



REVIEW ARTICLE

Emerging roles of activating transcription factor (ATF) family members in tumourigenesis and immunity: Implications in cancer immunotherapy

Meilin Chen, Yijun Liu, Yuqin Yang, Yanbing Qiu, Zhicheng Wang, Xiaoxu Li, Wenling Zhang*

Department of Medical Laboratory Science, The Third Xiangya Hospital, Central South University, Changsha, Hunan 410013, PR China

Received 17 October 2020; received in revised form 20 April 2021; accepted 26 April 2021
Available online 3 June 2021

KEYWORDS

Anti-tumor effect;
ATF;
bZIP;
Cancer;
Immunity;
Tumorigenesis

Abstract Activating transcription factors, ATFs, are a group of bZIP transcription factors that act as homodimers or heterodimers with a range of other bZIP factors. In general, ATFs respond to extracellular signals, indicating their important roles in maintaining homeostasis. The ATF family includes ATF1, ATF2, ATF3, ATF4, ATF5, ATF6, and ATF7. Consistent with the diversity of cellular processes reported to be regulated by ATFs, the functions of ATFs are also diverse. ATFs play an important role in cell proliferation, apoptosis, differentiation and inflammation-related pathological processes. The expression and phosphorylation status of ATFs are also related to neurodegenerative diseases and polycystic kidney disease. Various miRNAs target ATFs to regulate cancer proliferation, apoptosis, autophagy, sensitivity and resistance to radiotherapy and chemotherapy. Moreover, ATFs are necessary to maintain cell redox homeostasis. Therefore, deepening our understanding of the regulation and function of ATFs will provide insights into the basic regulatory mechanisms that influence how cells integrate extracellular and intracellular signals into genomic responses through transcription factors. Under pathological conditions, especially in cancer biology and response to treatment, the characterization of ATF dysfunction is important for understanding how to therapeutically utilize ATF2 or other pathways controlled by transcription factors. In this review, we will demonstrate how ATF1, ATF2, ATF3, ATF4, ATF5, ATF6, and ATF7 function in promoting or suppressing cancer development and identify their roles in tumour immunotherapy.

* Corresponding author. Department of Medical Laboratory Science, the Third Xiangya Hospital, Central South University, Tongzipo Road 172, Yuelu District, Changsha, Hunan 410013, PR China.

E-mail address: zhangwenling73@126.com (W. Zhang).

Peer review under responsibility of Chongqing Medical University.

Introduction

The ATF/CREB family in mammals represents a large group of basic-region leucine zipper (bZIP) transcription factors (TFs) with many physiological functions. In the late 1980s, these transcription factors were named due to their ability to bind to the cyclic AMP response element (CRE) site "TGACGTCA".¹ The characteristic feature of these proteins is the bZIP element. The basic region of this domain is responsible for specific DNA binding, while the leucine zipper region is responsible for forming homodimers or heterodimers with other proteins containing bZIPs, such as the AP-1, C/EBP or Maf families.² According to the amino acid sequence of these proteins in the bZIP region, dendrogram analysis showed that some of these proteins were more similar to other bZIP proteins, such as AP-1 (Fos/Jun) and C/EBP, than other ATF/CREB proteins.¹ Members of the ATF/CREB family share the same ability to cope with environmental signals and maintain intracellular homeostasis³ (Table 1).

The common feature of the ATF family and how they are grouped

TFs play a vital role in maintaining cell homeostasis by combining DNA regulatory sequences to regulate gene transcription rates. Activator protein 1 (AP-1) is one of the earliest identified mammalian TFs.⁴ AP-1 is a dimer complex consisting of the following members: JUN (c-JUN, JUNB and JUND), FOS (c-FOS, FOSB, FRA-1 and FRA-2), ATF (ATF1, ATF2, ATF3, ATF4, ATF5, ATF6, ATF6B, ATF7) or MAF (c-MAF, MAFA, MAFB, MAFF, MAFK and MAFK) protein family.^{5,6} bZIP domains are a common trait of AP-1 members (Fig. 1A). An X-shaped α -helical structure in the AP-1 complex is formed by the leucine-zipper domain and the adjacent basic domain, which binds to the DNA backbone (Fig. 1B).⁷ ATF TFs have a bZIP domain, which is a two-part element, the basic region of which is in continuous sequence contact with DNA. The leucine zipper mediates heterodimerization and homodimerization. The sequence elements bound by AP-1 TFs vary according to the unique homodimer or heterodimer combination. For example, JUN/JUN and JUN/FOS recognize the 12-O-tetradecanoyl phorbol-13-acetate response element (TRE) sequence, while ATF TFs bind to CRE at the common site 5'-TGACGTCA-3'. Using the data from the TCGA database, we analyzed the expression of ATF1-7 in different tumours on the GEPIA website and chose the tumour types with significant differences ($P < 0.01$) between the tumour group and the control group as shown in Figure. 2.

The known upstream signalling pathways that regulate ATF activities

There are numerous pathways in cells that respond to external signals and maintain homeostasis of the intracellular environment by regulating the activity of ATF. For example, phosphorylation of ATF1 by MAPK Sty1 is necessary for oxidative stress responses in fission yeast cells.⁸ p38 MAPK can regulate phosphorylated ATF1 and ATF2 to regulate the functions of dendritic cells (DCs) and T lymphocytes, respectively.^{9,10} TGF- β can inhibit the killing ability of cytotoxic T cells by regulating the ATF1-Smad dimer.¹¹ In addition to being regulated by intracellular signalling pathways, ATF is also regulated by small intracellular molecules, such as long noncoding RNAs (lncRNAs) and miRNAs. For example, the lncRNA RP11-552M11.4 promotes the occurrence and development of cervical cancer by regulating miR-3941/ATF1 signalling.¹² The TRAF6-JNK/p38-ATF2 axis may promote the inflammatory activation of microglia, thereby aggravating neuronal damage in the brain.¹³ ATF3 and ATF4 form dimers to stimulate MMP13 expression after stimulation with TGF- β 1.¹⁴ The PERK and SIRT1/2 signalling pathways can promote or suppress tumours by regulating ATF4.^{15,16} HAP70 enhances the stability of ATF5 to extend the life span of glioma cells.¹⁷ ATF6 is usually the downstream target molecule of the STAT and PERK signalling pathways.^{18,19} The transcriptional activation of ATF7 is usually mediated by p38.²⁰

ATF1

ATF1 as an oncogene

ATF1 is a transcription factor belonging to the ATF/CREB family, and it binds to the consensus ATF/CRE site "TGACGTCA".²¹ The expression of ATF1 in lung cancer tissues and lung cancer cells is higher than that in normal tissues and cells. Cui et al.²² demonstrated that ATF1 silencing inhibited the migration and invasion of lung cancer cells by regulating epidermal growth factor receptor (EGFR) and matrix metalloproteinase (MMP)-2. Moreover, they hypothesized that fusion between *EWSR1* and *ATF1* may be present in lung cancer because several reports have found *EWSR1-ATF1* fusion genes in some cancer cells.^{23–25} Thus, *EWSR1* rearrangements and fusion with the *ATF1* gene are hallmarks for tumour diagnosis. The first report of ATF1 in malignant melanoma identified the fusion gene *EWS/ATF1*, which acts as a tumour promoter.²⁶ Consistently, the expression of the anti-ATF1 single-chain antibody fragment in melanoma cells decreased the activation of the CRE-dependent promoter

Table 1 ATFs' roles in different cancers.

ATF family members	Tumors/tumor cells	Immune cells	ATF status (activating/inhibited)	ATF function on target gene	Mechanism	Target gene	Result
ATF1	lung cancer		silencing	inducer	regulating epidermal growth factor receptor(EGFR) and matrix metalloproteinases(MMP)-2 signaling	<i>EGFR</i> and <i>MMP2</i>	inhibit the migration and invasion of lung cancer
	malignant melanoma		Activating		EWS and ATF-1 gene fusion induced by t(12; 22) translocation		playing an oncogenic role in Ewing's sarcoma
	colorectal cancer		suppressed	suppressor	acting as a suppressor in CRC		higher ATF1 suppress CRC progression
	thyroid cancer		Activating	repressor	binding to the TSP-1-CRE site, inducing down-regulation of TSP-1 promoter activity, increasing hepatocyte growth factor (HGF)	<i>TSP-1</i>	leading to thyroid tumor cell invasion
	hepatocellular carcinoma		Activating	—	H3K27 acetylation increases the expression of LncRNA GHET, which fasten occurrence and development of HCC through regulating ATF1.	—	increase proliferation, migration, invasion and EMT of HCC cells
	cervical cancer		Activating	—	not in detail	—	could be used as a diagnostic marker for cervical cancer in the future
	breast cancer		differential expression of ATF1 in different parity periods	—	not in detail	—	lower expression of ATF1 in early parity than in late parity and nulliparity
		Dendritic Cell	Activating		loss of Nrf2 increases the expression of MHCII and CD86, and leads to the hyperphosphorylation of CREB/ATF1 transcription factors.		Phosphorylation of CREB is known to be associated with up-regulation of CD86 and secretion of the cytokine, IL-10
		cytotoxic T lymphocytes (CD8 + T)	Inhibited		ATF1 inhibited the transcriptional of granzyme B and interferon γ		killing ability of cytotoxic T lymphocytes is reduced. Tumor cells escape from immune surveillance
		CD4+ Th2	Inhibited		CREB/ATF-1 bind to the proximal element of the IFN γ promoter.		impede the transcription of IFN γ in Th2 cells
ATF2	dermal fibroblasts		Activating	inducer	IL-1 β induces MMP3 expression in dermal fibroblasts via the ERK1/ATF2 signal axis.	<i>MMP3</i>	Enhance cell migration, which seems essential for the occurrence of skin wound healing and genodermatosis
	T-cell acute lymphoblastic leukemia (T-ALL)		activating	—	loss of KLF4 in T-ALL leads to the aberrant activation of MAP2K7 and the phosphorylations of JNK and ATF2	—	promote expansion of leukemia-initiating cells
	Melanoma		activating	repressor	PKC ϵ -ATF2 signal transcription inhibits FUK and cellular fucosylation	<i>FUK</i>	promote melanoma motility, adhesion, and invasiveness

(continued on next page)

Table 1 (continued)

ATF family members	Tumors/tumor cells	Immune cells	ATF status (activating/inhibited)	ATF function on target gene	Mechanism	Target gene	Result
	renal cell carcinoma (RCC) cells		activating	inducer	ATF2 promoted the transcription of Cyclin B1 and Cyclin D1 by bounding to their proximal promoter regions	<i>Cyclin B1</i> and <i>Cyclin D1</i>	promote the proliferation of renal cell carcinoma(RCC) cells and predict poor prognosis of RCC patients
	cervical cancer cells		activating		miR-204 can inhibit the proliferation and autophagy of cervical cancer cells and induce apoptosis by targeting ATF2, but its expression in cervical cancer tissues and cells is low.		The low of miR-204 and high expression of ATF2 in cervical cancer can enhance the proliferation and autophagy of cervical cancer cells
	glioblastoma skin cancer		activating inhibited	repressor	Same as above skin cancer is in the absence of ATF2 transcription, which leads to increase -catenin and decrease PS1	–:–catenin/+PS1	promote skin cancer progression
	human cancers		inhibited	inducer	JNK Suppresses Tumor Formation via a Gene-Expression Program Mediated by ATF2	<i>PPP2R5B</i> , <i>GABRA1</i> , and <i>RCAN1</i>	promote tumor formation
		activated T cells	activating		ATF2/Jun complex and NFATp respectively combine with CRE/k3 composite site		increase the transcription of TNF- α gene by T-cell receptor ligands or by calcium ionophore
		dendritic cells	in a balance status		CD99 long form (CD99LF) up-regulates the phosphorylated form of the ATF2 to maintain a lower level of CD1a transcription and requires a short form of CD99 (SF) to counteract this regulatory mechanism		regulate DCs differentiation and its involvement in the immune response
ATF3	HCT 116 human colorectal cancer cells		overexpressed	inducer	ATF3 activated TIMP3 and 4 (metallopeptidase Inhibitor 3 and 4)genes to inhibit MMP activity in β -catMut cells(ATF3 expression is constitutively activated, because Wnt/ β catenin activation is aberrant in these cells due to the β -catenin mutation)	<i>TIMP3</i> and <i>TIMP4</i>	inhibit the invasion and migration of HCT 116 human colorectal cancer cells
	lewis lung cancer cells (LLC)		knocked out	repressor	ATF3 and JDP2 directly regulate the expression of SDF-1, so their double defects (especially in fibroblasts) promote the growth of SDF-1 dependent tumors.	stromal cellderived factor 1 (SDF-1)	promote tumor growth
	pancreatic cancer cells			inducer	MTA2TR recruit ATF3 to the promoter region of MTA2	<i>MTA2</i>	enhance proliferation and metastasis of pancreatic cancer cells and xenograft
	prostate cancer		knocked out	repressor	ATF3 promotes the activation of oncogenic AKT signaling	<i>AKT</i>	Loss of ATF3 promotes cell proliferation and survival in Pten-null prostate lesions
	skin cancer cells		overexpressed	repressor	inhibit p53 expression and then activating Stat3 phosphorylation	<i>p53</i>	promote the proliferation of skin cancer cells and enhance the

