *Biol. Chem.* **393**, 93-100.
- Diring, J., Camuzeaux, B., Donzeau, M., Vigneron, M., Rosa-Calatrava, M., Kedinger, C. and Chatton, B. (2011). A cytoplasmic negative regulator isoform of ATF7 impairs ATF7 and ATF2 phosphorylation and transcriptional activity. *PLoS ONE* **6**, e23351.
- Dutton-Reed, K. and Hayward, N. K. (2012). Reviewing the somatic genetics of melanoma: from current to future analytical approaches. *Pigment Cell Melanoma Res.* **25**, 144-154.
- Duyndam, M. C., van Dam, H., Smits, P. H., Verlaan, M., van der Eb, A. J. and Zantema, A. (1999). The N-terminal transactivation domain of ATF2 is a target for the co-operative activation of the c-jun promoter by p300 and 12S E1A. *Oncogene* **18**, 2311-2321.
- Falvo, J. V., Thanos, D. and Maniatis, T. (1995). Reversal of intrinsic DNA bends in the IFN beta gene enhancer by transcription factors and the architectural protein HMG I(Y). *Cell* **83**, 1101-1111.
- Falvo, J. V., Parekh, B. S., Lin, C. H., Fraenkel, E. and Maniatis, T. (2000). Assembly of a functional beta interferon enhanceosome is dependent on ATF-2-c-jun heterodimer orientation. *Mol. Cell. Biol.* **20**, 4814-4825.
- Firestein, R. and Feuerstein, N. (1998). Association of activating transcription factor 2 (ATF2) with the ubiquitin-conjugating enzyme HUBC9. Implication of the ubiquitin/proteasome pathway in regulation of ATF2 in T cells. *J. Biol. Chem.* **273**, 5892-5902.
- Franchimont, N., Durant, D., Rydziel, S. and Canalis, E. (1999). Platelet-derived growth factor induces interleukin-6 transcription in osteoblasts through the activator protein-1 complex and activating transcription factor-2. *J. Biol. Chem.* **274**, 6783-6789.
- Fritz, G. and Kaina, B. (2001). Transcriptional activation of the small GTPase gene rhoB by genotoxic stress is regulated via a CCAAT element. *Nucleic Acids Res.* **29**, 792-798.
- Fu, L., Balasubramanian, M., Shan, J., Dudenhhausen, E. E. and Kilberg, M. S. (2011). Auto-activation of c-JUN gene by amino acid deprivation of hepatocellular carcinoma cells reveals a novel c-JUN-mediated signaling pathway. *J. Biol. Chem.* **286**, 36724-36738.
- Fuchs, S. Y. and Ronai, Z. (1999). Ubiquitination and degradation of ATF2 are dimerization dependent. *Mol. Cell. Biol.* **19**, 3289-3298.
- Fuchs, S. Y., Xie, B., Adler, V., Fried, V. A., Davis, R. J. and Ronai, Z. (1997). c-Jun NH<sub>2</sub>-terminal kinases target the ubiquitination of their associated transcription factors. *J. Biol. Chem.* **272**, 32163-32168.
- Georgopoulos, K., Morgan, B. A. and Moore, D. D. (1992). Functionally distinct isoforms of the CRE-BP DNA-binding protein mediate activity of a T-cell-specific enhancer. *Mol. Cell. Biol.* **12**, 747-757.
- Gong, P., Stewart, D., Hu, B., Vinson, C. and Alam, J. (2002). Multiple basic-leucine zipper proteins regulate induction of the mouse heme oxygenase-1 gene by arsenite. *Arch. Biochem. Biophys.* **405**, 265-274.
- Gueorguiev, V. D., Cheng, S. Y. and Sabban, E. L. (2006). Prolonged activation of cAMP-response element-binding protein and ATF-2 needed for nicotine-triggered elevation of tyrosine hydroxylase gene transcription in PC12 cells. *J. Biol. Chem.* **281**, 10188-10195.
- Gupta, S., Campbell, D., Dérrijard, B. and Davis, R. J. (1995). Transcription factor ATF2 regulation by the JNK signal transduction pathway. *Science* **267**, 389-393.
- Hagmeyer, B. M., Angel, P. and van Dam, H. (1995). Modulation of AP-1/ATF transcription factor activity by the adenovirus-E1A oncogene products. *Bioessays* **17**, 621-629.
- Hai, T. W., Liu, F., Coukos, W. J. and Green, M. R. (1989). Transcription factor ATF cDNA clones: an extensive family of leucine zipper proteins able to selectively form DNA-binding heterodimers. *Genes Dev.* **3**, 2083-2090.
