Review

MOLECULAR METABOLISM

Atf6α impacts cell number by influencing survival, death and proliferation

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ABSTRACT

Background: A growing body of literature suggests the cell—intrinsic activity of Atf6α during ER stress responses has implications for tissue cell number during growth and development, as well as in adult biology and tumorigenesis [1]. This concept is important, linking the cellular processes of secretory protein synthesis and endoplasmic reticulum stress response with functional tissue capacity and organ size. However, the field contains conflicting observations, especially notable in secretory cell types like the pancreatic beta cell.

Scope of review: Here we summarize current knowledge of the basic biology of Atf6α, along with the pleiotropic roles Atf6α plays in cell life and death decisions and possible explanations for conflicting observations. We include studies investigating the roles of Atf6α in cell survival, death and proliferation using well-controlled methodology and specific validated outcome measures, with a focus on endocrine and metabolic tissues when information was available.

Major conclusions: The net outcome of Atf6α on cell survival and cell death depends on cell type and growth conditions, the presence and degree of ER stress, and the duration and intensity of Atf6α activation. It is unquestioned that Atf6α activity influences the cell fate decision between survival and death, although opposite directions of this outcome are reported in different contexts. Atf6α can also trigger cell cycle activity to expand tissue cell number through proliferation. Much work remains to be done to clarify the many gaps in understanding in this important emerging field.

Keywords Activating transcription factor 6; Pancreatic beta cell; Cell survival; Apoptosis; Replication

1. INTRODUCTION

The mammalian unfolded protein response (UPR) is an elegant cellular process originating in the endoplasmic reticulum (ER) which adapts ER protein folding capacity to meet protein folding load [2,3]. The ER is a critical multifunctional cellular organelle with roles including secretory protein synthesis, folding, quality control and targeting; calcium homeostasis; and glucose and lipid metabolism. Like many other biological systems, ER mass and function are actively determined by the relative rates of catabolic destruction and de novo synthesis [2,3].

The UPR, triggered by ER stressors such as excess unfolded proteins, redox imbalance, or calcium depletion, is the principal regulator of ER expansion. The biology of the UPR, which is conserved across phyla, has been extensively reviewed [2—6]. Three ER transmembrane proteins, Perk, Ire1 and Atf6α, respond to ER stress and activate a coordinated translational and transcriptional program to slow new peptide entry into the ER, enhance ER associated degradation of misfolded protein, and increase biosynthesis of ER components to expand ER capacity. If the adaptation is successful, the cell resumes function at a new higher capacity. However, if adaptation fails, unresolvable ER stress and chronic UPR activation lead to cell death [7].

The original understanding of the UPR was as a cell-autonomous mechanism by which a cell adapts secretory-pathway protein production capacity to demand. However, emerging evidence suggests important roles for the UPR at the level of complex tissues and even whole organism health and metabolism, by influencing tissue function and cell number through death, survival, and proliferation decisions [5,6]. Of the three ER transmembrane proteins sensing stress and initiating the UPR, Atf6α may be the least well understood. Roles of Atf6α in organogenesis and development have been reviewed [1]. Here we summarize current understanding of the roles played by Atf6α in influencing cell proliferation and death, with attention paid to conflicting conclusions and possible explanations. When possible, we focus on data generated in primary tissues and cancers.

2. OVERVIEW OF ATF6α BIOLOGY

Atf6α was identified as an ER stress response mediator in 1998 in the laboratory of Kazutoshi Mori in Kyoto, Japan, using a yeast-one-hybrid

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Abbreviations: Atf6α, Activating transcription factor alpha; Bcl-2, B-cell lymphoma 2; cFos, human homolog of Finkel—Biskis—Jinkins murine osteogenic sarcoma virus oncogene; Chop, C/EBP homologous protein; ER, endoplasmic reticulum; ERAD, ER associated degradation; Jnk, c-Jun N-terminal kinase; mTor, mammalian target of rapamycin; Rheb, Ras homolog, mTor binding; Runx2, Runt-related transcription factor 2; S1P, site 1 protease; S2P, site 2 protease; Vegf, Vascular endothelial growth factor

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screen with a promoter element found to be common to genes upregulated by the UPR [8]. Initially found to be an activating transcription factor (ATF) family member that weakly bound a cAMP response element [9] and an SRF-binding protein [10], Atf6α is now known to be a member of a family of stress-responsive bZip transcription factors called OASIS factors [11]. The pace of Atf6α-related discovery has accelerated recently; most papers on the function of this important factor have been published in the past 5 years.

2.1. ATF6α gene structure

The human *ATF6α* gene, conserved across plants and metazoans [12], is located on chromosome 1. *ATF6α* contains only a single protein-coding transcript, with 16 exons and no known splice isoforms, which codes for the 670aa ATF6α protein (Figure 1). The mouse *Atf6α* gene is also encoded on chromosome 1, also contains 16 exons with no known splice variants, and encodes a 656aa protein.