ATF4	human breast cancer cells (MDA-MB231)	overexpressed	inducer	TGF- β 1 stimulated the formation of an ATF3 and Smad4 complex at the MMP13 promoter		development of skin keratinocyte tumors Accelerate the progress of breast cancer.
	non-small cell lung cancer	over-expressed	—	—	—	contributes to Non-small cell lung cancer (NSCLC) tumorigenesis
	HT29 and CaCO2 colon cancer cells	over-expressed	—	—	—	enhances the invasion and tumor metastasis of HT29 and CaCO2 colon cancer cells <i>in vivo</i>
	TFH (follicular helper T) cells	over-expressed	inducer	The overexpression of ATF3 enhances the activity of Bcl6 gene, and the mutation of ATF3 binding site eliminates this effect.	B cell lymphoma 6(Bcl6)	ATF3 deficiency in CD4 + T cells exacerbates colitis in mice.
	melanoma/ NSCLC	knocked out	inducer	Inhibition of ADORA1 can increase the expression of PD-L1 through ATF3 binding to the PD-L1 promoter, thereby promoting immune escape	PD-L1	Promotes Tumor Immune Evasion
	glioma	over-expressed	inducer	DHA activates GPX4 via PERK/ATF4/HSPA5 pathway	HSPA5	up regulation of ATF4 can attenuate ferroptosis induced by DHA in glioma cells
	lymphoma	over-expressed	inducer	MYC up-regulates ATF4, which suppresses mTORC1-dependent signalling to prevent proteotoxicity following MYC activation via enhances the expression of 4E-BP1	eukaryotic translation initiation factor 4E binding protein 1 (4E-BP1)	MYC-induced ATF4 inhibits apoptosis and promotes lymphoma cells survival
	pancreatic adenocarcinoma cells	over-expressed	inducer	PUM1 knockdown prevents tumor progression by activating the PERK/eIF2/ATF4 signaling pathway	inhibited cell proliferation, migration, invasion, and EMT, and promoted apoptosis <i>in vitro</i>	PUM1 knockdown prevents tumor progression by activating the PERK/eIF2/ATF4 signaling pathway in pancreatic adenocarcinoma cells
	NSCLC	over-expressed	inducer	SIRT1/2 inhibition activates ATF4-DDIT4-mTOR axis, which down-regulates mTOR and induces autophagy in NSCLC cells.	Promote survival autophagy	Inhibition of SIRT1/2 upregulates HSPA5 acetylation and induces pro-survival autophagy via ATF4-DDIT4-mTORC1 axis in human lung cancer cells
	osteosarcoma	over-expressed	inducer/ repressor	ATF4 overexpression activated Cbl-c transcription and recruited Cbl-c to accelerate RET degradation	inducer: Cbl-c; repressor:GRP78(heat shock protein family A member 5)	overcome BTZ resistance
	gastric cancer	knocked down	—	LXR β up-regulates ATF4	—	inhibit the progression of gastric cancer and promote chemosensitivity of gastric cancer cells
	HER2+ breast cancer	over-expressed	inducer/ repressor	Activate the PKR-eIF2 α -ATF4 axis, and ATF4 activated p21 transcription and inhibit DUSP1	+p21/-DUSP1	suppresses HER2+ cancers and improves trastuzumab therapy

(continued on next page)

Table 1 (continued)

ATF family members	Tumors/tumor cells	Immune cells	ATF status (activating/inhibited)	ATF function on target gene	Mechanism	Target gene	Result
ATF5	C6 and U87 Glioma Cells ovarian carcinoma hepatocellular carcinoma		activated	inducer	HSP70 stabilize ATF5 to promote survival of C6 and U87 Glioma Cells	<i>BCL2</i> and <i>Egr-1</i>	promote cell survival in glioma cells.
			activated	inducer	ATF5 up-regulates BCL2 expression to promote the progression of ovarian cancer	<i>BCL2</i>	Accelerate the development of ovarian cancer.
			inhibited(low expression in HCC)	repressor	ATF5 in hepatocellular carcinoma induces G2-M arrest and down regulate the expression of ID1	<i>ID1</i>	suppress HCC
ATF6	head and neck squamous carcinoma cells		activated		ATF-6 α up-regulated		Induce cells to enter dormancy
	Hep3 cells		activated		promote Hep3 cells survival through the mTOR signaling pathway		promote Hep3 cells survival
	CRC		activating		as a marker of pre-cancerous atypical change in ulcerative colitis-associated colorectal cancer		a potential role in the management of dysplasia
	colon cancer cells		activating	inducer	ATF6 directly binds to the CIP2A promoter and induces CIP2A gene expression	<i>CIP2A</i>	prolong the survival of colon cells
	colorectal cancer cells		activating		XBP1(s) and ATF6 1–373 activation results in cell cycle arrest in distinct phases by activating PERK signaling		reduce colorectal cancer cell proliferation and stemness
ATF7	ovarian carcinoma		activated		ID1 first activates NF- κ B signaling by promoting nuclear translocation of NF- κ Bp65, thereby enhancing the expression and secretion of IL-6 in cancer cells, thereby activating signal transducer and activator of transcription 3 (STAT3) Through protein phosphorylation at Y705. STAT3 promotes the transcription of activated transcription factor 6 (ATF6), which induces endoplasmic reticulum stress to promote autophagy,		confer cancer cells resistance to cisplatin and paclitaxel treatment.
	B-lymphoma cells		activated		ATF2 and ATF7 activities suppress tumorigenesis in mouse lymphoma models		suppress lymphoma
	CRC				ATF7 expression was positively correlated with 5-year overall survival or 5-year progression-free survival		suppress CRC
	gastric cancer cells		suppressed		miRNA-103a-3p targets and suppresses ATF7 in gastric cancer cells		promotes the proliferation of human gastric cancer cells
	Hepatocellular carcinoma (HCC)		activated		miR-340–5p is downregulated by HBV, which enhances ATF7 expression		enhanced cell proliferation and inhibition of apoptosis

and inhibited the tumourigenicity and metastasis potential of the CRE-dependent promoter in nude mice. Inhibition of ATF1 can effectively reduce oesophageal cancer cell proliferation, induce cell cycle arrest in S phase, and inhibit cell migration and invasion. In addition, ATF1 silencing significantly enhanced the sensitivity of oesophageal cancer cells to paclitaxel.²⁷

Hepatocyte growth factor (HGF)-induced down-regulation of TSP-1 expression is mediated by the interaction of ATF1 with the CRE binding site in the TSP-1 promoter, and this transcription factor plays a crucial role

in tumour invasiveness in papillary carcinoma of the thyroid triggered by HGF.²⁸ LncRNAs are aberrantly expressed in many malignant tumours and are involved in regulating the malignant phenotype of cancer cells. LncRNA GHET1 (gastric carcinoma high expressed transcript 1) activated by H3K27 acetylation is upregulated in hepatocellular carcinoma (HCC) tissues and cell lines, promoting cell tumourigenesis by binding to ATF1 protein in HCC.²⁹ LINC00665 contributes to the progression of CRC by regulating the miR-9-5p/ATF1 axis.³⁰ These results indicate that ATF1 can be used as a new therapeutic target in cancer treatment.

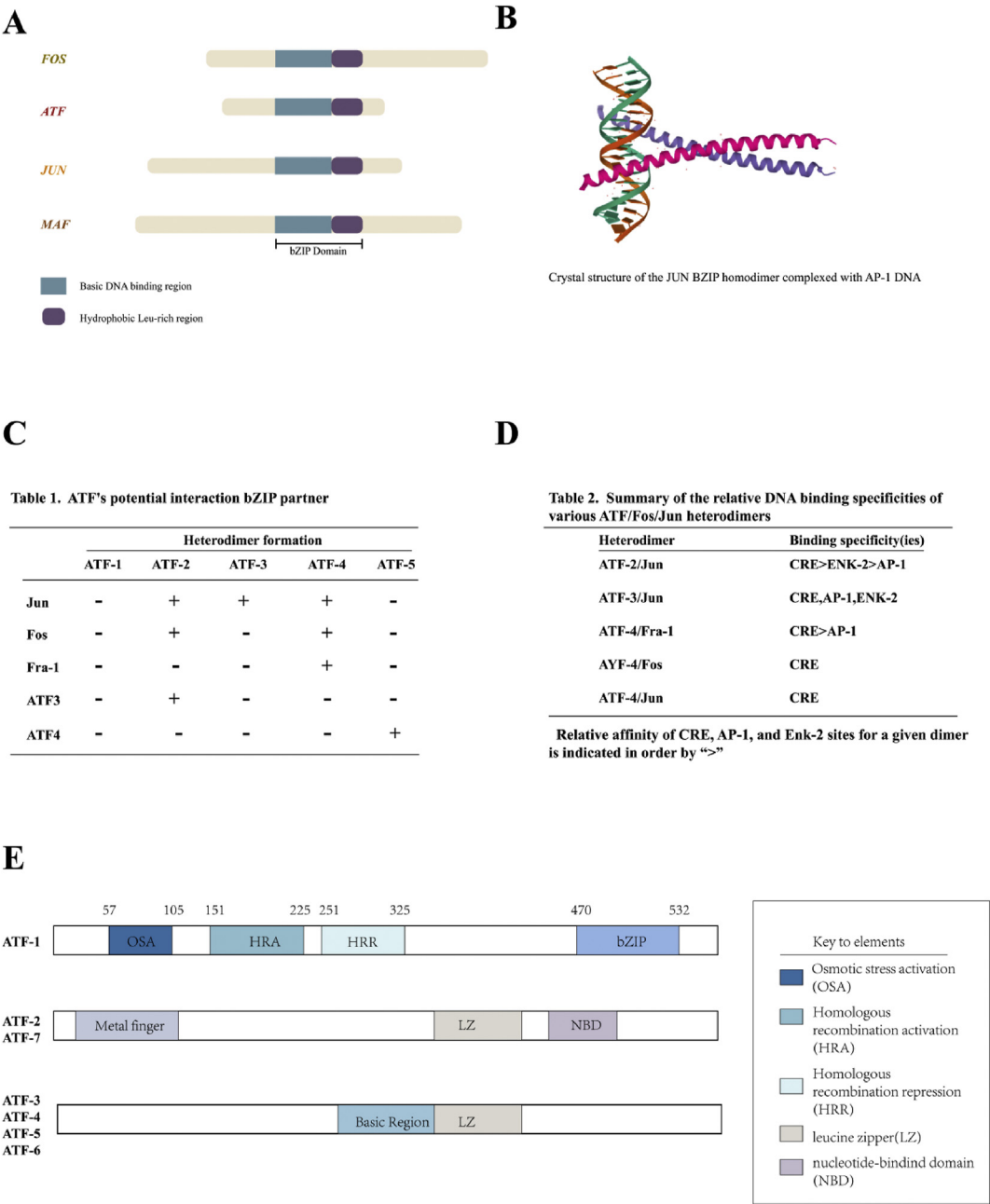


Figure 1 The AP-1 transcription factor family members. **(A)** Schematic diagram of the structure of AP-1 protein (including FOS, ATF, JUN, and MAF). AP-1 TF has two common areas, namely the basic motif and leucine zipper. Together, these areas form a bZIP domain **(B)** Crystal structure of the JUN BZIP homodimer complexed with AP-1 DNA from Protein Data Bank(PDB) **(C)** ATFs' potential interaction bZIP partners **(D)** summary of the relative DNA binding specificities of various ATF/Fos/Jun heterodimers **(E)** More detailed functional domains of ATFs.

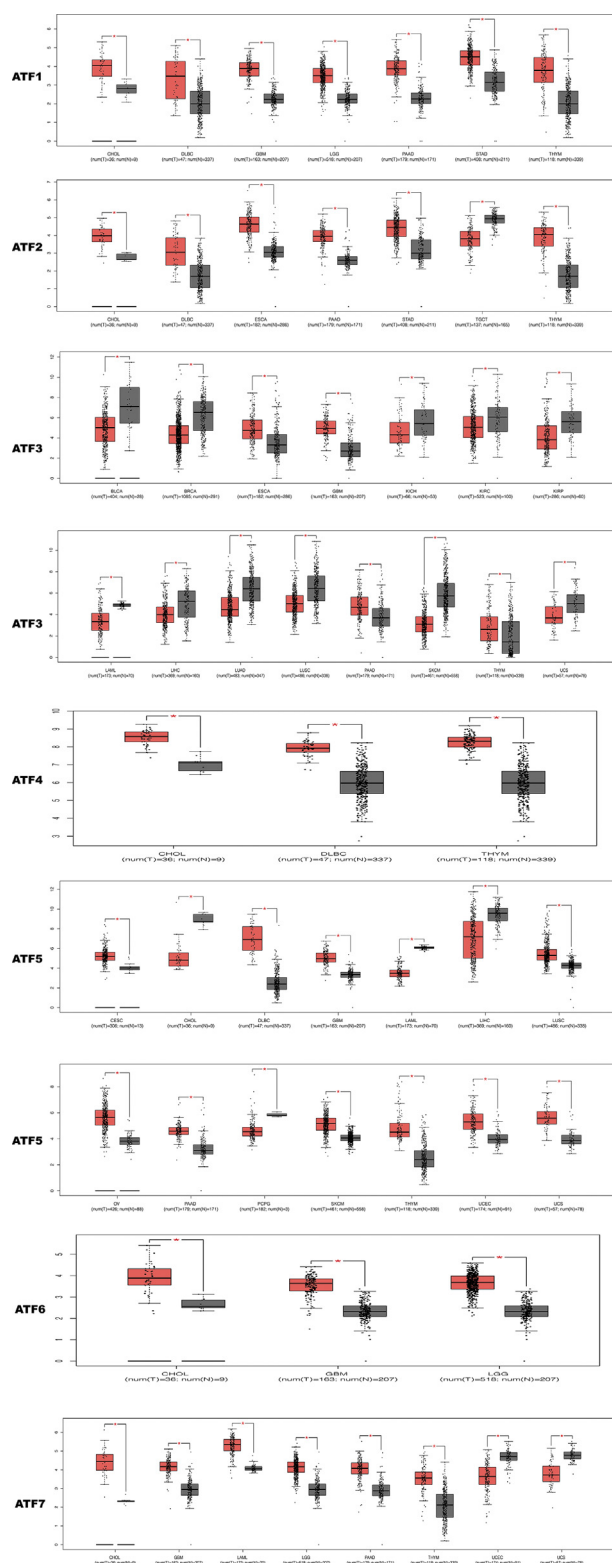


Figure 2 Box plot made on GEPIA. $|\text{Log}_2\text{FC}|$ Cutoff = 1, P Cutoff = 0.01. CHOL: Cholangio carcinoma; DLBC: Lymphoid neoplasm diffuse large B-cell lymphoma; GBM: Glioblastoma multiforme; LGG: Brain lower grade glioma; PAAD: Pancreatic adenocarcinoma; STAD: Stomach adenocarcinoma; THYM: Thymoma; ESCA: Esophageal carcinoma; TGCT: Testicular germ cell tumors; BLCA: Bladder urothelial carcinoma; BRCA: Breast invasive carcinoma; KICH: Kidney chromophobe; KIRC: Kidney