- Han, S. I., Yasuda, K. and Kataoka, K. (2011). ATF2 interacts with beta-cell-enriched transcription factors, MafA, Pdx1, and beta2, and activates insulin gene transcription. *J. Biol. Chem.* **286**, 10449-10456.

- Hay, C. W., Ferguson, L. A. and Docherty, K. (2007). ATF-2 stimulates the human insulin promoter through the conserved CRE2 sequence. *Biochim. Biophys. Acta* **1769**, 79-91.
- Hilberg, F., Aguzzi, A., Howells, N. and Wagner, E. F. (1993). c-jun is essential for normal mouse development and hepatogenesis. *Nature* **365**, 179-181.
- Hirose, N., Maekawa, T., Shinagawa, T. and Ishii, S. (2009). ATF-2 regulates lipopolysaccharide-induced transcription in macrophage cells. *Biochem. Biophys. Res. Commun.* **385**, 72-77.
- Hondares, E., Iglesias, R., Giralt, A., Gonzalez, F. J., Giralt, M., Mampel, T. and Villarroya, F. (2011). Thermogenic activation induces FGF21 expression and release in brown adipose tissue. *J. Biol. Chem.* **286**, 12983-12990.
- Jia, S., Noma, K. and Grewal, S. I. (2004). RNAi-independent heterochromatin nucleation by the stress-activated ATF/CREB family proteins. *Science* **304**, 1971-1976.
- Jin, C., Li, H., Murata, T., Sun, K., Horikoshi, M., Chiu, R. and Yokoyama, K. K. (2002). JDP2, a repressor of AP-1, recruits a histone deacetylase 3 complex to inhibit the retinoic acid-induced differentiation of F9 cells. *Mol. Cell. Biol.* **22**, 4815-4826.
- Johnson, R. S., van Lingen, B., Papaioannou, V. E. and Spiegelman, B. M. (1993). A null mutation at the c-jun locus causes embryonic lethality and retarded cell growth in culture. *Genes Dev.* **7**, 1309-1317.
- Kara, C. J., Liou, H. C., Ivashkiv, L. B. and Glimcher, L. H. (1990). A cDNA for a human cyclic AMP response element-binding protein which is distinct from CREB and expressed preferentially in brain. *Mol. Cell. Biol.* **10**, 1347-1357.
- Karanam, B., Wang, L., Wang, D., Liu, X., Marmorstein, R., Cotter, R. and Cole, P. A. (2007). Multiple roles for acetylation in the interaction of p300 HAT with ATF-2. *Biochemistry* **46**, 8207-8216.
- Kawasaki, H., Song, J., Eckner, R., Ugai, H., Chiu, R., Taira, K., Shi, Y., Jones, N. and Yokoyama, K. K. (1998). p300 and ATF-2 are components of the DRF complex, which regulates retinoic acid- and E1A-mediated transcription of the c-jun gene in F9 cells. *Genes Dev.* **12**, 233-245.
- Kim, H. S., Choi, E. S., Shin, J. A., Jang, Y. K. and Park, S. D. (2004). Regulation of Swi6/HP1-dependent heterochromatin assembly by cooperation of components of the mitogen-activated protein kinase pathway and a histone deacetylase Crf6. *J. Biol. Chem.* **279**, 42850-42859.
- Kim, S. J., Wagner, S., Liu, F., O'Reilly, M. A., Robbins, P. D. and Green, M. R. (1992). Retinoblastoma gene product activates expression of the human TGF-beta 2 gene through transcription factor ATF-2. *Nature* **358**, 331-334.
- Koch, U. and Radtke, F. (2007). Notch and cancer: a double-edged sword. *Cell. Mol. Life Sci.* **64**, 2746-2762.
- Kodeboyina, S., Balamurugan, P., Liu, L. and Pace, B. S. (2010). cJun modulates Ggamma-globin gene expression via an upstream cAMP response element. *Blood Cells Mol. Dis.* **44**, 7-15.
- Kool, J., Hamdi, M., Cornelissen-Stejger, P., van der Eb, A. J., Terlent, C. and van Dam, H. (2003). Induction of ATF3 by ionizing radiation is mediated via a signaling pathway that includes ATM, Nibrin1, stress-induced MAPkinases and ATF-2. *Oncogene* **22**, 4235-4242.
