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Emerging roles of ATF2 and the dynamic AP1 network in cancer

Pablo Lopez-Bergami,
Instituto de Biologia y Medicina Experimental, Vuelta de Obligado 2490, Buenos Aires1428, Argentina, pablo.bergami@gmail.com

Eric Lau, and
Signal Transduction Program, Burnham Institute for Medical Research, La Jolla, CA 92037, USA, elau@burnham.org

Ze'ev Ronai
Signal Transduction Program, Burnham Institute for Medical Research, La Jolla, CA 92037, USA

Abstract

Cooperation among transcription factors is central for their ability to execute specific transcriptional programmes. The AP1 complex exemplifies a network of transcription factors that function in unison under normal circumstances and during the course of tumour development and progression. This Perspective summarizes our current understanding of the changes in members of the AP1 complex and the role of ATF2 as part of this complex in tumorigenesis.

Activator protein 1 (AP1)[1,2] functions in almost all areas of eukaryotic cellular behaviour, from cell cycle proliferation and development to stress response and apoptosis. Indeed, AP1 is activated in response to a plethora of extracellular signals from cytokines and growth factors to stress and inflammation[3,4]. The expansive transcriptional repertoire executed by AP1 complexes is propagated from the diverse compositional array of homodimeric or heterodimeric combinations formed by members of the Jun, Atf, Fos and Maf transcription factor families (BOX 1). The dimeric combinations and transcriptional activity observed *in vivo* are largely influenced by the tissue-specific expression patterns of the individual proteins, and importantly by their specific activating mechanisms and post-translational modifications that facilitate their individual ability to dimerize with other basic leucine zipper (bZIP) domain proteins. This inherently diverse composition of AP1 complexes and their central role in transcriptional regulation places AP1 complexes at a functional epicenter for pathological signal relay in disease, particularly in the context of malignant cellular transformation in which AP1 proteins are often deregulated by oncoprotein signalling[4–6]. This Perspective describes the function and cooperation of Jun, Fos and Atf family members in tumour cells, and the emerging function of ATF2 as part of the dynamic AP1 complex.

Competing interests statement: The authors declare no competing financial interests.

Databases: **Entrez Gene:** http://www.ncbi.nlm.nih.gov/gene
JUN
UniProtKB: http://www.uniprot.org
ATF2 | ATF3 | ATF4 | cathepsin L | CREB1 | cyclin A | ezrin | FBXW7 | FOS | FOSB | FRA1 | FRA2 | HMGA1 | JNK1 | JNK2 | JUNB | JUND | MMP1 | MMP2 | MMP3 | MMP9 | SENP1 | Stathmin | VEGFA
Pathway interaction Database: http://pid.nci.nih.gov/
ATF2

Further Information: Ze'ev Ronai's homepage: http://www.ronailab.net

Supplementary Information: See online article: S1 (table) | S2 (table) | S3 (table)
ALL LINKS ARE ACTIVE IN THE ONLINE PDF

Box 1

The Ap1 transcription factor complex

The mammalian AP1 proteins are homodimers and heterodimers composed of proteins from the Jun (JUN, JUNB and JUND) and Fos (FOS, FOSB, FRA1 and FRA2) families, and the closely related activating transcription factor (Atf and Creb) subfamily and the Maf subfamily[5]. AP1 constituent proteins are structurally distinguished by a basic leucine zipper (bZIP) domain that is composed of leucine zipper and basic domains. It is through these domains that AP1 proteins dimerize and bind to DNA. These proteins are typically activated through phosphorylation by the indicated upstream kinases. The different AP1 dimers bind to DNA with varying affinities and differ in their transactivation efficiencies[8,15]. Jun proteins can form stable dimers that bind to the AP1 DNA recognition element 5′-TGAC/GTCA-3′ (also known as TPA response element (TRE)) based on their ability to mediate transcriptional induction in response to the phorbol ester tumour promoter TPA[2,15]. Atf proteins, conversely, form dimers that preferentially bind to cyclic AMP responsive elements (CRE; 5′-TGACGTCA-3′)[15]. AP1 proteins also dimerize efficiently with other transcription factors, including some that are not members of the bZIP family[193].

JUN and the Jun family

JUN was originally identified as the normal cellular counterpart of the avian sarcoma (ASV17) viral Jun oncoprotein (v-jun)[7]. The Jun family consists of JUN, JUNB and JUND, and each protein has distinct characteristics. JUN is important for cell proliferation, survival and apoptosis, and accordingly mice lacking JUN die between day 12.5 and 13.5 of embryonal development owing to hepatic failure and heart defects[8,9]. Similarly, JUNB is essential for embryonal development, however, JUND is dispensable[10]. Although the *JUN* locus is not mutated in human cancer, it was recently shown to be a target of 1p32 amplifications in undifferentiated and aggressive human sarcomas[11,12]. Moreover, many human cancers exhibit overexpression of JUN and/or other Jun family members (TABLE 1), which in most cases, is the result of upstream oncogene activation[13]. There is now good evidence that JUN activation is a crucial contributing factor for transformation and tumorigenesis, rather than an indirect effect of oncogenesis.

JUN activation

JUN is an ‘immediate early gene’ and is responsive to mitogenic stimuli, as well as DNA damage and stress. JUN expression levels are tightly controlled by a combination of protein stability and a short mRNA half-life of 20–25 minutes, owing to an AU-rich RNA destabilizing element in the 3′-untranslated region. Post-translational modifications trigger a positive autoregulatory loop that involves the binding of AP1 dimers to a phorbol TPA response element (TRE; also known as a JUN1 site) and a cyclic AMP responsive element CRE (also known as a JUN2 site) in the *JUN* promoter resulting in increased transcription[14]. The AP1 dimers primarily involved in *JUN* transcription are JUN– FOS and JUN–ATF2 for TRE and CRE, respectively[15]. *JUN* transcription is also induced by SP1, nuclear factor-κB (NF-κB), ternary complex factors (TCFs), MEF2 or CCAAT-binding transcription factors[16,17]. ERK contributes to *JUN* transcription by activating FOS, TCFs and MEF2[17]. The signals that trigger *JUN* transcription also activate RNA-binding proteins that increase *JUN* mRNA stability. In all cases, JUN exhibits a rapid, but transient upregulation, which effectively stimulates the transcription of genes important for entry into the G1 and S phases of the cell cycle such as cyclin D1 (REF. 11), cyclin A[18] and cyclin E. However, JUN also controls anti-proliferative cell cycle regulators such as p53 (REFS 19,20), p21, INK4A[13] and ARF[19,21] (for an extensive review of JUN transcriptional targets see REF. 8; representative JUN targets are shown in

Supplementary information S1 (table)). Despite the high degree of sequence homology shared between the three Jun proteins, they have distinct transactivation properties and biological effects, mainly attributed to the lower degree of conservation of the amino-terminal region (residues 1–95). Although JUN and JUND have strong transactivation activity, the transcriptional activity of JUNB is much weaker[22], and unlike JUN, both JUNB and JUND can repress transcription[22–24].