Early diagnosis is vital for the treatment of tumours, and ATF1 can be used as a biomarker for the early diagnosis of tumours. ATF1 mRNA expression was significantly increased in primary and recurrent cervical cancer mouse models. ATF1 was also detected in blood exosomes, indicating that ATF1 can be used as a potential candidate biomarker for the early diagnosis of cervical cancer.³¹ Studies have found that the risk of breast cancer in early parity is lower than that in late parity and nulliparity because early pregnancy can reduce the expression of key proteins involved in the mitotic signalling pathway in breast tissue by downregulating ATF1 and other proteins. Early parity also has higher genomic stability and less tissue inflammation, which is based on differential expression of ATF1, among other proteins.³²

ATF1 as a tumour suppressor

The expression of ATF1 protein in colorectal cancer (CRC) tissues was significantly lower than that in corresponding normal tissues. High expression of ATF1 can predict better outcomes for overall survival and progression-free survival in patients with CRC.³³ However, a recent study noted that the synergistic effect of ATF1 and its target genes related to apoptosis, Wnt, TGF- β , and the MAPK pathway is closely related to the early pathogenesis of the TCGA cohort and their CRC-affected patients, and these effects could cooperatively increase the risk of CRC.³⁴

Identifying the role of ATF1 in immune regulation

Regarding immunization, the deletion of nuclear factor-erythroid 2 (NF-E2) p45-related factor-2 (Nrf2) changes the function of DCs and leads to the hyperphosphorylation of CREB/ATF1 transcription factors. Inhibition of p38 MAPK resulted in a prominent but incomplete reversal of DC function in Nrf2-deficient DCs, indicating that other pathways or factors are also involved, suggesting that the p38 MAPK-CREB/ATF1 axis is involved in Nrf2-mediated DC function regulation.⁹ Phosphorylation of CREB is known to be associated with the upregulation of CD86 and secretion of the cytokine IL-10.^{35,36}

Transforming growth factor- β (TGF- β) can inhibit the expression of multiple cytotoxic genes in cytotoxic T lymphocytes and enable tumour cells to escape immune surveillance. TGF- β can mediate Smad-ATF1 to directly bind to the granzyme B (GzmB) and interferon γ (IFN γ) promoter regions, resulting in decreased expression of GzmB and IFN γ . The killing ability of cytotoxic T lymphocytes is reduced, indicating that ATF1 plays a critical transcriptional inhibitory role on GzmB and IFN γ .¹¹ Research on Jurkat T cells revealed that CREB/ATF1 is also involved in the repression of IFN γ during the differentiation of CD4⁺

renal clear cell carcinoma; KIRP: Kidney renal papillary cell carcinoma; LAML: Acute myeloid leukemia; LIHC: Liver hepatocellular carcinoma; LUAD: Lung adenocarcinoma; LUSC: Lung squamous cell carcinoma; SKCM: Skin cutaneous melanoma; UCS: Uterine carcinosarcoma; CESC: Cervical squamous cell carcinoma and endocervical adenocarcinoma; OV: Ovarian serous cystadenocarcinoma; PCPG: Pheochromocytoma and paraganglioma; UCEC: Uterine corpus endometrial carcinoma.

Th2 cells by binding to the proximal element (273–248 bp) of the IFN γ promoter.³⁷

ATF2

ATF2 — also known as cAMP response element binding protein 2 (CREB2) and CRE-BP1—is a member of the activating protein-1 (AP-1) transcription factor family that regulates gene expression through homodimerization or heterodimerization with other AP-1 family members, such as the CREB, Fos, Maf, or Jun family transcription factors.³⁸ ATF2 contains basic/leucine zipper motifs (bZIPs) and participates in inflammation by regulating gene expression.^{39,40}

ATF2 as an oncogene

ATF2 can contribute to regulating the expression of matrix metalloproteases (MMPs), which are zinc-dependent neutral endopeptidases that play an essential role in the process of tissue remodelling by degrading extracellular matrix (ECM) components.^{41,42} A recent study confirmed that ERK1 mediates IL-1 β activation of the ERK1/ATF2 signalling axis in dermal fibroblasts and that ERK1 promotes cell migration through MMP-3 expression.⁴³ However, fibroblast activation and abnormal ECM remodelling can be typical hallmarks in three cancer-prone genodermatoses.⁴⁴ Although most T-cell acute lymphoblastic leukaemia (T-ALL) patients show activation mutations in *Notch 1*, the cogenetic events required to accelerate the occurrence and progression of leukaemia are largely unclear. However, the loss of Krüppel-like factor 4 (KLF4) in T-ALL in mice and children leads to the abnormal activation of MAP2K7 and downstream effectors JNK and ATF2, promoting the expansion of leukaemia-initiating cells.⁴⁵ Studies have shown that progression in leukaemia models (T-ALL mouse model and pediatric T-ALL model) can be limited by inhibiting the activation of the stress kinase MAP2K7 and its downstream targets JNK, c-JUN, and ATF2.⁴⁵

Among transcription factors regulated by the MAPK and PDK1 pathways, ATF2 is a member of the AP-1 complex. The phosphorylation of ATF2 on Thr^{69/71} by p38, c-Jun N-terminal kinase (JNK), or the ERK cascade can have transcriptional activity, while its phosphorylation on Thr⁴⁶ by PKC ϵ can guide its nuclear localization, thereby increasing its overall transcription output. Compared with early-stage melanoma, the expression and phosphorylation of ATF2 by PKC ϵ was increased in advanced melanoma. Increased ATF2 transcriptional activity was associated with decreased FUK expression, cellular protein fucosylation, cell adhesion, and increased cell motility.⁴⁷ Wu et al⁴⁸ revealed the enrichment of ATF2 in the proximal promoter regions of cyclin B1 and cyclin D1, suggesting that ATF2 promoted the transcription of cyclin B1 and cyclin D1, thus promoting the proliferation of renal cell carcinoma (RCC) cells. High expression of ATF2 was associated with aggressive clinicopathological features in RCC patients and predicted poor prognosis.

ATF2 as a tumour suppressor

Although most studies have shown the cancer-promoting properties of ATF2, a few studies have found that ATF2 plays

a role in suppressing growth in specific cancers. The expression of ATF2 in the nucleus of human skin cancer tissue is significantly lower than that of normal skin. In the absence of transcriptionally active ATF2, presenilin 1 (PS1) expression decreased, while β -catenin expression increased, resulting in epidermal hyperproliferation.⁴⁹ Unlike an oncogene of liver tumours in mouse studies, clinical data showed that ATF2 played a tumour suppressive role in human tumours by targeting PPP2R5B, GABRA1, and RCAN1.⁵⁰

The role of ATF2 in molecular therapy of tumours

Consistent with the carcinogenic effect of ATF2 in melanoma, the use of small molecules or peptides to inhibit its transcriptional activity or nuclear localization will impair the development of melanoma and reduce metastasis *in vivo*.^{51,52} The expression of miR-204 is low in cervical cancer tissues and cells, and it can inhibit the proliferation and autophagy of cervical cancer cells and induce apoptosis by targeting the ATF2 3'-UTR.⁴⁶ In addition, previous studies⁵³ have demonstrated that miR-204 can specifically inhibit the expression of ATF2 protein and regulate the proliferation, migration, and invasion of human glioblastoma.

Identifying the role of ATF2 in immune regulation

Regarding immunity, p38 MAPK may induce c-Jun activation in primary mouse T cells by phosphorylation of ATF2, and this process is related to the proliferation of T cells. Studies have demonstrated that the cAMP-responsive element (CRE) site (rather than AP-1 or AP-2) plays a crucial role in the induction of the TNF- α gene by T cell receptor ligands or calcium ionophores binding to ATF2/Jun proteins.¹⁰ The ATF2 and Jun proteins cooperate with NFATp (a member of the nuclear factor of activated T cells [NFAT] family of proteins) at the TNF- α CRE/k3 site.¹⁰ CD1a expression is one of the main characteristics identified during *in vitro* human dendritic cell generation. It is believed that CD1a^{high} MoDCs produced *in vitro* are closest to inflammatory CD1a DCs *in vivo*.^{54,55} These inflammatory DCs are critical antigen-presenting cells that initiate pathogen-specific immune responses and play a key role in controlling inflammation and infection.^{56,57} To this end, a study demonstrated that the CD99 long form (CD99LF) maintains a lower level of CD1a transcription by upregulating the phosphorylated form of ATF2 and requires a short form of CD99 (SF) to counteract this regulatory mechanism.⁵⁸ Moreover, cytokines and growth factors also participate in the regulation of CD1a through the cyclic AMP pathway activation of transcription factors ATF2 and CREB.^{59,60}

The role of ATF2 in inflammation

Consistent with the diversity of cellular processes reported to be regulated by ATF2 transcription, there are also numerous pathologies related to ATF2 changes. For example, the expression of p-ATF2 through the JNK and p38 signalling pathways is related to the apoptosis of KBD cartilage chondrocytes,⁶¹ consistent with its role in osteoclast differentiation.⁶² In addition to its role in inflammation-related signal

transduction pathways, changes in ATF2 expression and activity are also related to inflammation-related pathologies, including high expression in infiltrating macrophages, and may suppress ATF3 transcription in M1 macrophages of white adipose tissue in obesity.⁶³ ATF2 is a serological marker of inflammation and lung involvement in systemic sclerosis (SSc).⁶⁴ ATF2 activation can also be observed in hepatitis and gastritis.⁶⁵ Changes in the expression and phosphorylation status of ATF2 are also associated with a variety of pathologies, including various neurodegenerative diseases, polycystic kidney disease, and diabetic amylin-induced pancreatic β -cell death.^{66–68} Inflammatory-cancer transformation is challenging in cancer research. The role of ATF2 in cancer and inflammation may be related, but there are no clear data to prove it. In addition to participating in inflammation-related pathological processes, a recent study reported that ATF2 and ATF7 are essential for epithelial homeostasis, but in the process of intestinal epithelial injury and repair, they need to maintain epithelial regeneration and prevent cell death.⁶⁹

ATF3

ATF3 is an adaptive response gene involved in cellular processes that adapt to extracellular and/or intracellular changes, including DNA damage, cellular injury, and oxidative stress. ATF3 activates or inhibits gene expression by transmitting signals from different receptors.² ATF3 was isolated from the serum-induced HeLa cell cDNA library and encodes 181 amino acids with a molecular weight of 22 kDa.⁷⁰ To date, five alternative isoforms, ATF3 Δ zip, ATF3 Δ zip2 (ATF3 Δ zip2a and ATF3 Δ zip2b), ATF3 Δ zip2c, ATF3 Δ zip3, and ATF3b, of ATF3 have been reported in different cell systems, all of which are formed by a canonical ATF3 truncation of the C- or N-terminal region.⁷¹ Functionally, other subtypes (leucine zipper domain defects), except ATF3b, cannot bind DNA and counteract the transcriptional repression of ATF3.^{71,72}

ATF3 as a tumour suppressor

In the cellular context of cancer, ATF3 may be a tumour suppressor gene or an oncogene.⁷³ ATF3 is the target gene of multiple signalling pathway networks, including JNK,^{74–76} p53,^{77,78} c-Myc^{79,80} and Smad.⁸¹ The stress response gene *ATF3* is transcriptionally activated by binding of β -catenin and T-cell specific transcription factor (TCF4) to the redundant TCF4 site at the proximal promoter region of the *ATF3* gene, indicating that *ATF3* is a direct target of the Wnt/ β -catenin pathway. Moreover, *ATF3* acts as a negative regulator of the migration and invasion of HCT116 human colon cancer cells exhibiting aberrant Wnt/ β -catenin activity, which was consistent with a previous report.⁸² Activating transcription factor 3 (ATF3) and c-Jun dimerization protein 2 (JDP2) are members of the bZIP family of transcription factors. A recent study showed that mice with dual defects in ATF3 and JDP2 (dKO) have larger tumours with higher vascular perfusion and cell proliferation rates than wild-type (WT) mice. JDP2 and ATF3 can inhibit the promoter of stromal cell-derived factor 1 (SDF-1) in tumour-associated fibroblasts to repress tumour growth.⁸³

High levels of phosphorylated AKT and S6 protein were observed in ATF3-deficient prostate lesions, demonstrating that the absence of ATF3 promotes the activation of oncogenic AKT signalling. Consistent with these *in vivo* results, single guided RNA (sgRNA)-mediated targeting reduces ATF3 expression in human prostate cancer cells, thereby activating AKT and increasing MMP9 expression.⁸⁴ This result indicates that ATF3 can serve as an anticancer barrier, and it functions to eliminate carcinogenic stress to prevent the development of prostate cancer.