- Kravets, A., Hu, Z., Miralem, T., Torno, M. D. and Maines, M. D. (2004). Biliverdin reductase, a novel regulator for induction of activating transcription factor-2 and heme oxygenase-1. *J. Biol. Chem.* **279**, 19916-19923.
- Kristiansen, M., Hughes, R., Patel, P., Jacques, T. S., Clark, A. R. and Ham, J. (2010). Mkp1 is a c-Jun target gene that antagonizes JNK-dependent apoptosis in sympathetic neurons. *J. Neurosci.* **30**, 10820-10832.
- Kumawat, K., Pathak, S. K., Spetz, A. L., Kundu, M. and Basu, J. (2010). Exogenous Nef is an inhibitor of Mycobacterium tuberculosis-induced tumor necrosis factor-alpha production and macrophage apoptosis. *J. Biol. Chem.* **285**, 12629-12637.
- Larsson, L. G. and Henriksson, M. A. (2010). The Yin and Yang functions of the Myc oncoprotein in cancer development and as targets for therapy. *Exp. Cell Res.* **316**, 1429-1437.
- Lau, E., Kluger, H., Varsano, T., Lee, K., Scheffler, I., Rimm, D. L., Ideker, T. and Ronai, Z. A. (2012). PKC $\epsilon$  promotes oncogenic functions of ATF2 in the nucleus while blocking its apoptotic function at mitochondria. *Cell* **148**, 543-555.
- Lawrence, M. C., Naziruddin, B., Levy, M. F., Jackson, A. and McGlynn, K. (2011). Calcineurin/nuclear factor of activated T cells and MAPK signaling induce TNF-alpha gene expression in pancreatic islet endocrine cells. *J. Biol. Chem.* **286**, 1025-1036.
- Lee, S. H., Bahn, J. H., Whitlock, N. C. and Baek, S. J. (2010). Activating transcription factor 2 (ATF2) controls tolafenamic acid-induced ATF3 expression via MAP kinase pathways. *Oncogene* **29**, 5182-5192.
- Li, S., Ezhevsky, S., Dewing, A., Cato, M. H., Scortegagna, M., Bhoumik, A., Breitwieser, W., Braddock, D., Eroshkin, A., Qi, J. et al. (2010). Radiation sensitivity and tumor susceptibility in ATM phospho-mutant ATF2 mice. *Genes Cancer* **1**, 316-330.
- Li, X. Y. and Green, M. R. (1996). Intramolecular inhibition of activating transcription factor-2 function by its DNA-binding domain. *Genes Dev.* **10**, 517-527.
- Liao, H., Hyman, M. C., Baek, A. E., Fukase, K. and Pinsky, D. J. (2010). cAMP/CREB-mediated transcriptional regulation of ectonucleoside triphosphate diphosphohydrolase 1 (CD39) expression. *J. Biol. Chem.* **285**, 14791-14805.
- Licht, A. H., Pein, O. T., Florin, L., Hartenstein, B., Reuter, H., Arnold, B., Lichter, P., Angel, P. and Schorpp-Kistner, M. (2006). JunB is required for endothelial cell morphogenesis by regulating core-binding factor beta. *J. Cell Biol.* **175**, 981-991.
- Lin, D. W., Chang, I. C., Tseng, A., Wu, M. L., Chen, C. H., Patenaude, C. A., Layne, M. D. and Yet, S. F. (2008). Transforming growth factor beta up-regulates cysteine-rich protein 2 in vascular smooth muscle cells via activating transcription factor 2. *J. Biol. Chem.* **283**, 15003-15014.
- Liu, H., Deng, X., Shyu, Y. J., Li, J. J., Taparowsky, E. J. and Hu, C. D. (2006). Mutual regulation of c-Jun and ATF2 by transcriptional activation and subcellular localization. *EMBO J.* **25**, 1058-1069.
- Liu, W., Ouyang, X., Yang, J., Liu, J., Li, Q., Gu, Y., Fukata, M., Lin, T., He, J. C., Abreu, M. et al. (2009). AP-1 activated by toll-like receptors regulates expression of IL-23 p19. *J. Biol. Chem.* **284**, 24006-24016.
- Livingstone, C., Patel, G. and Jones, N. (1995). ATF-2 contains a phosphorylation-dependent transcriptional activation domain. *EMBO J.* **14**, 1785-1797.
- Lopez-Bergami, P., Lau, E. and Ronai, Z. (2010). Emerging roles of ATF2 and the dynamic AP1 network in cancer. *Nat. Rev. Cancer* **10**, 65-76.