Consistent with its important role in cell cycle regulation, JUN levels and N-terminal phosphorylation (which is crucial for its activation) are cell cycle regulated[25,26]. Ectopic overexpression of JUN promotes cell growth in many cell lines[27,28], whereas mouse fibroblasts lacking JUN and cancer cells expressing TAM67 — a dominant-negative form of JUN that lacks the transactivation domain encompassing amino acids 3–122 — exhibit severely impaired or inhibited proliferation, demonstrating the central role that JUN has in cell growth and tumorigenesis[20,29–31]. It should be noted that TAM67 generally inhibits AP1, regardless of the specific binding partner, owing to its promiscuous interaction with most AP1 proteins. The role of JUNB and JUND is more complex, and they can promote or inhibit growth under different conditions. In *Jun*-knockout mice *Junb* can rescue *Jun*-induced phenotypes in a dose-dependent manner[32] and prevent p53 expression. These experiments suggest that, in the absence of *Jun*, *Junb* exhibits proliferative effects and its anti-proliferative activity requires the formation of a growth-inhibiting JUN–JUNB heterodimer. Similarly, *Jund* can suppress p53-induced senescence and apoptosis in fibroblasts[19], although it has also been observed to function as a tumour suppressor[10,13]. It is thought that this dual role depends on an interaction with the tumour suppressor Menin[33]. However, most of the evidence indicates that JUND antagonizes JUN in cell growth regulation and transformation[19]. Notably, JUNB and JUND are regulated by different protein kinases than the kinases that regulate JUN. Therefore, stimuli that differentially activate JUNB and JUND regulatory kinases might dictate positive or negative effects on the interaction of JUNB or JUND with JUN and so on their corresponding response elements.

JUN function, stability[34] and transactivation potential[35] are crucially enhanced by phosphorylation of Ser63 and Ser73 by JUN N-terminal kinase (JNK)[17], which docks with JUN primarily through the δ-domain (amino acids 34–60) of JUN[8] (FIG. 1). Increasing evidence implicates differential regulation of JUN by JNK1 compared with JNK2, which may explain the variable binding affinity that JUN exhibits to JNK family members[36,37]. JNK-mediated phosphorylation can stimulate JUN transcriptional activity by promoting either interaction with basal transcriptional machinery or co-activators[38–40], or by promoting dissociation of transcriptional repressor complexes containing histone deacetylase 3 ([REF. 41]). Therefore, JUN can regulate gene transcription through the regulation of transcriptional machinery including RNA polymerase II, as well as other co-activators or co-repressors, and chromatin structural changes. Although JNK phosphorylation sites on Ser63 and Ser73 are conserved, the Jun proteins differ markedly in their regulation by JNK[42]. JUNB has a JNK docking site, but the lack of phospho-acceptor residues prevents its phosphorylation by JNK. By contrast, JUND lacks an effective docking site, resulting in only weak phosphorylation by JNK[42]. These residues of JUND can still be phosphorylated by ERK1 and ERK2 ([REF. 43]). Whether these phosphorylations affect differential dimerization with other AP1 partners remains largely unexplored.

JUN degradation

In most cells, JUN is a labile protein (with a half-life of approximately 2 hours), and its expression levels are tightly regulated by polyubiquitylation on multiple lysine residues and concomitant degradation by the 26S proteasome[34] (FIG. 2). Stabilization of JUN occurs following inactivation of GSK3, attributable to ERK and PI3K–Akt signalling cascades[44,45].

Inhibition of GSK3-dependent phosphorylation of JUN on Ser243 prevents binding of the E3 ligase F-box and WD domain repeated 7 (FBXW7), which targets JUN for polyubiquitylation and proteasomal degradation[46,47]. Whether FBXW7 degrades active (N-terminally phosphorylated by JNK) or inactive JUN molecules, is controversial[47,48]. JUN stability is increased after phosphorylation by JNK, which promotes degradation of JUN under non-stressed conditions[17,36,49,50]. JUN is also subject to sumoylation, which reduces the transcriptional activity of the JUN–FOS heterodimer[51]. Interestingly, the SUMO protease, SENP1, increases JUN-mediated transcription through the desumoylation of the p300 CRD1 domain, offering an alternative mechanism for the regulation of JUN transcription[52]. Although ubiquitin and SUMO modifications were also identified for other members of the AP1 family, the role of these modifications remains largely unexplored. For example, JUNB seems to undergo ubiquitylation-mediated proteasomal degradation, although the ubiquitin ligase that controls this modification is still unknown[53]. JUNB was shown to be sumoylated in T cells, resulting in its transcriptional activation[54]. Although JUND is also ubiquitylated, the consequences of this modification are yet to be determined, as its ubiquitylation does not result in its degradation[55].

FOS and the Fos family

The Fos family of transcription factors is composed of FOS, FOSB, FOS-related antigen 1 (FRA1; also known as FOSL1) and FRA2 (also known as FOSL2). Apart from the classic bZIP domain and basic DNA binding domain in other AP1 proteins, FOS and FOSB also have strong transactivation domains, which FRA1 and FRA2 do not possess[56]. Fos family members can heterodimerize with JUN and some Atf family members, giving rise to complexes with different biochemical and transcriptional behaviour[15]. The negative charge of residues adjacent to the hydrophobic interphase of their leucine zipper electrostatically destabilizes Fos homodimers[57] and favours the formation of JUN–FOS heterodimers, which exhibit increased stability, DNA-binding activity and greater transforming potential.

Fos activation and degradation

Like Jun family members, FOS and FOSB are immediate early genes expressed at low or undetectable levels in most cell types, with rapid and transient transcriptional activation following mitogenic stimuli or cellular stress[58]. Within minutes of growth factor stimulation and subsequent ERK activation, transcription of both genes is induced by ELK1, the cyclic AMP response element-binding protein (CREB) and serum-response factor (SRF). Although transcription of *FRA1* and *FRA2* also increases as a result of mitogenic stimulation through TRE, SRE, MYC and Atf sites, they are often expressed under non-stimulated conditions[59]. Similar to *JUN*, *FRA1* transcription is partly autoregulated by an AP1 site[60].

FOS activity and degradation are primarily regulated by phosphorylation. The major phospho-acceptor sites include Thr325, Thr331 and Ser374, which are phosphorylated by ERK, Ser362, phosphorylated by RSK1 and RSK2 (which are substrates of ERK), and Thr232, phosphorylated by an unknown kinase[61]. Transient activation of ERK alone results in Ser374 and Ser362 phosphorylation and stabilization of FOS, but these are insufficient to increase its transcriptional activity. Rather, these two modifications expose a docking site for ERK, which facilitates ERK-mediated phosphorylation of Thr331 and Thr325 that increases FOS transcriptional activity[62]. FOS is also phosphorylated by p38 at Thr232, Thr325, Thr331 and Ser374 in response to ultraviolet light treatment[63]. Unlike JUN, FOS is primarily degraded by the proteasome through ubiquitin-independent mechanisms. FOS degradation is differentially regulated by autonomous degrons at its N-terminal and carboxy-terminal ends. The activity of the C-terminal degron is reduced by phosphorylation of Ser362 and Ser374 ([REF. 64]). Similarly, FRA1 stabilization relies on the inhibition of a C-terminal degron by ERK-mediated phosphorylation of Ser252 and Ser265 ([REF. 61]). FOS shuttles between the nucleus and the

cytoplasm owing to the presence of two nuclear localization signals. Dimerization with Jun proteins inhibits FOS nuclear export (notably, the strongest nuclear retention of FOS is observed when dimerized with JUN), thereby preventing the degradation of monomeric FOS in the cytoplasm[65]. Like other integral members of the AP1 transcriptional complex, Fos family members are reportedly deregulated in numerous human pathologies, and particularly in cancer (Supplemental information S2 (table)).