ATF3 as an oncogene

Recently, it has been reported that metastasis-associated protein 2 (MTA2) transcriptional regulator lncRNA (MTA2TR) upregulates MTA2 expression by recruiting activating transcription factor 3 (ATF3) to the promoter region of MTA2, resulting in MTA2TR enhancing proliferation and metastasis in pancreatic cancer cells and xenograft models.⁸⁵ A study showed that ATF3 accumulates in skin cancer tissues and promotes the proliferation of skin cancer cells by inhibiting p53 expression and then activating Stat3 phosphorylation.⁸⁶ TGF- β 1 enhances ATF3 expression in human breast cancer cells.⁸⁷ After TGF- β 1 stimulation, ATF3 and ATF4 form a heterodimer in the promoter region of MMP13 and promote the expression of MMP13.¹⁴ Compared with normal bronchial epithelial cells, the expression of ATF3 in NSCLC cells is increased, suggesting that the upregulation of ATF3 expression contributes to non-small cell lung cancer (NSCLC) tumourigenesis.⁸⁸ ATF3 inhibits colon cancer cell invasion and migration, which was contrary to a previous report. Another study showed that ATF3 expression enhanced the invasive characteristics and tumour metastasis of HT29 and CaCO2 colon cancer cells *in vivo*.⁸⁹ These observations indicate that ATF3 plays a dual role in colon cancer. In many human breast cancers, the expression of ATF3 is upregulated, which may be attributed to the amplification of the ATF3 gene located in the amplicon of chromosome 1q, which is the most common amplified region in breast cancer.⁹⁰ Overexpression of ATF3 can increase the level of Akt phosphorylation in the PI3K/Akt signalling pathway to increase radiation resistance.⁹¹ TGF β induces ATF3 in malignant breast cancer cells, and ATF3 upregulates the expression of the TGF β gene itself, forming a positive feedback loop. Functionally, ATF3 enhances the function of epithelial to mesenchymal transition (EMT) and cancer initiating cells.⁹²

Identifying the role of ATF3 in immune regulation

Recently, a study showed that ATF3 is a regulator of intestinal follicular helper T (TFH) cells, which determines susceptibility to colitis. The lower the expression of ATF3, the more susceptible one is to colitis. B cell lymphoma 6 (Bcl6) was identified as a transcriptional target of ATF3 in intestinal T_{FH} cells.⁹³ In recent years, an increasing number of studies have been conducted on the blockade of immune checkpoints, resulting in considerable clinical benefits for various malignant tumours, such as metastatic melanoma and NSCLC.^{94,95} ATF3 acts as an immunomodulator in lipopolysaccharide (LPS)-treated mice by interacting with

nuclear factor- κ B (NF- κ B) and inhibiting proinflammatory cytokines (such as interleukin 6 [IL-6], IL-12b and Toll-like receptor 4 [TLR-4]) in innate immunity.^{96,97} ATF3 inhibits LPS-induced chemokine (CXC motif) ligand 1 production in the mouse airway but promotes neutrophil chemotaxis through T-cell lymphoma infiltration and metastasis 2 (TIAM2) expression.⁹⁸ In addition, compared with ATF3^{+/+} mice, ATF3^{-/-} mice have higher levels of basal and LPS-stimulated chemokine (C-C motif) ligand 4 (CCL4) mRNA and protein in BMDMs.⁹⁹ Moreover, Liu et al indicated that the downregulation of the tumour suppressor ADORA1 induces the upregulation of PD-L1 via ATF3. Inhibition of ADORA1 can increase the expression of PD-L1 through ATF3 binding to the PD-L1 promoter, thereby promoting immune escape. The ADORA1 antagonist can synergistically enhance the antitumour effect of an anti-PD-1 mAb in mice. The levels of ADORA1 and ATF3 can predict the effectiveness of PD-1 mAb treatment in cancer patients.¹⁰⁰ ATF3 induction was observed after interferon (INF) treatment. Type I interferon (IFN α/β) induces the expression of ATF3 in human and mouse immune cells. ATF3 further regulates a subset of IFN- β stimulation genes, including CCL12, CCL3, Ch25h, and Clec4e.¹⁰¹ ATF3 activates tenascin-C through the Wnt/ β -catenin signalling pathway to promote the migration and M1/M2 polarization of RAW 264.7 macrophages.¹⁰² These phenomena indicate that ATF3 may play a role in tumour immunity.

ATF4

ATF4 mRNA is present in all tissues examined thus far.²¹ Although various extracellular signals can upregulate the level of ATF4 in different cell types, its regulatory pattern mainly occurs at the transcriptional initiation and post-transcriptional levels.²¹ ATF4 mRNA contains short upstream open reading frames (uORFs) in its 5' untranslated region (5'UTR). These uORFs lead to the synthesis of the ATF4 protein, similar to the yeast protein GCN4: transcription initiation from the coding AUG is inhibited under nonstimulated conditions. However, under stressed conditions, the protein is assembled and leads to eIF2- α phosphorylation. Moreover, ATF4 helps to cope with ER stress by activating genes for antioxidant and amino acid metabolism.¹⁰³ After endoplasmic reticulum stress, ATF4 is preferentially translated and then translocated to the nucleus, where ATF4 directs the transcription of UPR regulatory genes.¹⁰⁴

ATF4 as an oncogene

Dihydroartemisinin (DHA) induces endoplasmic reticulum (ER) stress in glioma cells, resulting in upregulation of ATF4 by protein kinase R-like ER kinase (PERK) to induce heat shock protein family A (Hsp70) member 5 (HSPA5) expression. Subsequent upregulation of HSPA5 increases the expression and activity of glutathione peroxidase 4 (GPX4), which neutralizes DHA-induced lipid peroxidation, thereby protecting glioma cells from ferroptosis. Therefore, inhibition of the adverse feedback pathway will be a promising therapeutic strategy to enhance DHA against glioma activity.¹⁵ In addition to being activated by PERK, ATF4 can be

upregulated by general control nonderepressible 2 (GCN2) kinase, which is activated by MYC through uncharged transfer RNAs. Subsequently, ATF4 can occupy more than 30 promoter regions of MYC target genes, mainly genes that regulate amino acid and protein synthesis, including eukaryotic translation initiation factor 4E binding protein 1 (4E-BP1), a negative regulator of translation. 4E-BP1 relieves MYC-induced protein toxicity stress and is essential for balancing protein synthesis. 4E-BP1 activity is negatively regulated by mammalian target of rapamycin complex 1 (mTORC1)-dependent phosphorylation. Inhibition of mTORC1 signalling can rescue ATF4-deficient cells from MYC-induced ER stress. Acute deletion of ATF4 significantly delays MYC-driven tumour progression and increases survival in mouse models.¹⁰⁵ Moreover, compared with normal tissues, the activation/overexpression of GCN2 and the increase in phosphorylated eIF2 α were observed in human and mouse tumours. Abolishing the expression of ATF4 or GCN2 significantly inhibited tumour growth *in vivo*.¹⁰⁶ These results indicate that the GCN2-eIF2 α -ATF4 pathway is essential for maintaining metabolic homeostasis in tumour cells, making it a novel and attractive target for antitumour strategies. ATF4 can induce prosurvival autophagy, protecting cells from apoptosis in other cases. For example, mechanistically, SIRT1/2 (sirtuin 1/2) inhibition induces autophagy in NSCLC through the acetylated heat shock 70-kDa protein 5 (HSPA5)-mediated ATF4-DDIT4 (DNA damage-inducible transcript 4)-mTOR signalling pathway.¹⁰⁷ These findings suggest that combinatorial treatment with SIRT1/2 inhibitors and pharmacological autophagy inhibitors is an effective strategy for cancer therapy. p-Ser245 ATF4 has been shown to increase VEGF expression in prostate cancer cells.¹⁰⁸ The expression of ATF4 is also related to cisplatin, doxorubicin, etoposide, SN-38 and vincristine resistance.¹⁰⁹ These results indicate that ATF4 is a sensitive rheostat that can ensure that the increased translation rate is compatible with survival and tumour progression.

ATF4 as a tumour suppressor

In contrast, recent articles have shown that the PERK/eIF2/ATF4 pathway promotes tumour cell apoptosis, inhibits tumour proliferation, invasion and migration of pancreatic cancer by resisting Pumilio RNA-binding family member 1 (PUM1), which has been reported to function as an oncogene in ovarian cancer¹¹⁰ and NSCLC.^{111,112} These results suggest that ATF4 promotes autophagy. Additionally, low expression of ATF4 was detected in both osteosarcoma clinical samples and bortezomib-resistant sublines (OS/BTZ), and the study showed that ATF4 overexpression markedly reversed BTZ resistance in OS/BTZ cells by activating Cbl proto-oncogene C (Cbl-c) transcription and then recruiting Cbl-c to accelerate RET degradation.¹¹³ Consistent with the anticancer properties of ATF4, one study showed that the expression of liver X receptor β (LXR β) and ATF4 in paracancerous tissues and gastric mucosal epithelial cells was significantly higher than that in gastric cancer tissues and cells. LXR β upregulates ATF4 to inhibit the progression of gastric cancer and promote the apoptosis and chemosensitivity of gastric cancer cells.¹¹⁴ Activation of the PKR-eIF2 α -ATF4 axis

upregulates the CDK inhibitors p21^{CIP1} and p-JNK1/2 to improve HER2⁺ breast cancer sensitivity to trastuzumab therapy.¹⁶ However, the ambiguous role of ATF4 in promoting cell survival and apoptosis makes targeting ATF4 a dangerous approach.

Identifying the role of ATF4 in immune regulation

A recent article reported that the HRI (haeme-regulated inhibitor)/eIF2a/ATF4/HSPB8 (heat shock protein B8) signalling axis is essential for controlling the assembly of NOD signalosomes and the continued activation of NF- κ B signals, demonstrating that this pathway plays a vital role in innate immune signalling.¹¹⁵ Arsenic trioxide (ATO) mediates the dysfunction of macrophages through the continuous activation of ATF4, including the release of cytokines, removal of bacteria, and apoptosis of macrophages.¹¹⁶ These studies identified a new role of ATF4 in the potential pathogenesis of macrophage dysregulation and immunotoxicity of arsenic.¹¹⁶ Liu et al¹¹⁷ found that ATF4 promotes tumour growth of endometrial cancer by promoting CCL2 and subsequent macrophage recruitment, and the ATF4/CCL2 axis may be a potential therapeutic target for EC. ATF4 can be induced by oxidizing environments and amino acid starvation in CD4⁺ T cells. *Atf4*-deficient CD4⁺ T cells have defects in redox homeostasis, proliferation, differentiation, and cytokine production. Th1 cells are decreased in ATF4-deficient mice, but the Th17 immune response is elevated.¹¹⁸ In contrast to ATF3, ATF4 acts as a positive regulator of TLR4-triggered cytokine production. ATF4 is activated and translocates to the nucleus following LPS stimulation via the TLR4-MyD88-dependent pathway. Mechanistically, upon LPS stimulation, MyD88 is recruited to TLR4 via its TIR domain, and then MyD88 recruits IRAK and TRAF6, which activate the TAK1 and TAB1/2/3 complex. JNK is phosphorylated by the activated complex and then phosphorylates c-Jun, which forms heterodimers with ATF4 via the leucine zipper. This dimer binds to DNA and promotes the transcription of specific genes, thereby resulting in the secretion of relevant inflammatory cytokines.¹¹⁹

ATF5

The transcription factor ATF5 belongs to the bZIP transcription factor family. This family includes other well-known proteins, such as cCREB, FOS, and NRF2. These bZIP proteins are composed of amphiphilic leucine zippers that mediate heterologous and homodimerization through a coiled-coil domain and a fundamental N-terminus involved in DNA binding.^{120,121} ATF5 is classified into the ATF4 subfamily of bZIP transcription factors based on the dimerization characteristics of the leucine zipper domain of ATF5.¹²² Compared with the main heterodimer FOS or the predominant homodimer CREB, ATF5 is prone to heterologous and homodimerization with transcription factors and is considered to be promiscuous in its binding capacity,¹²² although few ATF5 dimerization partners have been published. CCAAT/enhancer-binding protein- γ (C/EBP γ) is a proposed ATF5 binding partner.¹²³ Studies with overexpression of d/n forms indicate that ATF5 can heterodimerize with ATF4 and C/EBP (another group of bZIP transcription factors) but not with CREB, Fos, Jun or

ATF2.¹²³ ATF5 plays a role in neurosynaptic plasticity and memory, endoplasmic reticulum and cellular stress, maintenance of neural progenitor cells, and cell proliferation.¹²⁴