- Ma, C., Ying, C., Yuan, Z., Song, B., Li, D., Liu, Y., Lai, B., Li, W., Chen, R., Ching, Y. P. et al. (2007). dp5/HRK is a c-Jun target gene and required for apoptosis induced by potassium deprivation in cerebellar granule neurons. *J. Biol. Chem.* **282**, 30901-30909.
- Maekawa, T., Bernier, F., Sato, M., Nomura, S., Singh, M., Inoue, Y., Tokunaga, T., Imai, H., Yokoyama, M., Reimold, A. et al. (1999). Mouse ATF-2 null mutants display features of a severe type of meconium aspiration syndrome. *J. Biol. Chem.* **274**, 17813-17819.
- Maekawa, T., Shinagawa, T., Sano, Y., Sakuma, T., Nomura, S., Nagasaki, K., Mikki, Y., Saito-Obara, F., Inazawa, J., Kohno, T. et al. (2007). Reduced levels of ATF-2 predispose mice to mammary tumors. *Mol. Cell. Biol.* **27**, 1730-1744.
- Maekawa, T., Sano, Y., Shinagawa, T., Rahman, Z., Sakuma, T., Nomura, S., Licht, J. D. and Ishii, S. (2008). ATF-2 controls transcription of Maspin and GADD45 alpha genes independently from p53 to suppress mammary tumors. *Oncogene* **27**, 1045-1054.
- Markovics, J. A., Araya, J., Cambier, S., Somanath, S., Gline, S., Jablons, D., Hill, A., Wolters, P. J. and Nishimura, S. L. (2011). Interleukin-1beta induces increased transcriptional activation of the transforming growth factor-beta-activating integrin subunit beta8 through altering chromatin architecture. *J. Biol. Chem.* **286**, 36864-36874.
- Martin-Villalba, A., Winter, C., Brecht, S., Buschmann, T., Zimmermann, M. and Herdegen, T. (1998). Rapid and long-lasting suppression of the ATF-2 transcription factor is a common response to neuronal injury. *Brain Res. Mol. Brain Res.* **62**, 158-166.
- Matsuuo, N., Tanaka, S., Gordon, M. K., Koch, M., Yoshioka, H. and Ramirez, F. (2006). CREB-AP1 protein complexes regulate transcription of the collagen XXIV gene (Col24a1) in osteoblasts. *J. Biol. Chem.* **281**, 5445-5452.
- Mayer, S. I., Dexheimer, V., Nishida, E., Kitajima, S. and Thiel, G. (2008). Expression of the transcriptional repressor ATF3 in gonadotrophs is regulated by Egr-1, CREB, and ATF2 after gonadotropin-releasing hormone receptor stimulation. *Endocrinology* **149**, 6311-6325.
- Merika, M., Williams, A. J., Chen, G., Collins, T. and Thanos, D. (1998). Recruitment of CBP/p300 by the IFN beta enhanceosome is required for synergistic activation of transcription. *Mol. Cell* **1**, 277-287.
- Min, B. W., Kim, C. G., Ko, J., Lim, Y., Lee, Y. H. and Shin, S. Y. (2008). Transcription of the protein kinase C-delta gene is activated by JNK through c-Jun and ATF2 in response to the anticancer agent doxorubicin. *Exp. Mol. Med.* **40**, 699-708.
- Nagadoi, A., Nakazawa, K., Uda, H., Okuno, K., Maekawa, T., Ishii, S. and Nishimura, Y. (1999). Solution structure of the transactivation domain of ATF-2 comprising a zinc finger-like subdomain and a flexible subdomain. *J. Mol. Biol.* **287**, 593-607.
- Nagase, T., Sudo, T., Maekawa, T., Yoshimura, T., Fujisawa, J., Yoshida, M. and Ishii, S. (1990). Promoter region of the human CRE-BP1 gene encoding the transcriptional regulator binding to the cyclic AMP response element. *J. Biol. Chem.* **265**, 17300-17306.
- Nogueira, E. F. and Rainey, W. E. (2010). Regulation of aldosterone synthase by activator transcription factor/cAMP response element-binding protein family members. *Endocrinology* **151**, 1060-1070.
- O'Neil, J. D., Owen, T. J., Wood, V. H., Date, K. L., Valentine, R., Chukwuma, M. B., Arrand, J. R., Dawson, C. W. and Young, L. S. (2008). Epstein-Barr virus-encoded EBNA1 modulates the AP-1 transcription factor pathway in nasopharyngeal carcinoma cells and enhances angiogenesis in vitro. *J. Gen. Virol.* **89**, 2833-2842.