ATF2

ATF2 is one of 16 members of the Atf and Creb group of bZIP transcription factors that contribute to multiple cellular functions, from development to cellular responses to stresses, such as hypoxia or DNA damage response[66–68]. Although particularly enriched in brain tissue[69], ATF2 is an ubiquitously expressed protein that is implicated in transcriptional control, chromatin remodelling and the DNA damage response[70–72]. Complete somatic loss of *Atf2* results in postnatal lethality, whereas partial deregulation of ATF2 is implicated in cancer[73–79].

ATF2 is located on chromosome 2q32 and comprises 12 exons, and in its full-length form, is translated into a protein 505 amino acids in length[80]. Like JUN and FOS, ATF2 is also characterized by a basic structural region and a leucine zipper domain that are crucial for AP1 homodimerization and heterodimerization[81]. ATF2 contains two canonical nuclear localization sequences (NLS) and one export sequence (NES) in its basic and leucine zipper regions, respectively. Its nuclear export has been shown to be CRM1-dependent[82]. Further complexity is added by tissue-specific expression of ATF2 splice variants, although to date studies evaluating the function of the splice variants have been limited (BOX 2).

ATF2 phosphorylation

ATF2 is negatively regulated by intramolecular auto-inhibitory binding of its C-terminal DNA binding domain to its N-terminal activation domain[83]. This prevents ATF2 monomers from dimerizing with partner proteins during unstimulated (unstressed) conditions. Whether ATF2 monomers have a cellular function is unknown. In response to stress stimuli or cytokines, ATF2 is phosphorylated on Thr69 and/or Thr71 by either JNK or p38. Certain growth factors have also been shown to induce ERK-dependent phosphorylation of ATF2 on Thr71 followed by RALGDS–SRC–p38-dependent phosphorylation of Thr69 (REF. 84). In all cases, phosphorylation of these residues is required to de-repress ATF2 intramolecular inhibition allowing its homodimerization or heterodimerization with other members of the AP1 transcription factor family, such as JUN (Supplemental information S3 (table)), CREB, Fos and Fra[85]. The N-terminal phosphorylation of ATF2 and its dimerization, which facilitate ATF2 transcriptional function, also promote its ubiquitylation and degradation — a mechanism that limits ATF2 transcriptional output. Indeed, ATF2 mutants that are incapable of dimerization exhibit enhanced protein stability[86–88]. Phosphorylation of ATF2 at C-terminal Ser490 and Ser498 by ataxia-telangectasia mutated (ATM) is required for the contribution of ATF2 to the DNA damage response. ATM phosphorylation of ATF2 is important for the intra-S phase checkpoint following ionizing radiation (IR), essential for halting entry into the DNA replication phase of cell cycle. Furthermore, this phosphorylation was also found to promote ATF2 localization at irradiation-induced foci where it localizes with components of the DNA repair machinery, including MRE11, RAD50 and NBS1 (REF. 89). Another kinase shown to phosphorylate ATF2 on Ser121 is PKC, and this is essential for ATF2-mediated late-phase response to stress[90].

ATF2 transcriptional targets

The basic DNA binding region of ATF2 homodimers exhibits binding specificity for CRE sequences, *TGACGTCA*[91]. However, depending on specific stimulus and cell type context, ATF2 can interact with other promoter elements including, but not limited to, other AP1 sequences, the proximal promoter of interferon-γ, stress-response element and the URE promoter. Like Jun and Fos family members, ATF2 dimerization with different partners significantly influences DNA binding specificity and affinity[15,78,92,93], and ultimately the transcriptional outcome.

Although it is unknown whether ATF2 itself is cell cycle regulated, ATF2 does regulate cell cycle progression through the transcriptional control of several key genes, including *RB1*, cyclin A, cyclin D, *GADD45A*, *GADD45B* and maspin (TABLE 2). ATF2 can further enhance proliferation by promoting survival through regulation of *Bcl2* expression in certain cell types[94]. ATF2 transcriptionally regulates a wide array of gene targets controlling other cellular pathways, ranging from Atf, Jun and Fos transcription factors, to extracellular, cytokine and intracellular signalling pathways (TABLE 2).

JUN, FOS and ATF2 in tumorigenesis

JUN overexpression *in vitro* is sufficient, in certain cases, to transform mammalian cells[8]. Consistently, loss of JUN decreases the incidence of papilloma outgrowth by abrogation of epidermal growth factor receptor (EGFR) signalling in skin subjected to the two-stage skin carcinogenesis protocol[95]. However, transformation of other cells, such as rat embryonic fibroblasts, require the presence of either additional oncogenes such as Ras and SRC or other AP1 components such as FRA1 ([REFS 8,96]). Despite its oncogenic potential *in vitro*, JUN overexpression in transgenic mice does not result in the development of tumours[8,13]. HRAS-induced transformation of immortalized mouse fibroblasts requires JUN expression, as transformation is suppressed in the absence of JUN or the presence of a dominant-negative JUN[97]. Fibroblasts with JUN Ala63 and Ala73 can be efficiently transformed by v-ras, but show reduced tumorigenicity in nude mice[98]. This is consistent with the ability of v-jun to contribute to cell transformation despite a lack of phosphorylation on the Ser63 and Ser73 sites. The expression of oncogenic HRAS can increase AP1 transcriptional activity by activating ERK and JNK, leading to increased expression of Fos proteins and N-terminal phosphorylation of JUN[99]. An alternative mechanism was recently proposed by Talotta *et al.*[100], who showed that HRAS can trigger a positive AP1 feedback loop in solid tumours through promoting JUN–FRA1 heterodimer formation with subsequent upregulation of microRNA-21. As a result, miR-21 causes the downregulation of tumour suppressors and negative AP1 regulators, including the tumour suppressor PTEN and programmed cell death 4 (PDCD4)[100].

Fos family proteins have oncogenic potential both *in vitro* and *in vivo* by regulating proliferation and transformation, angiogenesis, tumour invasion and metastasis[101]. Expression of FRA1 confers anchorage-independent growth in rat fibroblasts *in vitro* and promotes tumour development in athymic mice[102]. Similar to JUN, FOS overexpression correlates with tumour grade and adverse outcome in some cancers. Its overexpression alone is sufficient to transform chicken embryonic fibroblasts[103], and its oncogenicity is linked to JUN, as immortalized fibroblasts expressing v-ras, v-fos and a non-JNK phosphorylatable JUN mutant showed reduced tumorigenicity in nude mice[98]. Transgenic expression of *Fos* promoted the transformation of chondroblasts and osteoblasts, resulting in chondrogenic and osteogenic tumour formation in mice[104]. Overexpression of FRA2 in mice can also induce tumour formation in the pancreas, thymus and lung[4]. Knockdown or dominant-negative mutants of FOS can abrogate transformation by upstream oncogenes, such as activated Ras[105,106]. However, in contrast to their oncogenic contributions, recent reports suggest a possible tumour suppressor role for the Fos family. For instance, ubiquitous FRA1 overexpression accelerates

osteoblast differentiation and subsequent osteosclerosis[107], whereas overexpression of FOS inhibits cell cycle progression, stimulating mouse hepatocyte cell death and strongly suppresses tumour formation *in vivo*[108]. Based on findings from human familial breast and ovarian cancer, one possible mechanism for the tumour-suppressor activity of FOS could be its potential involvement in the regulation of BRCA1 ([REF. 109]). The function of FOS in apoptosis might also influence its capacity to suppress tumour formation (see below). Together, these data highlight the functional duality of Fos family transcription factors and the importance of their tissue-specific context and resulting heterodimerization partners.