ATF5 as an oncogene

ATF5 expression is highly upregulated in various forms of cancer, such as glioma, breast cancer, lung cancer,¹²⁵ rectal cancer,¹²⁶ etc. Therefore, ATF5 may have a carcinogenic effect in these cancers and be overexpressed in malignant tissue. HAP70-mediated stabilization of ATF5 led to increased ATF5 activity and transcription of downstream ATF5 targets, such as BCL2 and Egr-1, in C6 and U87 glioma cells.¹⁷ ATF5 promoter methylation in gliomas is significantly reduced in advanced gliomas compared to low-grade gliomas and normal tissues, suggesting that changes in promoter methylation drive abnormal ATF5 expression in high-grade gliomas.¹²⁷

Compared with other cancer types, the mechanism by which ATF5 promotes cell survival has been well studied in gliomas. For example, studies by Karpel-Massler et al showed that the interference ATF5 activity by CP-d/n-ATF5-S1 administration downregulates the ubiquitinase Usp9x. Because Usp9x stabilizes the antiapoptotic proteins BAG3, MCL1 and Bcl-2, CP-d/n-ATF5-S1 mediates the downregulation of Usp9x and leads to an apoptotic response.¹²⁸

As in gliomas, nuclear ATF5 expression is significantly upregulated in breast cancer relative to paired normal breast tissues, and it is also significantly upregulated in invasive ductal carcinoma, invasive lobular carcinoma, *in situ* ductal carcinoma and *in situ* lobular carcinoma.¹²⁹

Chen et al¹³⁰ analysed the expression of ATF5 in clinical samples of epithelial ovarian cancer and found that ATF5 was significantly upregulated compared to benign and normal ovarian tissues, and the expression of ATF5 was also related to the cancer stage. Additionally, the interference of ATF5 activity by transient transfection of dnATF5 led to increased apoptotic reactions, accompanied by downregulation of Bcl-2 expression. Whether Bcl-2 downregulation is responsible for apoptosis or whether dnATF5 has any effect independent of ATF5 was not investigated. In addition to being involved in tumour apoptosis, ATF5 also plays a regulatory role in tumour EMT. ATF5 promotes radioresistance in nasopharyngeal carcinoma by promoting EMT.¹³¹

Initially, ATF5 was considered to be an antiapoptotic factor because it regulates the expression of the antiapoptotic components Bcl-2 and MCL1,^{130,132,133} and multiple studies have shown that ATF5 inhibition leads to the death of a variety of cancer cell types. ATF5 also regulates growth and metabolism coordination factors, such as EGR1, mTOR and FGF21, as well as mitochondrial protection genes.^{134–136} In addition to the growth-promoting and antiapoptotic phenotype, ATF5 also enhances the resistance to radiotherapy¹³⁷ and the invasiveness of tumour cells by inducing integrin- α_2 and integrin- β_1 .¹³⁸

ATF5 as a tumour suppressor

Another interesting feature of ATF5 in cancer has been observed in hepatocellular carcinoma, where ATF5 seems to have a tumour-suppressive effect.¹³⁹ According to

reports, ATF5 is involved in growth inhibition via cell cycle arrest at the G₂-M phase. Through differential gene expression analysis, the downstream target of ATF5 was analysed, and the helix-loop-helix protein ID1 was identified as the target of ATF5. Mobility change analysis showed that ATF5 binds to the cyclic AMP response element (CRE) in the promoter of ID1. Consistent with the inhibitory effect of ATF5 on CRE, ATF5 expression was negatively correlated with ID1 expression. Studies on the mechanism of ATF5 downregulation in hepatocellular carcinoma demonstrated that DNA mutations, promoter methylation, histone modification, and gene copy loss were all responsible for the loss of ATF5 expression.¹³⁹ One study supported the tumour suppressor effect of ATF5 in liver cancer and emphasized that ID1 is a potential downstream target.¹³⁹ ATF5 expression is also significantly correlated with tumour grade in several cancer types, including rectal cancer, glioma, and ovarian carcinoma.^{126,130,140}

The role of ATF5 in molecular therapy of tumours

In a proof-of-principle experiment, a retrovirus with a function-blocking mutant form of ATF5 was injected into a rat glioma model, causing death in infected tumour cells but not in infected brain cells outside of the tumour.¹⁴¹ These results have led to the development of a systemically deliverable dnATF5 peptide fused to a penetration motif, allowing extracellular access.^{128,142} The broad expression of ATF5 in glioblastoma and the selective effects of interference with ATF5 function/expression on survival suggest that ATF5 may be an attractive target for the treatment of such tumours.

The ATF5 antagonist (mainly negative ATF5; d/n-ATF5) is designed as an N-terminal truncated construct whose DNA binding domain is replaced by an acidic amphiphilic α -helix sequence that contains leucine (mostly heptad repeats of leucine) and an unchanged leucine zipper and C-terminus.¹⁴³

Relative to other cancers, the mechanism by which ATF5 promotes cell survival has been well studied in gliomas. For example, Karpel-Massler et al.¹²⁸ showed that administration of CP-d/n-ATF5-S1 (a chemically synthesized variant of this dominant-negative peptide) interferes with ATF5 activity, leading to the downregulation of Usp9x. Subsequently, Usp9x cannot stabilize the antiapoptotic proteins BAG3, MCL1, and Bcl-2. The anticancer mechanism of dnATF5 can be attributed to the disruption of ATF5 homodimers, heterodimers, or ATF5 associating bZIP homo/heterodimers.¹⁴⁴ Transfection of the d/n-ATF5 transgene triggered considerable apoptosis in glioma, breast, ovarian, and pancreatic cancer cell lines.^{124,130,145} Unfortunately, research on ATF5 in tumour immunotherapy has not been found thus far.

ATF6

ATF6 and its role in UPR

ATF6 is a transmembrane protein located in the endoplasmic reticulum (ER) and a member of the leucine zipper

transcription factor family. The 50 kDa activated form of ATF6 is known for its role in signal transduction related to ER stress.

Mammals express two homologous ATF6 proteins, ATF6 α (670 amino acids) and ATF6 β (703 amino acids). The biochemical and physiological properties of the former are significantly better than those of the latter. The C-terminus of the ATF6 isoforms extend into the lumen of the ER, while the N-terminus faces the cytoplasm. The cytoplasmic part of ATF6 contains the basic leucine zipper (bZIP) DNA binding and transcription activation domain, followed by a 20 amino acid transmembrane domain. Interestingly, although ATF6 α and ATF6 β have significant sequence homology, these isoforms exhibit different transcription activation domains. Indeed, ATF6 α is a potent transcription activator, while ATF6 β (a poor transcription activator) may inhibit the activation of ATF6 α .¹⁴⁶

The ER is a highly regulated system that modifies abnormal proteins and prevents their secretion. Several adverse conditions, such as hypoxia, accumulation of reactive oxygen species, lack of ATP, nutritional deficiencies, and mutations of specific proteins, may cause misfolded proteins to accumulate in the ER. To keep cells working normally and not harming other cells, ER stimulates the unfolded protein response (UPR). The UPR maintains and restores ER homeostasis by inducing ER chaperone proteins, thereby increasing the secretory function of the ER.¹⁴⁷ In the presence of excess unfolded proteins, Grp78, which acts as a molecular chaperone, is removed from its interaction with PERK, ATF6, and IRE-1. This allows ATF6, PERK and IRE-1 to dimerize and become active.¹⁴⁸ Once Grp78/Bip dissociates, ATF6 is transported to the Golgi apparatus and activated by RIP (regulating intramembrane proteolysis), including S1P (site-1 protease) and S2P (site-2 protease), to form an active transcription factor that can be transferred to the nucleus. Active ATF6 induces the expression of CHOP, chaperone, and ERAD (ER-associated degradation) components.¹⁴⁹

ATF6 as an oncogene

Resting cells are thought to be resistant to chemotherapy by inhibiting proliferation. The Hep3 cell line, derived from head and neck squamous carcinoma cells, upregulates all three transmembrane proteins of the UPR: ATF6 α , IRE-1 α , and PERK.¹⁵⁰ Additionally, ATF6 α can promote Hep3 cell survival through the mTOR signalling pathway.¹⁵¹ The diagnosis of low-grade dysplasia (LGD) is essential in the treatment of ulcerative colitis (UC), but it is often challenging to distinguish LGD from inflammatory epithelial regeneration. In non-UC and UC-related CRC, ATF6 is expressed in lesions undergoing atypical precancerous changes and can be used to distinguish LGD and inflammatory regenerating epithelium in UC patients.¹⁵² Cancerous inhibitor of protein phosphatase 2A (CIP2A, also known as p90 tumour-associated antigen or KIAA1524) is overexpressed in cancer and is an emerging predictor of prognosis for many cancers, including CRC.^{153,154} ER stress-related ATF6 upregulates CIP2A and leads to poor prognosis of colon cancer. Liu et al.¹⁵⁵ found that ATF6 directly binds to the CIP2A promoter and induces CIP2A gene expression, contributing to the survival of colon cancer cells. Inhibitor

of DNA binding 1 (ID1) induces chemoresistance of cancer cells through autophagy mediated by STAT3/ATF6 in ovarian cancer, suggesting that ATF6 may be a target for combination with chemotherapeutics to improve the survival rate of ovarian cancer patients.¹⁸

ATF6 as a tumour suppressor and its role in cancer immunity

The unfolded protein response (UPR) works through its downstream pathways, including PERK-eIF2 α signalling, IRE1 α XBP1 signalling and ATF6 signalling. One study showed that the expression of the UPR effector proteins ATF6 and XBP1 reduces the proliferation and stemness of colorectal cancer cells by activating PERK signalling.¹⁹ In contrast, other studies found that overexpressed XBP1 and ATF6 play a role in promoting tumours in cells.^{148,156} In the absence of inflammation, ATF6 activation in the colonic epithelium promotes intestinal dysbiosis and the innate immune response, leading to microbiota-dependent tumour formation. Aberrant ATF6 expression is associated with reduced disease-free survival in CRC patients.¹⁵⁷

ATF7

ATF7, a member of the basic leucine zipper protein family, is located on chromosome 12q13.13. ATF2 and ATF7 are two highly homologous AP-1 transcription factors, especially

within their bZIP DNA-binding and dimerization domains. ATF7 is phosphorylated by p38 at Thr51 and Thr53, leading to its transcriptional activation.²⁰

The B cell-specific deletion of ATF2 and ATF7 in mice resulted in a significant acceleration of the onset of *E μ -Myc*-induced lymphoma. In addition, the loss of ATF2/7 makes *E μ -Myc* lymphoma cells insensitive to spontaneous and stress-induced apoptosis.¹⁵⁸ The immunohistochemical results of 72 postoperative CRC tissue specimens showed that ATF7 expression was negatively correlated with pathological stage and positively correlated with 5-year overall survival or 5-year progression-free survival.¹⁵⁹ miRNA-103a-3p promotes the proliferation of human gastric cancer cells by targeting and inhibiting ATF7 *in vitro*.¹⁶⁰

Notably, ATF7 is upregulated in liver cancer tissues, indicating that HBV may target miR-340-5p *in vivo* to promote ATF7/HSPA1B (heat shock protein A member 1B)-mediated proliferation and apoptosis and regulate the progression of liver cancer.¹⁶¹ There is no relevant research on ATF7 in human tumour immunity. One study demonstrated that the phosphorylation of the conserved ATF7 by PMK-1 p38 MAPK regulates the innate immunity of *Caenorhabditis elegans*.¹⁶²

Challenge and prospective

Recently, ATFs have emerged in many popular fields due to their extensive and robust functions in universal conditions. To determine cell fate, each factor can transcriptionally activate a target through its unique pathway and exhibit

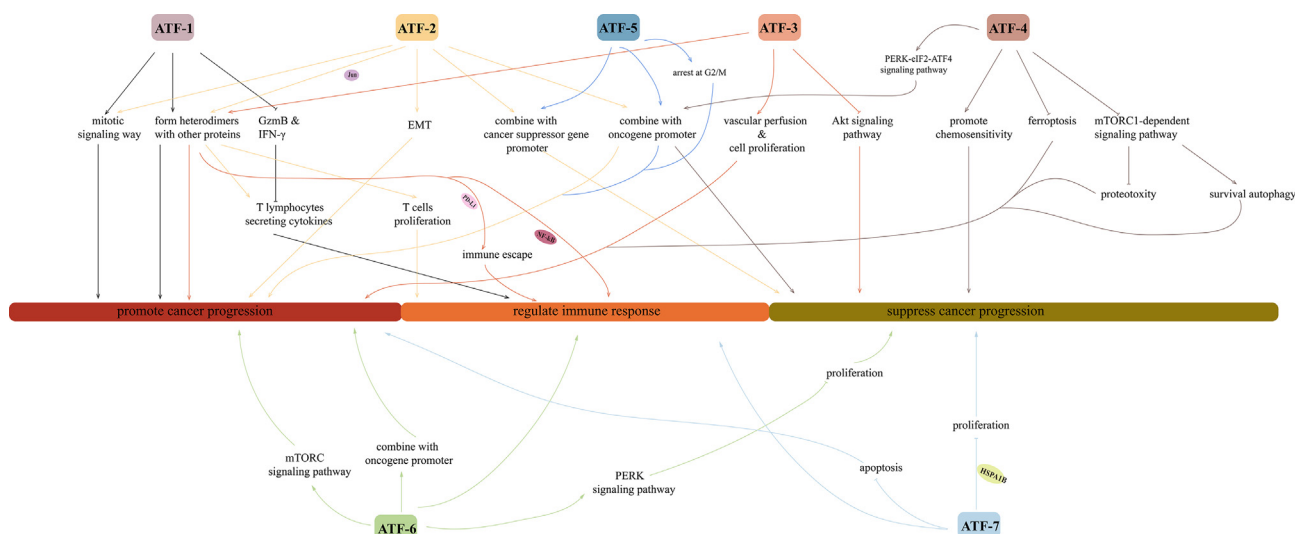


Figure 3 ATFs participate in carcinogenic processes, anti-carcinogenic processes, or mediate immune response through activating various signal-pathways and different mechanisms. ATF-1 accelerates tumor development via mitotic signalling pathway or forming heterodimers with other proteins. ATF-2 and ATF-1 can inhibit T lymphocytes from secreting cytokines. ATF-2 and ATF-5 can combine with oncogene promoter or cancer suppressor gene promoter to develop or delay cancer progression. ATF-2 also can aggravate tumor epithelial–mesenchymal transition. ATF-5 can arrest tumor cells at G₂/M to disturb the cell cycle. ATF-3 enhances vascular perfusion and proliferation of tumor cells and postpone cancer progression via the Akt signalling pathway. ATF-3 regulates tumor immunity by forming heterodimers with PD-L1 or NF- κ B. PERK-eIF2-ATF4 results that ATF4 combine with the oncogene promoter to disrupt the expression of PUM1. ATF-4 promotes ferroptosis, proteotoxicity, and survival autophagy of cancer cells to let them adapt to the stress environment better. ATF-4 also can enhance tumor chemosensitivity, which can improve the survival rate of patients. ATF-6 can regulate carcinoma progression through mTOR or PERK signalling pathway. ATF6 directly binds to the CIP2A promoter, which prolonged the survival of colon cancer cells. Both ATF-6 and ATF-7 can regulate innate immunity. ATF-7 can mediate the apoptosis and proliferation in some specific cancers.