- Ouwens, D. M., de Ruiter, N. D., van der Zon, G. C., Carter, A. P., Schouten, J., van der Burgt, C., Kooistra, K., Bos, J. L., Maassen, J. A. and van Dam, H. (2002). Growth factors can activate ATF2 via a two-step mechanism: phosphorylation of Thr71 through the Ras-MEK-ERK pathway and of Thr69 through RalGDS-Src-p38. *EMBO J.* **21**, 3782-3793.
- Pearson, A. G., Curtis, M. A., Waldvogel, H. J., Faull, R. L. and Dragunow, M. (2005). Activating transcription factor 2 expression in the adult human brain: association with both neurodegeneration and neurogenesis. *Neuroscience* **133**, 437-451.
- Penix, L. A., Sweetser, M. T., Weaver, W. M., Hoeffler, J. P., Kerppola, T. K. and Wilson, C. B. (1996). The proximal regulatory element of the interferon-gamma promoter mediates selective expression in T cells. *J. Biol. Chem.* **271**, 31964-31972.
- Read, M. A., Whitley, M. Z., Gupta, S., Pierce, J. W., Best, J., Davis, R. J. and Collins, T. (1997). Tumor necrosis factor alpha-induced E-selectin expression is activated by the nuclear factor-kappaB and c-JUN N-terminal kinase/p38 mitogen-activated protein kinase pathways. *J. Biol. Chem.* **272**, 2753-2761.

- Reimold, A. M., Grusby, M. J., Kosaras, B., Fries, J. W., Mori, R., Maniwa, S., Clauss, I. M., Collins, T., Sidman, R. L., Glimcher, M. J. et al.** (1996). Chondrodysplasia and neurological abnormalities in ATF-2-deficient mice. *Nature* **379**, 262-265.
- Ronai, Z., Yang, Y. M., Fuchs, S. Y., Adler, V., Sardana, M. and Herlyn, M.** (1998). ATF2 confers radiation resistance to human melanoma cells. *Oncogene* **16**, 523-531.
- Salameh, A., Galvagni, F., Anselmi, F., De Clemente, C., Orlandini, M. and Oliviero, S.** (2010). Growth factor stimulation induces cell survival by c-Jun. ATF2-dependent activation of Bcl-XL. *J. Biol. Chem.* **285**, 23096-23104.
- Sanalkumar, R., Indulekha, C. L., Divya, T. S., Divya, M. S., Anto, R. J., Vinod, B., Vidyarand, S., Jagatha, B., Venugopal, S. and James, J.** (2010). ATF2 maintains a subset of neural progenitors through CBF1/Notch independent Hes-1 expression and synergistically activates the expression of Hes-1 in Notch-dependent neural progenitors. *J. Neurochem.* **113**, 807-818.
- Seong, K. H., Li, D., Shimizu, H., Nakamura, R. and Ishii, S.** (2011). Inheritance of stress-induced, ATF-2-dependent epigenetic change. *Cell* **145**, 1049-1061.
- Sevilla, A., Santos, C. R., Vega, F. M. and Lazo, P. A.** (2004). Human vaccinia-related kinase 1 (VRK1) activates the ATF2 transcriptional activity by novel phosphorylation on Thr-73 and Ser-62 and cooperates with JNK. *J. Biol. Chem.* **279**, 27458-27465.
- Shah, M., Bhoumik, A., Goel, V., Dewing, A., Breitwieser, W., Kluger, H., Krajewski, S., Krajewska, M., Dehart, J., Lau, E. et al.** (2010). A role for ATF2 in regulating MITF and melanoma development. *PLoS Genet.* **6**, e1001258.
- Shimizu, M., Nomura, Y., Suzuki, H., Ichikawa, E., Takeuchi, A., Suzuki, M., Nakamura, T., Nakajima, T. and Oda, K.** (1998). Activation of the rat cyclin A promoter by ATF2 and Jun family members and its suppression by ATF4. *Exp. Cell Res.* **239**, 93-103.
- Shoshan-Barmatz, V., Zakar, M., Rosenthal, K. and Abu-Hamad, S.** (2009). Key regions of VDAC1 functioning in apoptosis induction and regulation by hexokinase. *Biochim. Biophys. Acta* **1787**, 421-430.
- Shuman, J. D., Cheong, J. and Coligan, J. E.** (1997). ATF-2 and C/EBPalpha can form a heterodimeric DNA binding complex in vitro. Functional implications for transcriptional regulation. *J. Biol. Chem.* **272**, 12793-12800.