Box 2

ATF2 splice variants

Differential splicing or promoter usage in a tissue-specific manner can result in the expression of alternative splice isoforms of ATF2. Of the studied isoforms, most are ubiquitously expressed, with particular variants exhibiting tissue-specific enrichment. Studies on murine T cells revealed three isoforms (CRE-BP1, CRE-BP2 and CRE-BP3) of ATF2. The basic leucine zipper domain (bZIP) domain is conserved between these isoforms and variation between them resides mostly in their amino- and extreme carboxy-termini[194,195], where ATF2 is frequently post-translationally modified and regulated[85]. Whereas CRE-BP2 lacks exons 1–7 and most of exon 12, CRE-BP2 varies from CRE-BP1 by an 8 amino acid substitution for the first 15 amino acids of CRE-BP1 only. This diversity suggests conservation of the transcription factor function between these isoforms, but variation in their regulation. ATF2-sm is an intriguing isoform of ATF2 that lacks all major bZIP functional domains and comprises the first and last two exons of full-length ATF2 only. It has been shown to be transcriptionally active, and exhibits polarized expression patterns in myometrial tissue and is differentially regulated before and during pregnancy and labour. Such differential expression patterns suggest that different ATF2 isoforms have tissue and temporal-specific functions, an idea that is supported by the finding that ATF2 and ATF2-sm transcriptionally regulate distinct subsets of genes[196].

Evidence to date indicates that ATF2 can elicit tumour suppressor or oncogene activities in a cell- and tissue-dependent context[4]. For example, in melanoma, inhibition of ATF2 activity by ATF2 inhibitory peptides results in the suppression of tumorigenesis and metastasis, concomitant with sensitization of melanoma tumour cells to genotoxic stress *in vitro* and *in vivo*[74,93,110,111]. Consistent with its cell cycle regulatory role, increased expression of ATF2 increased cell proliferation in mouse cancer models[112–114]. By contrast, expression of transcriptionally inactive ATF2 in the presence of oncogene activation (such as Ras mutations) in non-melanoma skin cancers increases papilloma formation owing to the deregulated expression of genes that promote proliferation, such as *CTNNB1* ([REF. 115]). In agreement with this, mammary tumour formation rates are accelerated in *Atf2* heterozygous mice that also carry a mutant allele of *Trp53* ([REF. 116]). Such results indicate that depending on the tissue type, ATF2 can elicit a tumour suppressive function, and that loss of ATF2 can cooperate with oncogenes and mutation of tumour suppressor genes to promote tumorigenesis[115]. As the loss of ATF2 alone does not induce tumour formation, but rather predisposes mouse models to more rapid onset and increased tumour incidence with additional genetic mutations, the functional loss of ATF2 might have a cooperative role as opposed to an initiator role in multistage tumorigenic processes[75,115].

A phenomenon that might shed light on the divergent function of ATF2 is its differential subcellular localization. Immunohistochemical studies have demonstrated an upregulation and activation of ATF2 in the nuclear compartment in certain cancer types[75,117–119]. Furthermore, immunohistochemical analysis of patient-derived tumour tissue microarrays found enriched

nuclear localization of ATF2 in advanced metastatic melanoma samples, which correlated with poor prognosis and survival[120]. By contrast, melanoma samples exhibiting strong cytoplasmic localization correlated with primary tumours and favourable prognosis. Analysis of tissue microarrays from patient-derived squamous and basal cell carcinoma samples revealed reduced nuclear levels and increased cytoplasmic levels of ATF2, further substantiating the idea that ATF2 transcriptional activity may be attenuated in non-melanoma and papillary tumours[115]. Recent studies using IR of prostate cancer cells showed that IR can induce cytoplasmic localization of ATF2, in contrast to its predominant nuclear localization during basal conditions[121]. Notably, cytoplasmic accumulation of ATF2 was associated with the appearance of a neuroendocrine-like (differentiation) phenotype. As ATF2 is known to promote differentiation in certain tissue contexts when dimerized with JUN, it is also possible that enhanced ATF2 binding with JUN might outcompete JUN binding with other factors, such as FOS and FRA2, both of which enhance cell cycle re-entry and progression[122]. Although the significance of the cytosolic localization of ATF2 is not known, its distinct distribution and activities probably depend on post-translational modification with available heterodimeric partners of the AP1 network (FIG. 3). Dimerization with JUN has been shown to promote nuclear import of ATF2 while monomeric ATF2 remained cytoplasmic, suggesting that monomeric forms of ATF2 in the cytoplasm have an alternative function[82].

AP1 in tumorigenesis

Chronic exposure to certain environmental or dietary carcinogens can promote tumorigenesis through the stimulation of a wide array of signalling pathways, ranging from inflammatory to pro-proliferative and survival pathways[23], and carcinogens have been observed to induce or at least correlate with increased AP1 activity. Long-term exposure to tobacco smoke or nicotine, for instance, activates AP1 activity in mouse brain or epithelial cell lines, and specifically, FOS and JUN are upregulated in rat and hamster cell lines during chronic asbestos exposure[123–126]. Chronic ethanol exposure of human neuroblastoma cells enhances AP1 activity[127]. In several studies, AP1 activity is crucial for tumorigenesis, as inhibition of AP1 function by dominant-negative JUN mutants or AP1 decoys, for example, effectively inhibits tumour formation *in vivo*. Such studies have also enabled the identification of AP1 target genes involved in different aspects of carcinogenesis[30,31,128,129]. Interestingly, AP1 activity is reported to be upregulated in certain tumour cell lines that acquire drug resistance after chronic anti-oestrogen therapy or cisplatin treatment, suggesting the possibility that some chemotherapeutic agents, similar to long-term carcinogenic stimuli, can elicit AP1 activation that can facilitate tumour survival and render them refractory to long-term treatments[130,131]. Numerous studies have shown the importance of AP1 in tumorigenesis.

Invasion and metastasis

Extensive evidence suggests that JUN and other AP1 proteins coordinate multigene expression programmes required for invasive and metastatic behaviour (Supplementary information S1, S3 (tables)). For example, AP1 has consistently been linked to invasive properties of aggressive breast cancer[132]. Overexpression of JUN in MCF7 breast cancer cells increased tumour formation in nude mice, as well as motility, invasiveness and liver metastasis[27]. Enforced expression of JUN in human bronchial epithelial cells significantly increased cell viability and colony formation in soft agar, whereas expression of TAM67 inhibited their anchorage-independent growth[29,133]. Similarly, the treatment of oral squamous cell carcinoma cells with AP1 decoys attenuates their invasiveness[134]. Consistently, cells from conditional *Jun*-knockout mice exhibit increased cellular adhesion, stress fibre formation and reduced cellular migration, a phenotype that was reverted by addition of stem cell factor (*SCF*; a JUN target gene)[135]. Among genes that are regulated by JUN and may mediate these changes are genes encoding Stathmin, HMGA1 or cyclin A[18,136,137]. Other JUN-induced genes that may

contribute to enhanced tumorigenesis are involved in cellular migration and invasion as well as inflammation (Supplementary information S1 (table)). These findings suggest that increased expression of JUN, as well as FOS (see below), may be involved in the acquisition of anchorage independence in the process of human carcinogenesis.