2.2. Atf6α protein size and intracellular localization

In unstressed human cells, ATF6α protein is detected at a 90 kDa size, larger than the calculated molecular weight of 74.6 kDa [8]. However, during ER stress conditions, such as exposure to the glycosylation inhibitor tunicamycin or SERCA inhibitor thapsigargin, Atf6α-directed antibodies detect an additional 50 kDa band [8,13]. Indirect immunofluorescence, cellular fractionation and tryptic digestion studies determined that p90Atf6α is a type II transmembrane ER resident glycoprotein with a single-pass hydrophobic transmembrane domain of 21aa near the middle of the protein [13,14]. In contrast, p50Atf6α is a soluble, short-lived nuclear protein that is most easily detected in the presence of the ALLN protease inhibitor [13–16]. Studies with mutant constructs suggest that the presence or absence of the transmembrane region determines the localization of the N-terminal (p50Atf6α, aa 1–373) domain, suggesting a model in which a cleavage event releases the cytosolic domain from the transmembrane and luminal domains, resulting in nuclear localization [13]. The structural elements of Atf6α are summarized in Figure 1.

2.3. p90Atf6α transit to Golgi during ER stress

Although full length p90Atf6α contains two Golgi localization signals [17], during normal conditions it is found in the ER [13,14]. The 272aa ER luminal domain is sufficient to sense stress, relocate the protein to the Golgi, and allow cleavage [18]. Stress sensing occurs through interaction with the Grp78 (also called BiP, Hspa5) chaperone [17]. In unstressed conditions Atf6α is retained in the ER by interaction with Grp78, but during stress Grp78 is titrated away, releasing Atf6α to proceed to the Golgi in a COPII dependent mechanism [19]. Transport is regulated; even with excess unfolded proteins in the ER, Atf6α is selectively allowed to move to the Golgi while unfolded proteins are retained in the ER [20]. In a pancreatic beta cell line, Atf6α translocation to Golgi required Sar1A, a small GTPase involved in COPII vesicle formation [21].

2.4. Mechanism of p90Atf6α cleavage in the Golgi

The mechanism of the Atf6α cleavage event was clarified by Brown and Goldstein [15]. Similarly to SREBP, p90Atf6α undergoes regulated intramembrane proteolysis, in which S1P first cleaves the peptide on the luminal side of the transmembrane domain, and then S2P cleaves the peptide within the transmembrane domain, liberating the cytoplasmic soluble domain [15]. In support of this model, a serine protease inhibitor had no impact on transit of p90Atf6α to the Golgi, but prevented Atf6α cleavage and target activation [22]. A novel feedback loop has been described, in which Atf6α transcriptional target and key Golgi calcium regulator Nucleobindin 1 inhibits S1P Atf6α cleavage, without impacting transit to Golgi [23]. In neurons, Calsenilin, encoded by the *KCNIP3* gene, regulates ATF6α processing and mediates protection by repaglinide on Huntington's disease [24].

2.5. Protein modifications impact Atf6α behavior

Post-translational modifications also impact Atf6α transport and activation by ER stress. Under unstressed conditions Atf6α is found in monomeric, dimeric and multimeric complexes due to intra- and intermolecular disulfide bonds [25]. Only reduced monomeric Atf6α transits to Golgi, but reduction was not sufficient to induce activation [25]. An siRNA screen for Atf6α activators in cancer cells identified a novel mechanism in which the protein disulfide isomerase Pdia5 promotes a disulfide bond rearrangement in the luminal domain of Atf6α, leading to Atf6α packaging in CopII vesicles [26]. Intriguingly, the Atf6α luminal domain has three conserved N-linked glycosylation sites, and glycosylation provides a negative signal, restricting Atf6α responsiveness to stress [27]. Under-glycosylated forms of Atf6α achieved by mutation of the glycosylation sites leads to reduced interaction with ER