multiple mechanisms of action against other targets.¹⁶³ ATFs are adaptive response genes that participate in cellular processes to adapt to extracellular and/or intracellular changes and transduce signals from various receptors to activate or inhibit gene expression. Therefore, ATFs can be modulators of tumourigenesis and host defence mechanisms. How ATFs function in tumour development and immunity is shown in Figure. 3.

Numerous articles have demonstrated that the ATF family is a double-edged sword in tumours. ATFs usually form homodimers or heterodimers with their own family members or other transcription factor families to induce their effects in tumours and immunity,¹⁶⁴ but they can also target cancer-related genes directly to transmit their signals. Scientists have discovered the role of ATF in the human immune system. Although research on tumour immunity is still incomplete, these findings provide a new direction for tumour immunotherapy.

Understanding the mechanism of ATF in tumours provides new targets for tumour treatment. For example, researchers used an anti-ATF1 single-chain antibody fragment to inhibit the tumourigenicity and metastasis of melanoma,²⁶ an example of how anti-ATF antibodies can repress tumour progression. However, ATFs seem to have opposite effects different cancers. Therefore, the function of ATFs in different tumours is an important issue that needs to be further studied.

Consistent with the abovementioned findings, ATFs exert opposite effects on the expression of many cytokines in different immune cells. The most notable is the emerging role of ATF3 in immune escape, as targeting ATF3 may help patients who are resistant to PD1 immunotherapy.

Given that ATFs are essential for host defence immunity and cancer progression, a more detailed understanding of how ATFs regulate immunity and oncogenic signalling pathways may make ATFs attractive targets in the multi-disciplinary treatment of cancer and immunotherapy.

Conclusion

Collectively, ATFs have a powerful transcriptional regulation function, and they can regulate gene transcription directly or mediate distant gene expression independently or by forming homodimers or heterodimers. During tumourigenesis, cell homeostasis is disrupted, thereby regulating the generation of ATFs. Tumourigenic ATFs activate multiple signalling pathways related to cell proliferation, EMT, apoptosis, autophagy, ECM remodelling, angiogenesis, and immune response, promoting cancer progression. However, ATFs can also inhibit the progression of tumours via different signalling pathways. Therefore, targeting ATFs may represent a new strategy for cancer treatment.

Conflict of interests

The authors declare no conflicts in this work.

References

- Hai T. The ATF transcription factors in cellular adaptive responses. In: *Gene Expression and Regulation*. New York, NY: Springer; 2006:329–340.
- Thompson MR, Xu D, Williams BR. ATF3 transcription factor and its emerging roles in immunity and cancer. *J Mol Med (Berl)*. 2009;87(11):1053–1060.
- Persengiev SP, Green MR. The role of ATF/CREB family members in cell growth, survival and apoptosis. *Apoptosis*. 2003;8(3):225–228.
- Angel P, Imagawa M, Chiu R, et al. Phorbol ester-inducible genes contain a common cis element recognized by a TPA-modulated trans-acting factor. *Cell*. 1987;49(6):729–739.
- Shaulian E, Karin M. AP-1 as a regulator of cell life and death. *Nat Cell Biol*. 2002;4(5):E131–E136.
- Eferl R, Wagner EF. AP-1: a double-edged sword in tumorigenesis. *Nat Rev Canc*. 2003;3(11):859–868.
- Glover JN, Harrison SC. Crystal structure of the heterodimeric bZIP transcription factor c-Fos-c-Jun bound to DNA. *Nature*. 1995;373(6511):257–261.
- Salat-Canela C, Paulo E, Sánchez-Mir L, et al. Deciphering the role of the signal- and Sty1 kinase-dependent phosphorylation of the stress-responsive transcription factor Atf1 on gene activation. *J Biol Chem*. 2017;292(33):13635–13644.
- Al-Huseini LM, Aw Yeang HX, Sethu S, et al. Nuclear factor-erythroid 2 (NF-E2) p45-related factor-2 (Nrf2) modulates dendritic cell immune function through regulation of p38 MAPK-cAMP-responsive element binding protein/activating transcription factor 1 signaling. *J Biol Chem*. 2013;288(31):22281–22288.
- Tsai EY, Jain J, Pesavento PA, Rao A, Goldfeld AE. Tumor necrosis factor alpha gene regulation in activated T cells involves ATF-2/Jun and NFATp. *Mol Cell Biol*. 1996;16(2):459–467.
- Thomas DA, Massague J. TGF-beta directly targets cytotoxic T cell functions during tumor evasion of immune surveillance. *Cancer Cell*. 2005;8(5):369–380.
- Xu Y, Zhou W, Zhang C, et al. Long non-coding RNA RP11-552M11.4 favors tumorigenesis and development of cervical cancer via modulating miR-3941/ATF1 signaling. *Int J Biol Macromol*. 2019;130:24–33.
- Li M, Zhang D, Ge X, et al. TRAF6-p38/JNK-ATF2 axis promotes microglial inflammatory activation. *Exp Cell Res*. 2019;376(2):133–148.
- Rohini M, Arumugam B, Vairamani M, Selvamurugan N. Stimulation of ATF3 interaction with Smad4 via TGF-beta1 for matrix metalloproteinase 13 gene activation in human breast cancer cells. *Int J Biol Macromol*. 2019;134:954–961.
- Chen Y, Mi Y, Zhang X, et al. Dihydroartemisinin-induced unfolded protein response feedback attenuates ferroptosis via PERK/ATF4/HSPA5 pathway in glioma cells. *J Exp Clin Cancer Res*. 2019;38(1):402.
- Darini C, Ghaddar N, Chabot C, et al. An integrated stress response via PKR suppresses HER2⁺ cancers and improves trastuzumab therapy. *Nat Commun*. 2019;10(1):2139.
- Li G, Xu Y, Guan D, Liu Z, Liu DX. HSP70 protein promotes survival of C6 and U87 glioma cells by inhibition of ATF5 degradation. *J Biol Chem*. 2011;286(23):20251–20259.
- Meng J, Liu K, Shao Y, et al. ID1 confers cancer cell chemoresistance through STAT3/ATF6-mediated induction of autophagy. *Cell Death Dis*. 2020;11(2):137.
- Spaan CN, Smit WL, van Lidth de Jude JF, et al. Expression of UPR effector proteins ATF6 and XBP1 reduce colorectal cancer cell proliferation and stemness by activating PERK signaling. *Cell Death Dis*. 2019;10(7):490.
- Gozdecka M, Breitwieser W. The roles of ATF2 (activating transcription factor 2) in tumorigenesis. *Biochem Soc Trans*. 2012;40(1):230–234.
- Hai T, Hartman MG. The molecular biology and nomenclature of the activating transcription factor/cAMP responsive element binding family of transcription factors: activating

- transcription factor proteins and homeostasis. *Gene*. 2001; 273(1):1–11.
22. Cui J, Yin Z, Liu G, et al. Activating transcription factor 1 promoted migration and invasion in lung cancer cells through regulating EGFR and MMP-2. *Mol Carcinog*. 2019;58(10): 1919–1924.
 23. Desmeules P, Joubert P, Zhang L, et al. A subset of malignant mesotheliomas in young adults are associated with recurrent EWSR1/FUS-ATF1 fusions. *Am J Surg Pathol*. 2017;41(7): 980–988.
 24. Thway K, Fisher C. Tumors with EWSR1-CREB1 and EWSR1-ATF1 fusions: the current status. *Am J Surg Pathol*. 2012; 36(7):e1–e11.
 25. Kujiraoka S, Tsunematsu T, Sato Y, et al. Establishment and characterization of a clear cell odontogenic carcinoma cell line with EWSR1-ATF1 fusion gene. *Oral Oncol*. 2017;69: 46–55.
 26. Zucman J, Delattre O, Desmaziere C, et al. EWS and ATF-1 gene fusion induced by t(12;22) translocation in malignant melanoma of soft parts. *Nat Genet*. 1993;4(4):341–345.
 27. Hao Q, Zhao X, Zhang Y, Dong Z, Hu T, Chen P. Targeting overexpressed activating transcription factor 1 (ATF1) inhibits proliferation and migration and enhances sensitivity to paclitaxel in esophageal cancer cells. *Med Sci Monit Basic Res*. 2017;23:304–312.
 28. Ghoneim C, Soula-Rothhut M, Blanchevove C, Martiny L, Antonicelli F, Rothhut B. Activating transcription factor-1-mediated hepatocyte growth factor-induced down-regulation of thrombospondin-1 expression leads to thyroid cancer cell invasion. *J Biol Chem*. 2007;282(21): 15490–15497.
 29. Ding G, Li W, Liu J, et al. LncRNA GHET1 activated by H3K27 acetylation promotes cell tumorigenesis through regulating ATF1 in hepatocellular carcinoma. *Biomed Pharmacother*. 2017;94:326–331.
 30. Zhao X, Weng W, Long Y, Pan W, Li Z, Sun F. LINC00665/miR-9-5p/ATF1 is a novel axis involved in the progression of colorectal cancer. *Hum Cell*. 2020;33(4):1142–1154.
 31. Shi Y, Wang W, Yang B, Tian H. ATF1 and RAS in exosomes are potential clinical diagnostic markers for cervical cancer. *Cell Biochem Funct*. 2017;35(7):477–483.
 32. Gutierrez CM, Lopez-Valdez R, Subramani R, et al. A breast tissue protein expression profile contributing to early parity-induced protection against breast cancer. *Cell Physiol Biochem*. 2015;37(5):1671–1685.
 33. Huang GL, Guo HQ, Yang F, et al. Activating transcription factor 1 is a prognostic marker of colorectal cancer. *Asian Pac J Cancer Prev*. 2012;13(3):1053–1057.
 34. Tian J, Chang J, Gong J, et al. Systematic functional interrogation of genes in GWAS loci identified ATF1 as a key driver in colorectal cancer modulated by a promoter-enhancer interaction. *Am J Hum Genet*. 2019;105(1):29–47.
 35. Ardeshtna KM, Pizzey AR, Devereux S, Khwaja A. The PI3 kinase, p38 SAP kinase, and NF-kappaB signal transduction pathways are involved in the survival and maturation of lipopolysaccharide-stimulated human monocyte-derived dendritic cells. *Blood*. 2000;96(3):1039–1046.
 36. Avni D, Ernst O, Philosoph A, Zor T. Role of CREB in modulation of TNFalpha and IL-10 expression in LPS-stimulated RAW264.7 macrophages. *Mol Immunol*. 2010;47(7–8): 1396–1403.
 37. Penix LA, Sweetser MT, Weaver WM, Hoeffler JP, Kerppola TK, Wilson CB. The proximal regulatory element of the interferon-gamma promoter mediates selective expression in T cells. *J Biol Chem*. 1996;271(50):31964–31972.
 38. Hai T, Curran T. Cross-family dimerization of transcription factors Fos/Jun and ATF/CREB alters DNA binding specificity. *Proc Natl Acad Sci U S A*. 1991;88(9):3720–3724.
 39. Yu T, Li YJ, Bian AH, et al. The regulatory role of activating transcription factor 2 in inflammation. *Mediat Inflamm*. 2014; 2014, e950472.
 40. Watson G, Ronai ZA, Lau E. ATF2, a paradigm of the multifaceted regulation of transcription factors in biology and disease. *Pharmacol Res*. 2017;119:347–357.
 41. Brinckerhoff CE, Matrisian LM. Matrix metalloproteinases: a tail of a frog that became a prince. *Nat Rev Mol Cell Biol*. 2002;3(3):207–214.
 42. Parks WC, Wilson CL, Lopez-Boado YS. Matrix metalloproteinases as modulators of inflammation and innate immunity. *Nat Rev Immunol*. 2004;4(8):617–629.
 43. Kitanaka N, Nakano R, Sakai M, et al. ERK1/ATF-2 signaling axis contributes to interleukin-1beta-induced MMP-3 expression in dermal fibroblasts. *PLoS One*. 2019;14(9):e0222869.
 44. Chacon-Solano E, Leon C, Diaz F, et al. Fibroblast activation and abnormal extracellular matrix remodelling as common hallmarks in three cancer-prone genodermatoses. *Br J Dermatol*. 2019;181(3):512–522.
 45. Shen Y, Park CS, Suppipat K, et al. Inactivation of KLF4 promotes T-cell acute lymphoblastic leukemia and activates the MAP2K7 pathway. *Leukemia*. 2017;31(6):1314–1324.
 46. Li N, Guo X, Liu L, Wang L, Cheng R. Molecular mechanism of miR-204 regulates proliferation, apoptosis and autophagy of cervical cancer cells by targeting ATF2. *Artif Cells Nanomed Biotechnol*. 2019;47(1):2529–2535.
 47. Lau E, Feng Y, Claps G, et al. The transcription factor ATF2 promotes melanoma metastasis by suppressing protein fucosylation. *Sci Signal*. 2015;8(406):ra124.
 48. Wu DS, Chen C, Wu ZJ, et al. ATF2 predicts poor prognosis and promotes malignant phenotypes in renal cell carcinoma. *J Exp Clin Cancer Res*. 2016;35(1):108.
 49. Bhoumik A, Fichtman B, Derossi C, et al. Suppressor role of activating transcription factor 2 (ATF2) in skin cancer. *Proc Natl Acad Sci U S A*. 2008;105(5):1674–1679.
 50. Gozdecka M, Lyons S, Kondo S, et al. JNK suppresses tumor formation via a gene-expression program mediated by ATF2. *Cell Rep*. 2014;9(4):1361–1374.
 51. Bhoumik A, Jones N, Ronai Ze. Transcriptional switch by activating transcription factor 2-derived peptide sensitizes melanoma cells to apoptosis and inhibits their tumorigenicity. *Proc Natl Acad Sci U S A*. 2004;101(12):4222–4227.
 52. Varsano T, Lau E, Feng Y, et al. Inhibition of melanoma growth by small molecules that promote the mitochondrial localization of ATF2. *Clin Cancer Res*. 2013;19(10):2710–2722.
 53. Song S, Fajol A, Tu X, Ren B, Shi S. miR-204 suppresses the development and progression of human glioblastoma by targeting ATF2. *Oncotarget*. 2016;7(43):70058–70065.
 54. Segura E, Touzot M, Bohineust A, et al. Human inflammatory dendritic cells induce Th17 cell differentiation. *Immunity*. 2013;38(2):336–348.
 55. Segura E, Amigorena S. Inflammatory dendritic cells in mice and humans. *Trends Immunol*. 2013;34(9):440–445.
 56. Goldszmid RS, Caspar P, Rivollier A, et al. NK cell-derived interferon-gamma orchestrates cellular dynamics and the differentiation of monocytes into dendritic cells at the site of infection. *Immunity*. 2012;36(6):1047–1059.
 57. Walsh KP, Mills KH. Dendritic cells and other innate determinants of T helper cell polarisation. *Trends Immunol*. 2013;34(11):521–530.
 58. Mahiddine K, Mallavialle A, Bziouech H, Larbret F, Bernard A, Bernard G. CD99 isoforms regulate CD1a expression in human monocyte-derived DCs through ATF-2/CREB-1 phosphorylation. *Eur J Immunol*. 2016;46(6):1460–1471.
 59. Colmone A, Li S, Wang CR. Activating transcription factor/cAMP response element binding protein family member regulated transcription of CD1A. *J Immunol*. 2006;177(10): 7024–7032.