FOS family members transcriptionally regulate numerous genes involved in cell movement and invasiveness, such as the genes encoding matrix metalloproteinase 1 (MMP1), MMP3, cathepsin L and ezrin[138,139]. Therefore, it is not surprising that epithelial–mesenchymal transition can be induced by FOS[140]. As FRA1-containing complexes can activate transcription from both TRE and CRE elements, most of the genes shown to be activated by FOS have also been shown to be activated by FRA1 ([REFS 141,142]).

Several observations support a contribution of ATF2 to the regulation of cellular invasiveness and migration. For example, increased expression and phosphorylation of ATF2 correlates with increased tumour invasiveness in patients with extramammary Paget's disease[143]. Furthermore, *in vitro* studies with MCF10A cells demonstrate that ATF2 signalling driven by p38 mediates the transcription of MMP2, thereby influencing invasive migration[78]. Other members of the Atf and Creb family are also implicated in invasion and migration. For example, the expression of a dominant-negative CREB mutant impairs the invasiveness of MeWo melanoma cells[144].

Angiogenesis

Activated JUN is predominantly found at the invasive front of tumours and is associated with replicating cells, microvessel density and vascular endothelial growth factor A (VEGFA) expression[145]. Targeting *JUN* by catalytic DNA molecules known as DNAzymes blocked endothelial cell proliferation, migration, chemoinvasion and tubule formation in mouse tumour models[146]. The same DNAzymes also suppressed the growth and angiogenesis of solid squamous cell carcinomas in severe combined immunodeficient (SCID) mice by inhibiting MMP2, MMP9, VEGFA and fibroblast growth factor 2 expression[147]. This is consistent with previous data showing that a transactivation domain deletion mutant of JUN attenuated the formation of squamous cell carcinoma[148]. JUN was also found to control expression of proliferin, an angiogenic placental hormone that also has a role in tumour angiogenesis[149]. Recently, it was shown that interleukin-7 (IL-7) promotes lymphangiogenesis in lung cancer by inducing VEGFD expression that is dependent on FOS–JUN dimers[150].

Survival and apoptosis

The pro-apoptotic or anti-apoptotic function of JUN is cell type specific and dependent on both the type of external or internal stimuli and the potential JUN binding partners (Supplementary information S1 (table)). In part, the overexpression of JUN has been implicated in the induction of apoptosis in neurons[151], endothelial[152], myeloma cells[153] and fibroblasts[154], although the JUN targets have remained mostly unidentified. Activation of JNK and subsequent JUN phosphorylation has been associated to apoptotic cell death. However, Atf family members, such as ATF3, can cooperatively promote survival with JUN through the induction of heat shock protein 27 in neurons during injury, indicating that the heterodimerization of JUN with other AP1 factors can antagonize its pro-apoptotic functions.

Enhanced growth conferred by induction of JUN has been attributed not only to cell cycle alterations, but also to enhanced cell survival that is concomitant with the reduction of cell death. Among the mediators for cell survival signalling, JUN suppresses *PTEN*[155], which inhibits cell growth through negative regulation of the Akt survival pathway. Eferl *et al.*[156] showed that mice with a targeted disruption of *Jun* in hepatocytes[156] presented with reduced liver tumour mass and higher survival rates than control mice in a chemically induced

hepatocellular carcinoma model. JUN deficiency resulted in the accumulation of p53 and increased apoptosis without affecting the proliferation rate of these cells, confirming a role for JUN in cell survival. This function of JUN seems to be distinct from its role in proliferation, which also involves p53 (REF. 157). Therefore, JUN may promote tumorigenesis by antagonizing the proapoptotic and anti-proliferative activities of p53 through different mechanisms.

FOS also seems to have a pro-apoptotic function, as do FRA1 and FRA2. FOS mediates MYC-induced cell death, probably through the p38 MAPK pathway and the induction of CD95L and tumour necrosis factor-related apoptosis-inducing ligand (TRAIL)[158,159]. Moreover, reduced levels of FOS, FRA1 or FRA2 might potentiate chemoresistance[160–162]. The proapoptotic downstream molecular targets of FOS are mostly poorly understood. Interestingly, JUN and FRA1 also induce the expression of the tumour suppressor ARF — a key link between oncogenic signalling and the p53 pathway — which resulted in the induction of growth arrest in primary mouse fibroblasts[21].

In contrast to its pro-proliferative function, ATF2 has been found to mediate apoptosis in various circumstances, although specific signalling mechanisms remain largely understudied. For example, in chondrocytes, ATF2 and CREB1 can heterodimerize to directly regulate the *Bcl2* promoter[94]. ATF2 was shown to mediate apoptosis in non-differentiated PC12 cells[163].

With strong evidence to support the role of JUN in normal and tumour cell biology, and the observations that JUN can also induce apoptosis, under certain conditions[111,154,164], it is likely that these diverse functions are dependent on the nature of its heterodimeric partners. For example, abrogation of ATF2 interaction with JNK sensitizes melanoma cells to anisomycin-induced cell death that is JUN- and JUND-dependent, suggesting that a pro-apoptotic JUN and/or JUND-containing AP1 complex is enriched in the absence of active ATF2 (REF. 111). In neurons, JUN dimerization to ATF2 promotes apoptosis through the transcription of harakiri, whereas this is abrogated by increases in FOS expression, probably because FOS competes with JUN for binding to ATF2 (REF. 165). Conversely, FOS–JUN dimers have been shown to induce apoptosis in prostate cancer cells by the transcriptional repression of the anti-apoptotic molecule CASP8 and FADD-like apoptosis regulator (FLIP)[166]. These data imply that perturbations in the fine balance between the tissue-specific compositions of AP1 dimers are sufficient to alter transcriptional programmes for either cell survival or cell death, and are likely to have a major role during tumorigenesis.

Stem cell self-renewal and differentiation

Several *in vitro* and *in vivo* studies have indicated that AP1 function is involved in stem cell and tumour cell self-renewal or differentiation. Whereas JUN is stabilized at the protein and mRNA levels during induced differentiation of teratocarcinoma and erythroid cells, respectively, other Jun family members, such as JUNB, can negatively regulate proliferation of long-term repopulating myeloid stem cells[167,168]. JUN is particularly implicated in hepatogenesis and cardiac development[9,169], and consistent with this JUN and FOS are implicated in icariin-induced cardiomyocyte differentiation of mouse embryonic stem cells[170]. Downregulation of cyclin A during differentiation of human embryonic carcinoma cells depends on promoter depletion of ATF1 and ATF2 (REF. 113). By contrast, ATF2 also interacts with undifferentiated embryonic cell transcription factor 1 (UTF1), an important transcriptional co-activator during early embryogenesis that apparently enhances ATF2-dependent transcription in F9 embryonic carcinoma cells[171], indicating specific AP1 transcriptional programme switches during differentiation.

Jun, Fos and ATF2 in human cancer

Many human cancers exhibit overexpression of JUN and/or other Jun family members (TABLE 1), which is predominantly the result of activation of upstream oncogenes, including Ras, BRAF and EGFR. Activating mutations of NRAS or BRAF, which occur in >70% of melanomas, super-activate ERK, driving increased expression of JUN by increasing its transcription and stability[44]. Moreover, inhibition of JUN function consistently attenuates the growth of various human tumour cell lines both *in vitro* and in mouse xenografts[172]. Consistent with the idea that JUN promotes tumorigenicity is its overexpression in some of the more aggressive CD30-positive lymphomas[173,174]. Similarly, increased JUN levels correlate with more advanced tumour stage and poor prognosis in prostate cancer[175]. In breast cancer, other altered pathways, including RB, VEGF and EGFR have been implicated in inducing increased JUN expression.