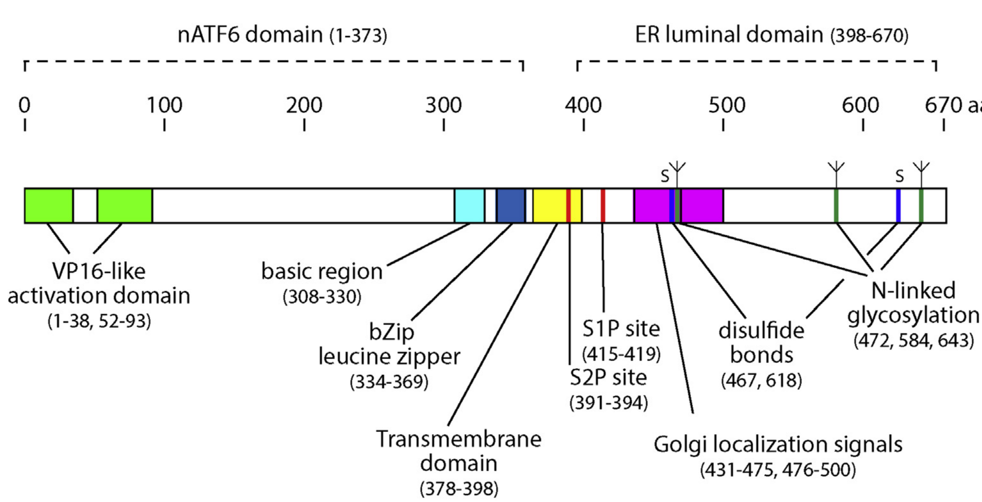

Figure 1: Schematic of the Atf6α protein, with known domain structures and functional elements. nAtf6, nuclear Atf6. S1P, site 1 protease. S2P, site 2 protease. VP16, herpes simplex virus protein vmw65 activating domain. Data contributing to this figure are from [13,15–17,25,51].

chaperone calreticulin and increased transit to Golgi, cleavage, and transactivation of target genes [27]. The role of stress kinases is controversial; one study found that p38-Mapk phosphorylated Atf6α at Thr-166, preventing cleavage and nuclear translocation [28]; in other conditions p38-Mapk phosphorylation of the N-terminal cytoplasmic domain was found to enhance Atf6α transcriptional activation of targets such as Grp78 [29,30].

2.6. Atf6α abundance is also regulated at the RNA level

In addition to the well-known protein-level activation by ER stress described above, Atf6α is also itself increased at the RNA level by ER stress. In MEFs, Atf6α mRNA was increased by tunicamycin exposure in sXbp dependent fashion [31]. On the other hand, thapsigargin was observed to increase Atf6α mRNA in a feed-forward autoregulation loop via Atf6α binding elements in the Atf6α promoter [32]. The proteasome-regulating transcription factor Nrf1, and ERRγ, also positively regulate Atf6α gene transcription through direct enhancer binding [33,34].

2.7. Nuclear p50Atf6α regulates gene transcription through direct DNA binding

Cleavage of Atf6α in the Golgi releases p50Atf6α, a 373aa cytoplasmic fragment which contains a basic leucine zipper DNA binding domain and several putative nuclear localization signals, and localizes to the nucleus [8,13—15]. As such, ER stress-induced transit and cleavage of Atf6α activates an ER-to-nucleus transcriptional regulatory program. The first identified DNA regulatory sequence bound by Atf6α was a 19 nucleotide motif, CCAATN$_9$CCACG, called the ER stress response element (ERSE) [8]. This bipartite motif contains a CCAAT box, bound by general factors, and a CCACG box, bound by Atf6α [8,35,36]. Subsequently, Atf6α was found to also bind to TGACGTG(G), now called the UPRE, which contains a partial complement of the ERSE sequence [36]; however, the UPRE is now considered to be more responsive to sXbp1 than Atf6α [37]. A third ER stress response element, ERSE-II, ATTGG-N-CCACG, contains the Atf6α-binding CCACG box next to an inverted CCAAT box with a much shorter spacer of only one base pair [37].
ERSE motifs are found in known ER stress responsive genes Grp78, Grp94 and calreticulin, and mediate stress-responsive transcription of a luciferase construct [8]. Base-by-base mutation mapped the ERSE critical nucleotides [8]. The bipartite ERSE motif engages general transcription factors YY1 and NF-Y/CBP at the CCAAT box; Atf6α binds at the CCACG box [8,35,36]. Atf6α interacts with the C-subunit of NF-Y [38]; co-binding of NF-Y and YY1 added selectivity and strength to the Atf6α transcriptional response [14]. In addition to SRF, NF-Y and YY1, Atf6α may regulate gene transcription by interacting with PGC1alpha [34]. Mutation of the bZip DNA binding domain eliminated transactivation of a Grp78-ERSE luciferase reporter [16]. Atf6α (1—373) transcription transactivating activity is mostly contained in a VP16-like domain at aa 1—38 and 52—93 [16].

2.8. Cross-talk between Atf6α and other UPR pathways

Teasing out the role of Atf6α in the UPR transcriptional response is complicated by overlapping functions of other UPR nuclear effectors, especially sXbp1 [39]. In general, the UPRE motif is activated by sXbp1, whereas ERSE and ERSE-II are activated by both sXbp1 and Atf6α [37]. In the presence of NF-Y, sXbp1 can replace Atf6α at the ERSE, but with lower binding efficiency [37]. Complicating matters, Atf6α transcriptionally induces Xbp1 [40], but may suppress Ire1 mRNA levels [41]. Further confounding separation of roles, Atf6α heterodimerizes with sXbp1, binding the UPRE with 8-fold higher affinity than sXbp1 homodimer [42].