60. Johannessen M, Delghandi MP, Moens U. What turns CREB on? *Cell Signal*. 2004;16(11):1211–1227.
61. Han J, Guo X, Tan W, et al. The expression of p-ATF2 involved in the chondrocytes apoptosis of an endemic osteoarthritis, Kashin-Beck disease. *BMC Musculoskel Disord*. 2013;14:209.
62. Li X, Udagawa N, Itoh K, et al. p38 MAPK-mediated signals are required for inducing osteoclast differentiation but not for osteoclast function. *Endocrinology*. 2002;143(8):3105–3113.
63. Miyata Y, Fukuhara A, Otsuki M, Shimomura I. Expression of activating transcription factor 2 in inflammatory macrophages in obese adipose tissue. *Obesity*. 2013;21(4):731–736.
64. Akiyama Y, Ogawa F, Iwata Y, et al. Autoantibody against activating transcription factor-2 in patients with systemic sclerosis. *Clin Exp Rheumatol*. 2009;27(5):751–757.
65. Shen T, Yang WS, Yi YS, et al. AP-1/IRF-3 targeted anti-inflammatory activity of andrographolide isolated from *Andrographis paniculata*. *Evid Based Complement Alternat Med*. 2013;2013:e210736.
66. Pearson AG, Curtis MA, Waldvogel HJ, Faull RL, Dragunow M. Activating transcription factor 2 expression in the adult human brain: association with both neurodegeneration and neurogenesis. *Neuroscience*. 2005;133(2):437–451.
67. Le NH, van der Wal A, van der Bent P, et al. Increased activity of activator protein-1 transcription factor components ATF2, c-Jun, and c-Fos in human and mouse autosomal dominant polycystic kidney disease. *J Am Soc Nephrol*. 2005;16(9):2724–2731.
68. Zhang S, Liu H, Liu J, Tse CA, Dragunow M, Cooper GJ. Activation of activating transcription factor 2 by p38 MAP kinase during apoptosis induced by human amylin in cultured pancreatic beta-cells. *FEBS J*. 2006;273(16):3779–3791.
69. Meijer BJ, Giugliano FP, Baan B, et al. ATF2 and ATF7 are critical mediators of intestinal epithelial repair. *Cell Mol Gastroenterol Hepatol*. 2020;10(1):23–42.
70. Hai TW, Liu F, Coukos WJ, Green MR. Transcription factor ATF cDNA clones: an extensive family of leucine zipper proteins able to selectively form DNA-binding heterodimers. *Genes Dev*. 1989;3(12b):2083–2090.
71. Hunt D, Raivich G, Anderson PN. Activating transcription factor 3 and the nervous system. *Front Mol Neurosci*. 2012;5:7.
72. Hashimoto Y, Zhang C, Kawauchi J, et al. An alternatively spliced isoform of transcriptional repressor ATF3 and its induction by stress stimuli. *Nucleic Acids Res*. 2002;30(11):2398–2406.
73. Rohini M, Haritha Menon A, Selvamurugan N. Role of activating transcription factor 3 and its interacting proteins under physiological and pathological conditions. *Int J Biol Macromol*. 2018;120(Pt A):310–317.
74. Cai Y, Zhang C, Nawa T, et al. Homocysteine-responsive ATF3 gene expression in human vascular endothelial cells: activation of c-Jun NH(2)-terminal kinase and promoter response element. *Blood*. 2000;96(6):2140–2148.
75. Hamdi M, Popeijus HE, Carlotti F, et al. ATF3 and Fra1 have opposite functions in JNK- and ERK-dependent DNA damage responses. *DNA Repair*. 2008;7(3):487–496.
76. Inoue K, Zama T, Kamimoto T, et al. TNFalpha-induced ATF3 expression is bidirectionally regulated by the JNK and ERK pathways in vascular endothelial cells. *Gene Cell*. 2004;9(1):59–70.
77. Liu J, Edagawa M, Goshima H, et al. Role of ATF3 in synergistic cancer cell killing by a combination of HDAC inhibitors and agonistic anti-DR5 antibody through ER stress in human colon cancer cells. *Biochem Biophys Res Commun*. 2014;445(2):320–326.
78. Wu X, Nguyen BC, Dziunycz P, et al. Opposing roles for calcineurin and ATF3 in squamous skin cancer. *Nature*. 2010;465(7296):368–372.
79. Tamura K, Hua B, Adachi S, et al. Stress response gene ATF3 is a target of c-myc in serum-induced cell proliferation. *EMBO J*. 2005;24(14):2590–2601.
80. Mathiasen DP, Egebjerg C, Andersen SH, et al. Identification of a c-Jun N-terminal kinase-2-dependent signal amplification cascade that regulates c-Myc levels in ras transformation. *Oncogene*. 2012;31(3):390–401.
81. Kang Y, Chen CR, Massagué J. A self-enabling TGFbeta response coupled to stress signaling: Smad engages stress response factor ATF3 for Id1 repression in epithelial cells. *Mol Cell*. 2003;11(4):915–926.
82. Inoue M, Uchida Y, Edagawa M, et al. The stress response gene ATF3 is a direct target of the Wnt/beta-catenin pathway and inhibits the invasion and migration of HCT116 human colorectal cancer cells. *PLoS One*. 2018;13(7):e0194160.
83. Avraham S, Korin B, Aviram S, Shechter D, Shaked Y, Aronheim A. ATF3 and JDP2 deficiency in cancer associated fibroblasts promotes tumor growth via SDF-1 transcription. *Oncogene*. 2019;38(20):3812–3823.
84. Wang Z, Xu D, Ding HF, et al. Loss of ATF3 promotes Akt activation and prostate cancer development in a Pten knockout mouse model. *Oncogene*. 2015;34(38):4975–4984.
85. Zeng Z, Xu FY, Zheng H, et al. LncRNA-MTA2TR functions as a promoter in pancreatic cancer via driving deacetylation-dependent accumulation of HIF-1alpha. *Theranostics*. 2019;9(18):5298–5314.
86. Hao ZF, Ao JH, Zhang J, Su YM, Yang RY. ATF3 activates Stat3 phosphorylation through inhibition of p53 expression in skin cancer cells. *Asian Pac J Cancer Prev*. 2013;14(12):7439–7444.
87. Kwok S, Rittling SR, Partridge NC, et al. Transforming growth factor-beta1 regulation of ATF-3 and identification of ATF-3 target genes in breast cancer cells. *J Cell Biochem*. 2009;108(2):408–414.
88. Song X, Lu F, Liu RY, et al. Association between the ATF3 gene and non-small cell lung cancer. *Thorac Cancer*. 2012;3(3):217–223.
89. Wu ZY, Wei ZM, Sun SJ, Yuan J, Jiao SC. Activating transcription factor 3 promotes colon cancer metastasis. *Tumour Biol*. 2014;35(8):8329–8334.
90. Wang A, Arantes S, Yan L, et al. The transcription factor ATF3 acts as an oncogene in mouse mammary tumorigenesis. *BMC Cancer*. 2008;8:268.
91. Zhao W, Sun M, Li S, Chen Z, Geng D. Transcription factor ATF3 mediates the radioresistance of breast cancer. *J Cell Mol Med*. 2018;22(10):4664–4675.
92. Yin X, Wolford CC, Chang YS, et al. ATF3, an adaptive-response gene, enhances TGF{beta} signaling and cancer-initiating cell features in breast cancer cells. *J Cell Sci*. 2010;123(Pt 20):3558–3565.
93. Cao Y, Yang Q, Deng H, et al. Transcriptional factor ATF3 protects against colitis by regulating follicular helper T cells in Peyer's patches. *Proc Natl Acad Sci U S A*. 2019;116(13):6286–6291.
94. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med*. 2010;363(8):711–723.
95. Brahmer JR, Tykodi SS, Chow LQM, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med*. 2012;366(26):2455–2465.
96. Whitmore MM, Iparraguirre A, Kubelka L, Weninger W, Hai T, Williams BRG. Negative regulation of TLR-signaling pathways by activating transcription factor-3. *J Immunol*. 2007;179(6):3622–3630.