Interestingly, altered FOS expression in tumours depends on the tissue of origin. Its increased expression is associated with poor clinical outcomes in osteosarcoma and endometrial carcinoma, and loss of FOS expression is associated with tumour progression and adverse outcome in ovarian carcinoma and gastric carcinoma[176,177]. FRA1 overexpression is associated with diverse tumours, including thyroid, breast, lung, brain, nasopharyngeal, oesophageal, endometrial, prostate and colon carcinomas, along with glioblastomas and mesotheliomas, and so may hold prognostic value[178] (Supplementary information S2 (table)).

Overexpression and activation (phosphorylation) of ATF2, altered subcellular localization and enhanced interaction with other AP1 proteins, in particular with oncogenic JUN, is observed in many cancer types and transformation models[46,117]. Such increased expression of ATF2 might be of diagnostic value in the clinic[118]. However, loss of ATF2 function is also observed in cancer. Although germline mutations in *ATF2* are infrequent, mutations that inactivate ATF2 have been observed in certain cancer types such as lung and breast cancer, and neuroblastoma[76,77].

The dynamic network of AP1 signalling

The diverse functions attributed to AP1 complexes have proved difficult to discern as each is dictated by the distinct heterodimeric combination that can be assembled from an array of potential complexes that these proteins can form. ATF2, for example, was reported to form 8 different complexes with other members of the Atf, Jun and Fos family, whereas JUN can form 15 different dimeric complexes. FOS was reported to form heterodimeric complexes with all Jun members, ATF2, ATF4, CREB1 and all Maf members. Differential dimerization between JUN, ATF2 and FOS with different family members is sufficient to alter their promoter-binding specificity, drastically changing the transcriptional capacity, protein stability and localization, and ultimately the transcriptional repertoire of these proteins[179]. Such dimerization and consequent functional differences are largely attributed to tissue- and cell type-specific expression levels of the individual AP1 proteins and the degree of activation of upstream pathways such as MAPK or SAPK pathways. For example, whereas JUN–ATF2[180,181] and/or JUN–FOS dimers[182] can promote proliferation in some cell types, in skin and breast cancer, ATF2 suppresses tumour outgrowth[115,116]. In addition to cell- and tissue-specific conditions, AP1 dimer composition is subject to influence by cell cycle progression and specific stimuli. For example, mitogenic stimulation upregulates FOS–JUN dimers, which are later displaced by FRA1 and FRA2 in accordance with the duration of ERK1 and ERK2 activity[183].

Apart from variation in transcriptional activity that can be attributed to altered promoter binding, individual AP1 proteins (particularly those exhibiting weak transactivation potential, such as JUNB, JUND, FRA1 and FRA2) can function as transcriptional repressors, by competitively out-binding partners of transcriptionally active AP1 complexes[165,184,185,186].

This explains why some dimers activate, and others repress transcription through binding at the same DNA promoter sites[187]. Accordingly, as the composition of the AP1 complexes is paramount to their function, deregulation of this composition in favour of more oncogenic partnerships may account for the transcriptional alterations observed during tumorigenesis.

A revealing example of altered AP1 composition relevant for cancer is that observed during Ras transformation. Oncogenic Ras constitutively activates ERK and increases transcription of JUN, JUNB, FRA1 and FRA2, but not of FOS, increasing the population of JUN–FRA1 dimers and thus increasing AP1 activity[188]. Similarly, the adenoviral protein E1A alters AP1 composition by promoting ATF2–JUN dimer formation, resulting in strong activation of ATF2, but weak activation of ATF1 or CREB1 ([REFS 189–191]). The implication of this dynamic heterodimerization is exemplified by CREB1 dimerization with ATF2, which abrogates the ability of E1A to bind to ATF2, presumably suppressing that particular axis of E1A-mediated transformation[189,192].

Collectively, these studies support the idea that manipulation of AP1 composition might have therapeutic applications in cancer treatment. The oncogenicity of JUN in the studies discussed above largely depends on its binding to ATF2, which is consistent with earlier studies showing that mutant v-jun with enhanced ATF2-binding capacity and mutant ATF2 that binds JUN with increased affinity can both enhance growth factor independence and tumorigenicity *in vivo*[111,180]. JUN–FOS and JUN–ATF2 dimers clearly have crucial roles in promoting tumorigenesis, however, the antagonistic effects of FOS- and ATF2-containing AP1 complexes implies that distinct cellular pathways are activated by each of these complexes. The complex changes in AP1 members at the transcriptional, translational and post-translational levels that enable their dynamic interchange during tumour development are still subject to intense investigation. The availability of genomic and proteomic technologies combined with the power of systems biology will, we hope, reveal the composition and therefore the mechanisms underlying this dynamic network in the near future.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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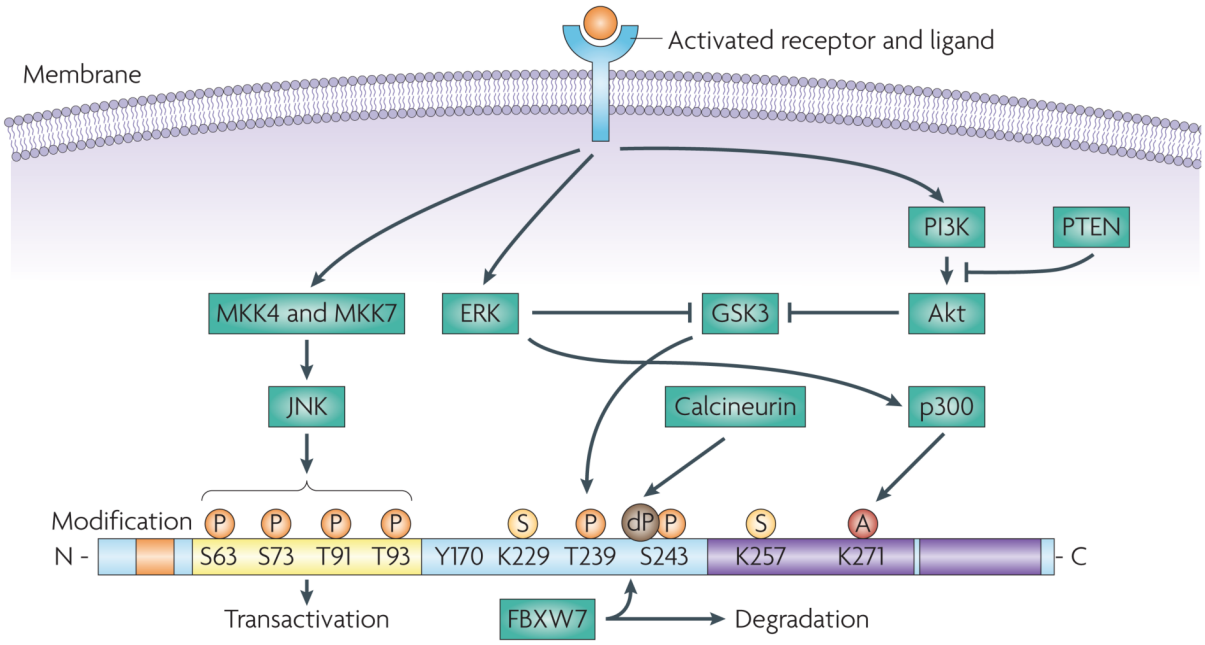