- Song, N., Kim, S. J., Kwon, H. Y., Son, S. W., Kim, K. S., Ahn, H. B. and Lee, Y. C.** (2011). Transcriptional activation of human GM3 synthase (hST3Gal V) gene by valproic acid in ARPE-19 human retinal pigment epithelial cells. *BMB Rep.* **44**, 405-409.
- Suzuki, T., Yamakuni, T., Hagiwara, M. and Ichinose, H.** (2002). Identification of ATF-2 as a transcriptional regulator for the tyrosine hydroxylase gene. *J. Biol. Chem.* **277**, 40768-40774.
- Takeda, J., Mackawa, T., Sudo, T., Seino, Y., Imura, H., Saito, N., Tanaka, C. and Ishii, S.** (1991). Expression of the CRE-BP1 transcriptional regulator binding to the cyclic AMP response element in central nervous system, regenerating liver, and human tumors. *Oncogene* **6**, 1009-1014.
- Towers, E., Gilley, J., Randall, R., Hughes, R., Kristiansen, M. and Ham, J.** (2009). The proapoptotic dp5 gene is a direct target of the MLK-JNK-c-Jun pathway in sympathetic neurons. *Nucleic Acids Res.* **37**, 3044-3060.
- Vale-Cruz, D. S., Ma, Q., Syme, J. and LuValle, P. A.** (2008). Activating transcription factor-2 affects skeletal growth by modulating pRb gene expression. *Mech. Dev.* **125**, 843-856.
- van Dam, H. and Castellazzi, M.** (2001). Distinct roles of Jun : Fos and Jun: ATF dimers in oncogenesis. *Oncogene* **20**, 2453-2464.
- Walia, V., Mu, E. W., Lin, J. C. and Samuels, Y.** (2012). Delving into somatic variation in sporadic melanoma. *Pigment Cell Melanoma Res.* **25**, 155-170.
- Wang, L., Payton, R., Dai, W. and Lu, L.** (2011). Hyperosmotic stress-induced ATF-2 activation through Polo-like kinase 3 in human corneal epithelial cells. *J. Biol. Chem.* **286**, 1951-1958.
- Xiao, L., Rao, J. N., Zou, T., Liu, L., Marasa, B. S., Chen, J., Turner, D. J., Zhou, H., Gorospe, M. and Wang, J. Y.** (2007). Polyamines regulate the stability of activating transcription factor-2 mRNA through RNA-binding protein HuR in intestinal epithelial cells. *Mol. Biol. Cell* **18**, 4579-4590.
- Xiao, L., Rao, J. N., Zou, T., Liu, L., Yu, T. X., Zhu, X. Y., Donahue, J. M. and Wang, J. Y.** (2010). Induced ATF-2 represses CDK4 transcription through dimerization with JunD inhibiting intestinal epithelial cell growth after polyamine depletion. *Am. J. Physiol. Cell Physiol.* **298**, C1226-C1234.
- Yamada, T., Yoshiyama, Y. and Kawaguchi, N.** (1997). Expression of activating transcription factor-2 (ATF-2), one of the cyclic AMP response element (CRE) binding proteins, in Alzheimer disease and non-neurological brain tissues. *Brain Res.* **749**, 329-334.
- Yamasaki, T., Takahashi, A., Pan, J., Yamaguchi, N. and Yokoyama, K. K.** (2009). Phosphorylation of Activation Transcription Factor-2 at Serine 121 by Protein Kinase C Controls c-Jun-mediated Activation of Transcription. *J. Biol. Chem.* **284**, 8567-8581.
- Villarreal, X. C. and Richter, J. D.** (1995). Analysis of ATF2 gene expression during early Xenopus laevis development. *Gene* **153**, 225-229.
- Zhang, J. Y., Jiang, H., Gao, W., Wu, J., Peng, K., Shi, Y. F. and Zhang, X. J.** (2008). The JNK/AP1/ATF2 pathway is involved in H2O2-induced acetylcholinesterase expression during apoptosis. *Cell. Mol. Life Sci.* **65**, 1435-1445.
- Zhu, W., Chandrasekharan, U. M., Bandyopadhyay, S., Morris, S. M., Jr, DiCorleto, P. E. and Kashyap, V. S.** (2010). Thrombin induces endothelial arginase through AP-1 activation. *Am. J. Physiol. Cell Physiol.* **298**, C952-C960.