97. Gilchrist M, Thorsson V, Li B, et al. Systems biology approaches identify ATF3 as a negative regulator of Toll-like receptor 4. *Nature*. 2006;441(7090):173–178.
98. Boespflug ND, Kumar S, McAlees JW, et al. ATF3 is a novel regulator of mouse neutrophil migration. *Blood*. 2014;123(13):2084–2093.
99. Khuu CH, Barrozo RM, Hai T, Weinstein SL. Activating transcription factor 3 (ATF3) represses the expression of CCL4 in murine macrophages. *Mol Immunol*. 2007;44(7):1598–1605.
100. Liu H, Kuang X, Zhang Y, et al. ADORA1 inhibition promotes tumor immune evasion by regulating the ATF3-PD-L1 Axis. *Cancer Cell*. 2020;37(3):324–339.
101. Labzin LI, Schmidt SV, Masters SL, et al. ATF3 is a key regulator of macrophage IFN responses. *J Immunol*. 2015;195(9):4446–4455.
102. Sha H, Zhang D, Zhang Y, Wen Y, Wang Y. ATF3 promotes migration and M1/M2 polarization of macrophages by activating tenascin-C via Wnt/ β -catenin pathway. *Mol Med Rep*. 2017;16(3):3641–3647.
103. Walter P, Ron D. The unfolded protein response: from stress pathway to homeostatic regulation. *Science*. 2011;334(6059):1081–1086.
104. Tameire F, Verginadis II, Leli NM, et al. ATF4 couples MYC-dependent translational activity to bioenergetic demands during tumour progression. *Nat Cell Biol*. 2019;21(7):889–899.
105. Ye J, Kumanova M, Hart LS, et al. The GCN2-ATF4 pathway is critical for tumour cell survival and proliferation in response to nutrient deprivation. *EMBO J*. 2010;29(12):2082–2096.
106. Mu N, Lei Y, Wang Y, et al. Inhibition of SIRT1/2 upregulates HSPA5 acetylation and induces pro-survival autophagy via ATF4-DDIT4-mTORC1 axis in human lung cancer cells. *Apoptosis*. 2019;24(9–10):798–811.
107. Jain S, Chakraborty G, Raja R, Kale S, Kundu GC. Prostaglandin E2 regulates tumor angiogenesis in prostate cancer. *Cancer Res*. 2008;68(19):7750–7759.
108. Igarashi T, Izumi H, Uchiumi T, et al. Clock and ATF4 transcription system regulates drug resistance in human cancer cell lines. *Oncogene*. 2007;26(33):4749–4760.
109. Guan X, Chen S, Liu Y, Wang LL, Zhao Y, Zong ZH. PUM1 promotes ovarian cancer proliferation, migration and invasion. *Biochem Biophys Res Commun*. 2018;497(1):313–318.
110. Xia LH, Yan QH, Sun QD, Gao YP. MiR-411-5p acts as a tumor suppressor in non-small cell lung cancer through targeting PUM1. *Eur Rev Med Pharmacol Sci*. 2018;22(17):5546–5553.
111. Dai H, Shen K, Yang Y, et al. PUM1 knockdown prevents tumor progression by activating the PERK/eIF2/ATF4 signaling pathway in pancreatic adenocarcinoma cells. *Cell Death Dis*. 2019;10(8):595.
112. Luo J, Xia Y, Yin Y, et al. ATF4 destabilizes RET through nonclassical GRP78 inhibition to enhance chemosensitivity to bortezomib in human osteosarcoma. *Theranostics*. 2019;9(21):6334–6353.
113. Liu J, Qi YB. Activation of LXR β inhibits proliferation, promotes apoptosis, and increases chemosensitivity of gastric cancer cells by upregulating the expression of ATF4. *J Cell Biochem*. 2019;120(9):14336–14347.
114. Abdel-Nour M, Carneiro LAM, Downey J, et al. The heme-regulated inhibitor is a cytosolic sensor of protein misfolding that controls innate immune signaling. *Science*. 2019;365(6448):eaaw4144.
115. Srivastava RK, Li C, Wang Y, et al. Activating transcription factor 4 underlies the pathogenesis of arsenic trioxide-mediated impairment of macrophage innate immune functions. *Toxicol Appl Pharmacol*. 2016;308:46–58.
116. Liu B, Chen P, Xi D, Zhu H, Gao Y. ATF4 regulates CCL2 expression to promote endometrial cancer growth by controlling macrophage infiltration. *Exp Cell Res*. 2017;360(2):105–112.
117. Yang X, Xia R, Yue C, et al. ATF4 regulates CD4⁺ T cell immune responses through metabolic reprogramming. *Cell Rep*. 2018;23(6):1754–1766.
118. Zhang C, Bai N, Chang A, et al. ATF4 is directly recruited by TLR4 signaling and positively regulates TLR4-triggered cytokine production in human monocytes. *Cell Mol Immunol*. 2013;10(1):84–94.
119. Baxevas AD, Vinson CR. Interactions of coiled coils in transcription factors: where is the specificity? *Curr Opin Genet Dev*. 1993;3(2):278–285.
120. Ellenberger TE, Brandl CJ, Struhl K, Harrison SC. The GCN4 basic region leucine zipper binds DNA as a dimer of uninterrupted alpha helices: crystal structure of the protein-DNA complex. *Cell*. 1992;71(7):1223–1237.
121. Vinson C, Myakishev M, Acharya A, Mir AA, Moll JR, Bonovich M. Classification of human B-ZIP proteins based on dimerization properties. *Mol Cell Biol*. 2002;22(18):6321–6335.
122. Newman JR, Keating AE. Comprehensive identification of human bZIP interactions with coiled-coil arrays. *Science*. 2003;300(5628):2097–2101.
123. Al Sarraj J, Vinson C, Thiel G. Regulation of asparagine synthetase gene transcription by the basic region leucine zipper transcription factors ATF5 and CHOP. *Biol Chem*. 2005;386(9):873–879.
124. Greene LA, Lee HY, Angelastro JM. The transcription factor ATF5: role in neurodevelopment and neural tumors. *J Neurochem*. 2009;108(1):11–22.
125. Ishihara S, Yasuda M, Ishizu A, Ishikawa M, Shirato H, Haga H. Activating transcription factor 5 enhances radioresistance and malignancy in cancer cells. *Oncotarget*. 2015;6(7):4602–4614.
126. Kong X, Meng W, Zhou Z, et al. Overexpression of activating transcription factor 5 in human rectal cancer. *Exp Ther Med*. 2011;2(5):827–831.
127. Hua XM, Wang J, Qian DM, et al. DNA methylation level of promoter region of activating transcription factor 5 in glioma. *J Zhejiang Univ - Sci B*. 2015;16(9):757–762.
128. Karpel-Massler G, Horst BA, Shu C, et al. A synthetic cell-penetrating dominant-negative ATF5 peptide exerts anti-cancer activity against a broad spectrum of treatment-resistant cancers. *Clin Cancer Res*. 2016;22(18):4698–4711.
129. Monaco SE, Angelastro JM, Szabolcs M, Greene LA. The transcription factor ATF5 is widely expressed in carcinomas, and interference with its function selectively kills neoplastic, but not nontransformed, breast cell lines. *Int J Canc*. 2007;120(9):1883–1890.
130. Chen A, Qian D, Wang B, et al. ATF5 is overexpressed in epithelial ovarian carcinomas and interference with its function increases apoptosis through the downregulation of Bcl-2 in SKOV-3 cells. *Int J Gynecol Pathol*. 2012;31(6):532–537.
131. Shuai Y, Fan E, Zhong Q, et al. ATF5 involved in radioresistance in nasopharyngeal carcinoma by promoting epithelial-to-mesenchymal phenotype transition. *Eur Arch Oto-Rhino-Laryngol*. 2020;277(10):2869–2879.
132. Sheng Z, Li L, Zhu LJ, et al. A genome-wide RNA interference screen reveals an essential CREB3L2-ATF5-MCL1 survival pathway in malignant glioma with therapeutic implications. *Nat Med*. 2010;16(6):671–677.
133. Dluzen D, Li G, Tacelosky D, Moreau M, Liu DX. BCL-2 is a downstream target of ATF5 that mediates the prosurvival function of ATF5 in a cell type-dependent manner. *J Biol Chem*. 2011;286(9):7705–7713.
134. Fiorese CJ, Schulz AM, Lin YF, Rosin N, Pellegrino MW, Haynes CM. The transcription factor ATF5 mediates a mammalian mitochondrial UPR. *Curr Biol*. 2016;26(15):2037–2043.

135. Li G, Li W, Angelastro JM, Greene LA, Liu DX. Identification of a novel DNA binding site and a transcriptional target for activating transcription factor 5 in c6 glioma and mcf-7 breast cancer cells. *Mol Cancer Res.* 2009;7(6):933–943.
136. Laeger T, Henagan TM, Albarado DC, et al. FGF21 is an endocrine signal of protein restriction. *J Clin Invest.* 2014;124(9):3913–3922.
137. Ishihara S, Haga H. ATF5: development of oncogenic resistance to radiotherapy. *Aging (Albany NY).* 2015;7(7):453–454.
138. Nukuda A, Endoh H, Yasuda M, Mizutani T, Kawabata K, Haga H. Role of ATF5 in the invasive potential of diverse human cancer cell lines. *Biochem Biophys Res Commun.* 2016;474(3):509–514.
139. Gho JW, Ip WK, Chan KY, Law PT, Lai PB, Wong N. Re-expression of transcription factor ATF5 in hepatocellular carcinoma induces G2-M arrest. *Cancer Res.* 2008;68(16):6743–6751.
140. Feldheim J, Kessler AF, Schmitt D, et al. Expression of activating transcription factor 5 (ATF5) is increased in astrocytomas of different WHO grades and correlates with survival of glioblastoma patients. *OncoTargets Ther.* 2018;11:8673–8684.
141. Angelastro JM, Canoll PD, Kuo J, et al. Selective destruction of glioblastoma cells by interference with the activity or expression of ATF5. *Oncogene.* 2006;25(6):907–916.
142. Cates CC, Arias AD, Nakayama Wong LS, et al. Regression/eradication of gliomas in mice by a systemically-deliverable ATF5 dominant-negative peptide. *Oncotarget.* 2016;7(11):12718–12730.
143. Moll JR, Olive M, Vinson C. Attractive interhelical electrostatic interactions in the proline- and acidic-rich region (PAR) leucine zipper subfamily preclude heterodimerization with other basic leucine zipper subfamilies. *J Biol Chem.* 2000;275(44):34826–34832.
144. Sun X, Jefferson P, Zhou Q, Angelastro JM, Greene LA. Dominant-negative ATF5 compromises cancer cell survival by targeting CEBPB and CEBPD. *Mol Cancer Res.* 2020;18(2):216–228.
145. Hu M, Wang B, Qian D, et al. Interference with ATF5 function enhances the sensitivity of human pancreatic cancer cells to paclitaxel-induced apoptosis. *Anticancer Res.* 2012;32(10):4385–4394.
146. Thuerlauf DJ, Marcinko M, Belmont PJ, Glembotski CC. Effects of the isoform-specific characteristics of ATF6 alpha and ATF6 beta on endoplasmic reticulum stress response gene expression and cell viability. *J Biol Chem.* 2007;282(31):22865–22878.
147. Namba T. Regulation of endoplasmic reticulum functions. *Aging.* 2015;7(11):901–902.
148. Luo B, Lee AS. The critical roles of endoplasmic reticulum chaperones and unfolded protein response in tumorigenesis and anticancer therapies. *Oncogene.* 2013;32(7):805–818.
149. Szegezdi E, Logue SE, Gorman AM, Samali A. Mediators of endoplasmic reticulum stress-induced apoptosis. *EMBO Rep.* 2006;7(9):880–885.
150. Sosa MS, Bragado P, Debnath J, Aguirre-Ghiso JA. Regulation of tumor cell dormancy by tissue microenvironments and autophagy. *Adv Exp Med Biol.* 2013;734:73–89.
151. Schewe DM, Aguirre-Ghiso JA. ATF6alpha-Rheb-mTOR signaling promotes survival of dormant tumor cells in vivo. *Proc Natl Acad Sci U S A.* 2008;105(30):10519–10524.
152. Hanaoka M, Ishikawa T, Ishiguro M, et al. Expression of ATF6 as a marker of pre-cancerous atypical change in ulcerative colitis-associated colorectal cancer: a potential role in the management of dysplasia. *J Gastroenterol.* 2018;53(5):631–641.
153. Liu CY, Hung MH, Wang DS, et al. Tamoxifen induces apoptosis through cancerous inhibitor of protein phosphatase 2A-dependent phospho-Akt inactivation in estrogen receptor-negative human breast cancer cells. *Breast Cancer Res.* 2014;16(5):431.
154. Teng HW, Yang SH, Lin JK, et al. CIP2A is a predictor of poor prognosis in colon cancer. *J Gastrointest Surg.* 2012;16(5):1037–1047.
155. Liu CY, Hsu CC, Huang TT, et al. ER stress-related ATF6 upregulates CIP2A and contributes to poor prognosis of colon cancer. *Mol Oncol.* 2018;12(10):1706–1717.
156. Romero-Ramirez L, Cao H, Nelson D, et al. XBP1 is essential for survival under hypoxic conditions and is required for tumor growth. *Cancer Res.* 2004;64(17):5943–5947.
157. Coleman OI, Lobner EM, Bierwirth S, et al. Activated ATF6 induces intestinal dysbiosis and innate immune response to promote colorectal tumorigenesis. *Gastroenterology.* 2018;155(5):1539–1552.
158. Walczynski J, Lyons S, Jones N, Breitwieser W. Sensitisation of c-MYC-induced B-lymphoma cells to apoptosis by ATF2. *Oncogene.* 2014;33(8):1027–1036.
159. Guo H-Q, Ye S, Huang G-L, Liu L, Liu O-F, Yang S-J. Expression of activating transcription factor 7 is correlated with prognosis of colorectal cancer. *J Cancer Res Therapeut.* 2015;11(2):319–323.
160. Hu X, Miao J, Zhang M, et al. miRNA-103a-3p promotes human gastric cancer cell proliferation by targeting and suppressing ATF7 in vitro. *Mol Cell.* 2018;41(5):390–400.
161. Song F, Wei M, Wang J, et al. Hepatitis B virus-regulated growth of liver cancer cells occurs through the microRNA-340-5p-activating transcription factor 7-heat shock protein A member 1B axis. *Cancer Sci.* 2019;110(5):1633–1643.
162. Shivers RP, Pagano DJ, Kooistra T, et al. Phosphorylation of the conserved transcription factor ATF-7 by PMK-1 p38 MAPK regulates innate immunity in *Caenorhabditis elegans*. *PLoS Genet.* 2010;6(4):e1000892.
163. Vandewynckel Y-P, Laukens D, Geerts A, et al. The paradox of the unfolded protein response in cancer. *Anticancer Res.* 2013;33(11):4683–4694.
164. Vesely PW, Staber PB, Hoefler G, Kenner L. Translational regulation mechanisms of AP-1 proteins. *Mutat Res.* 2009;682(1):7–12.