Figure 1. Structure and regulation of JUN

JUN is encoded by a 3.34 kb intronless gene, located on chromosome 1 (1p32-p31) and results in the expression of a 334 amino acid protein product composed of four main domains, which are involved in DNA binding, transcription and dimerization[197]. JUN activity is regulated by post-translational modifications, which are largely controlled by components of the MAPK family of serine and threonine kinases, including JUN N-terminal kinase (JNK), ERK and p38 isoforms[17]. JUN is phosphorylated on Ser63 and Ser73 by JNK, increasing its stability and transactivation potential[35]. JNK also phosphorylates Thr91 and Thr93, which are required for DNA binding and activation of its transcriptional activity. JUN is subject to ubiquitylation and this requires phosphorylation at Thr239 by glycogen synthase kinase 3 (GSK3). GSK3 can target JUN only once Ser243 is phosphorylated. Phosphorylation on these sites is required for recruitment of the F-box and WD domain repeated 7 (FBXW7) ubiquitin ligase[198]. Inactivation of GSK3, owing to the activation of ERK and PI3K–Akt signalling cascades results in JUN stabilization[44,45]. The effect of GSK3 can be antagonized by the dephosphorylation of Ser243 by calcineurin[199]. JUN can be sumoylated on Lys257 and Lys229, which leads to a reduced transcriptional activity[51]. ERK induces the acetylation of the lysine residues in the JUN DNA binding region[200], thereby increasing JUN transcriptional activity. Post-translational modifications are indicated as small coloured circles. The four domains are indicated as follows: the δ-domain is orange, the basic region (DNA binding) is blue, the transactivation domain is yellow and the leucine zipper is purple. A, acetylation; dP, dephosphorylation; P, phosphorylation; S, sumoylation.

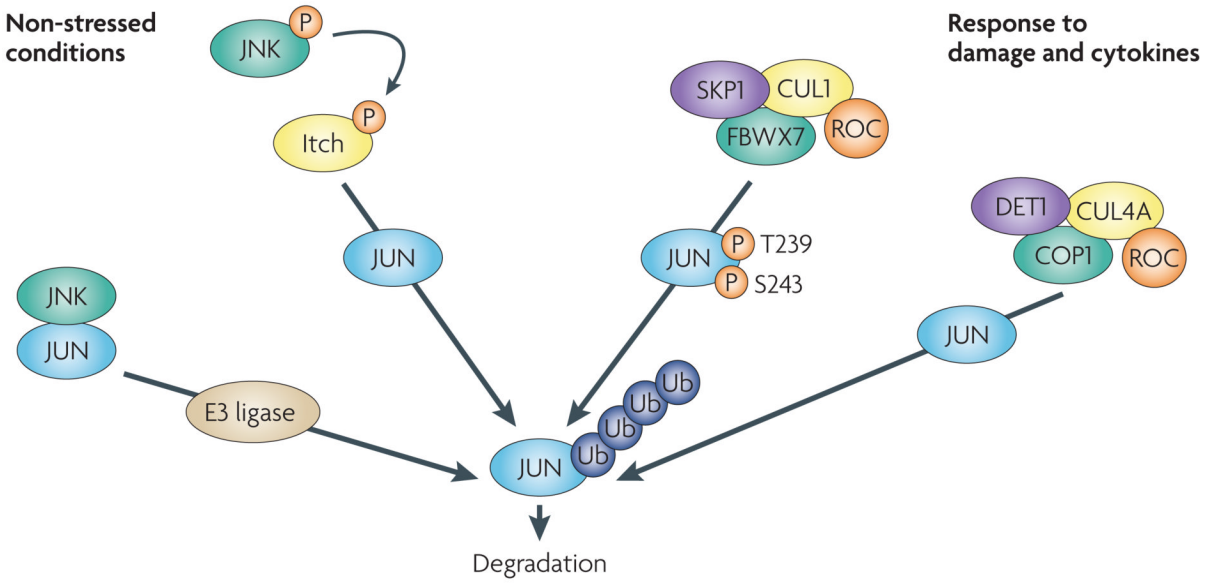

Figure 2. Mechanisms of JUN degradation

Several mechanisms exist to limit JUN stablity. Under non-stressed conditions, JUN N-terminal kinase (JNK) is tightly bound to JUN, targeting JUN for ubiquitylation and degradation. Activation of JNK by stress results in JUN phosphorylation and dissociation from JNK, enhancing its protein stability, although phosphorylation on Ser63 and Ser73 promotes the F-box and WD domain repeated 7 (FBXW7)-mediated degradation of JUN[48]. As part of a feedforward mechanism, JNK also phosphorylates the E3 ligase Itch in T cells after stimulation, accelerating degradation of JUN and JUNB, independently of Ser63 and Ser73 phosphorylation[34]. Phosphorylation on JUN at Thr239 by glycogen synthase kinase 3 (GsK3) (FIG. 1) allows FBXW7 binding and ubiquitin-mediated degradation by a Skp1-Cullin1-F-box (SCF) complex. Following osmotic stress, MEKK1 can activate JUN N-terminal phosphorylation by activating MKK4, an upstream kinase for JNKs that can also function as a JUN E3 ubiquitin ligase, promoting its ubiquitin–proteasome-dependent degradation[34] (not shown). De-etiolated 1 (DET1) contributes to JUN degradation by promoting the formation of a ubiquitin ligase complex containing DNA damage binding protein 1 (DDB1), cullin 4A (CUL4A), regulator of cullins 1 (ROC1) and constitutively photomorphogenic 1 (COP1)[201]. Other mechanisms modulating JUN ubiquitin-mediated degradation have been reported[34]. P, phosphorylation; Ub, ubiquitylation.

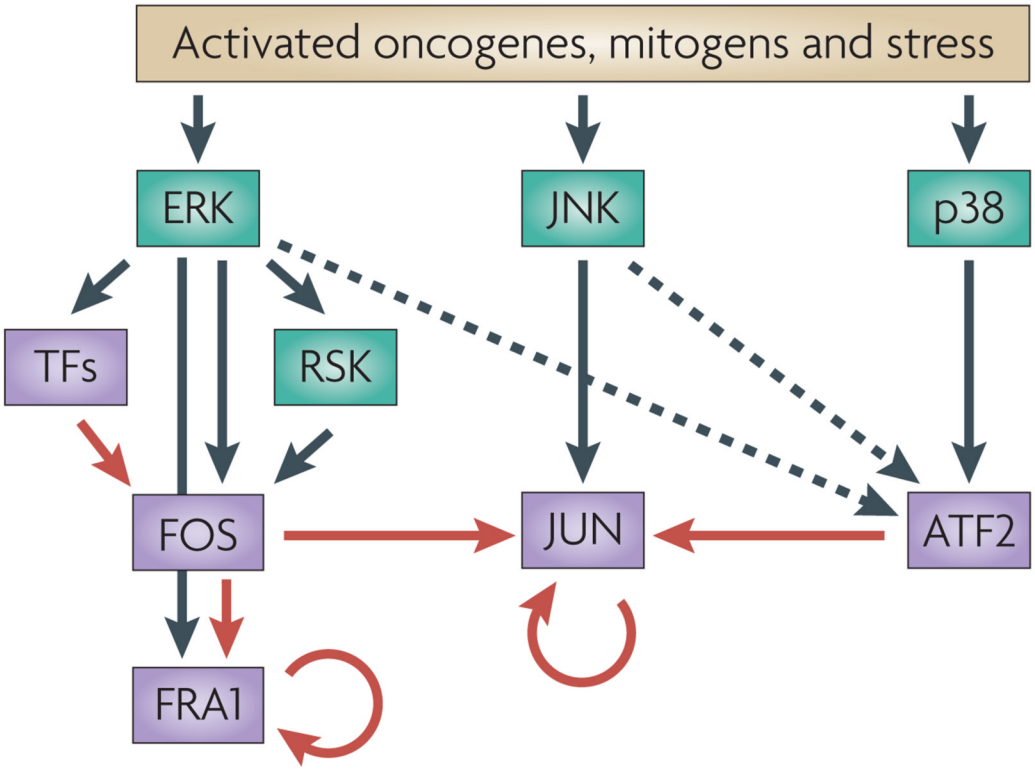

Figure 3. Network of AP1 signalling

ERK, JUN N-terminal kinase (JNK) and p38 are predominantly responsible for the phosphorylation and activation of FOS, JUN and ATF2 respectively (black arrows) in response to stress, mitogens or oncogene activation. ERK and JNK also regulate FOS and JUN degradation, respectively (not depicted) and participate in ATF2 activation (dashed arrows). ERK also induces the transcription of FOS through the activation of non-AP1 transcription factors (TFs). Transcription of some AP1 proteins (that is, JUN and FRA1) is regulated by crosstalk among AP1 complexes (red arrows) as well as by autoregulation (circular red arrows).

Table 1
Deregulation of Jun family members in cancer

Observation	Tumour type	Method	Refs
JUN amplification and JUN overexpression	Liposarcoma	CGH, FISH, Real-time PCR and WB	12
Increased JUN expression	Non-small-cell lung cancer	IHC	29,202
	Acute myeloid leukaemia	Microarray	203
	Colorectal neoplasm	IHC	204
	Pancreatic cancer	IHC	205
	Oral squamous cell carcinomas	IHC	206
Increased levels of phosphorylated JUN	Astrocytoma	IHC	207
	Invasive breast cancer	IHC	146
	Osteosarcoma	IHC	208
	Glioblastoma	IHC	209
	Melanoma	WB	204
JUN and FOS overexpression	Prostate cancer	TMA	175
JUN and JUND overexpression	Breast cancer	TMA	210
JUN and JUNB overexpression	$CD30^+$ lymphoma*	TMA and IHC	174
JUND overexpression	Primary cutaneous B cell lymphoma	IHC	211
JUNB and JUND overexpression	Colorectal adenocarcinoma	IHC and WB	212
Increased AP1 activity	Lung and bladder carcinoma	EMSA	213
Increased AP1 binding activity (FOS–JUNB)	Endometrial cancer	WB	214
	Cervical cancer	EMSA and WB	215

CGH, comparative genomic hybridization; EMSA, electrophoretic mobility shift assay; FISH, fluorescence *in situ* hybridization; IHC, immunohistochemistry; TMA, tumour microarray; WB, western blot.

*Classic Hodgkin lymphoma, anaplastic large cell lymphoma, diffuse large B cell lymphoma.

Table 2

ATF2 transcriptional targets

Gene	Context	Methods	Refs
Extracellular stimuli			
IL8	ATF2 recruits macroH2A nucleosome to repress *IL8* transcription	HeLa and Namalwa B-cells, WB and Luc	72
Pdgfra	ATF2-null mice exhibit decreased PDGFRα expression levels that are rescued on re-expression of ATF2	Mutant mice and CHO cells, WB and Luc	73
MMP2	ATF2 activates *MMP2* transcription	MCF10A cells and Luc	78
PLAU	ATF2 cooperatively induces PLAU in response to IL-1 and TPA	HepG2 cells, WB and Luc	216
Crip2	TGFβ upregulation of CRP2 requires ATF2	Rat and mouse vascular smooth muscle cells, WB and Luc	217
Psen1	Presenilin 1 expression is reduced in *Atf2*-null keratinocytes	Murine keratinocytes and WB	115
SELE	ATF2 contributes to E-selectin induction during inflammatory response	Human endothelial cells, WB and Luc	218
TNF	Autoamplification of death signals are mediated by ATF2	Jurkat and CEM cells, and WB	219
ATF3	Radiation-activated ATM signalling induces ATF3 through ATF2	Normal human diploid fibroblasts and WB	220
Nos2a	ATF2 mediates NOS2A upregulation in rat glial cells	C6 glial cells and Luc	221
IFNG	Jun–ATF2 dimers regulate *IFNG* transcription through proximal promoter	Jurkat cells, WB and Luc	222
Hspa5	ATF2 and CREB mediate stress induction of HSPA5	9L rat brain tumour cells and WB	223
Th	ATF2 positively regulates tyrosine hydroxylase transcription	PC12D cells, WB and Luc	224
Cell cycle and transcription			
CCND1	p38 and ATF2 induce cyclin D1 in breast cancer in response to oestradiol and spermine	MCF7 cells, WB and Luc	119
Ccna1	ATF2 mediates serum induction of cyclin A	Rat chondrosarcoma cells, WB and Luc	114
Rb1	ATF2 modulates RB during skeletal growth	ATDC cells and primary chondrocytes, WB and Luc	112
PI5	ATF2 binds directly to the *PI5* promoter (which encodes maspin)	Mutant mice, MEFs, MCF7 cells, WB and Luc	116
GADD45A	ATF2 is recruited by OCT1 and NF1 to the *GADD45A* promoter to activate transcription	Mutant mice, MEFs, MCF7 cells, WB and Luc	116
PKC	PKC phosphorylates ATF2 to activate JUN transcription	F9 teratoma, MEFs, HeLa cells, WB and Luc	90
Ppargc1a	ATF2 mediates exercise-induced PGC1α upregulation	C2C12 myocytes, WB and Luc	225
Atf and Creb, Jun and Fos family genes	ATF2 transcriptionally regulates other members of the Atf and Creb, and Jun and Fos families, contingent on cell type and stimulus context	F9 teratoma, COS-1, MCF7 cells, WB and Luc	4,82, 226
Mapk14	ATF2 negatively feeds back on p38 signalling through transcriptional induction of MAPK phosphatases	Mutant mouse tissue and cells, and WB	68
Cell death			

Gene	Context	Methods	Refs
Bcl2	ATF2 controls *Bcl2* promoter activation in chondrocytes	Mutant mice, WB and Luc	94
TRAIL	Auto-amplification of death signals are mediated by ATF2	Jurkat and CEM cells, and WB	219
ACHE	ATF2 mediates hydrogen peroxide-induction of acetylcholinesterase	293T cells, WB and Luc	227

ACHE, acetylcholinesterase; ATM, ataxia-telangectasia mutated; *CCND1*, cyclin D1; CHO, Chinese hamster ovary; *Crip2*, cysteine-rich intestinal protein 2; *Hspa5*, heat shock protein A5; *IFNG*, interferon (IFN)-γ; *IL8*, interleukin-8; Luc, luciferase assay; MEF, mouse embryonic fibroblast; MMP2, matrix metalloproteinase 2; *Nos2a*, nitric oxide synthase 2A; *Pdgfra*, platelet derived growth factor A; *PI5*, protease inhibitor 5; *PLAU*, urinary palminogen activator; *Ppargc1a*, peroxisome proliferator-activated receptor-γ coactivator 1α; *Psen1*, presenilin 1; *SELE*, E selectin; TGFβ, transforming growth factor-β; *Th*, tyrosine hydroxylase; *TNF*, tumour necrosis factor; TRAIL, tumour necrosis factor-related apoptosis-inducing ligand; WB, western blot.