Atf6α has a homologue, Atf6β, that shares similar biology: full length Atf6β is ER membrane localized and upon ER stress transits to Golgi, undergoes cleavage by S1P/S2P and releases an N-terminal transcription factor [43]. Atf6β exhibits some degree of functional redundancy with Atf6α, since gene deletion of either Atf6α or Atf6β has minimal biological impact but deletion of both Atf6α and Atf6β is embryonic lethal [42]. However, in vitro studies show important differences. Atf6α is solely responsible for the classical UPR-dependent gene regulation [42,44]; in fact, Atf6β has been reported to antagonize some Atf6α actions, such as transcriptional induction of Grp78 [45,46].
Atf6α also has a complex relationship with UPR death effector Chop. Atf6α transcriptionally induces *Chop* mRNA [47,48]. However, overexpression of Chop suppressed Atf6α activation of target gene Grp78 in dose-dependent manner. Chop is also a bZip transcription factor and may heterodimerize with Atf6α to suppress its activity [49]. On the other hand, CHIP assay showed that Chop binds to the Grp78 promoter, and a mutant Chop defective in DNA binding failed to suppress Atf6α mediated Grp78 induction, favoring a model in which Chop inhibits Atf6α gene regulation by competing for the regulatory motifs [49].

2.9. Canonical function of Atf6α

The principal outcome of Atf6α activation during ER stress is the expansion of functional ER capacity. Atf6α transcriptionally upregulates many genes involved in protein folding, including ER-resident chaperones, foldases, calcium transport proteins, and oxidation/reduction regulators [1,39,42]. Atf6α is also required for optimal clearance of misfolded proteins via Endoplasmic Reticulum-Associated Degradation (ERAD) genes and for expansion of the ER through induction of membrane synthesis [1,50]. Atf6α promotes ER expansion via heavily redundant and overlapping roles with the other UPR pathways, such that disentangling one from the others is challenging [2,4,39].

2.10. Mechanisms turning the Atf6α signal off

Full length p90Atf6α is subject to ubiquitination and proteasomal degradation, more pronounced after ER stress induction [51]. WFS1, an ER transmembrane protein mutated in Wolfram syndrome, was found to suppress Atf6α activation by inducing proteasome-mediated degradation of full-length Atf6α [52]. Supporting a role for chronic activation of Atf6α in Wolfram syndrome, Atf6α levels were increased in both Wfs1-deleted mice and Wolfram patient samples [52]. In addition, p90Atf6α was identified as a transmembrane target of ERAD, requiring both ERAD E3 ligase Sel1l and mannose trimming [50]. Nuclear Atf6α is short-lived, requiring protease inhibition to detect, suggesting a rapid degradation mechanism [13—16]. Observing that protein stability of N-terminal Atf6α mutants was correlated with transcriptional activity, the VP16-homologous domain identified by Christopher Glembotski's group was found to confer both transactivation and degradation capacity [16]. Intriguingly, the unspliced form of Xbp1 mRNA is also translated to a protein product, which accumulates in later stages of UPR recovery and may be responsible for targeting sXbp1 and nAtf6α for proteasome mediated degradation, implicating an Ire1-derived off-signal in shutting down the sXbp1 and nAtf6α transcriptional programs [53].

3. CONFLICTING ROLES: ATF6α CAN PROMOTE BOTH CELL SURVIVAL AND CELL DEATH

Atf6α has been reported to play numerous, disparate roles in processes regulating cell number (Figure 2). In its canonical role, Atf6α

activation drives a multi-pronged and robust effort by the cell to restore protein folding capacity, export misfolded protein from the ER for degradation by the proteasome, and ultimately, promote cell survival in response to diverse insults to the ER folding environment [44]. This pro-survival function may drive the pathology of achromatopsia, a genetic human retinal disease resulting from *ATF6α* mutations [54]. Mutations that impair ATF6α activation by disrupting ER-Golgi trafficking, regulated intramembrane proteolytic cleavage or transcriptional activity were found to increase cell death in patient-derived fibroblasts, although a role for cell death in achromatopsia pathogenesis remains uncertain [54].

On the other hand, Atf6α has also been found to increase cell death, through direct and indirect mechanisms, supporting a pro-apoptotic role for Atf6α under some conditions. Atf6α induces expression of Chop, which drives apoptosis through various mechanisms. A tissue highlighting the complicated coexisting pro- and anti-apoptotic functions of Atf6α is the pancreatic beta cell. For example, pathogenesis of Wolfram Syndrome, a progressive neurological syndrome characterized by hearing loss, optic atrophy and diabetes, may be due to ATF6α toxicity [52]. WFS1 provides feedback inhibition on ATF6α signaling, via targeting full length ER ATF6α for proteasomal degradation by recruiting the HRD1 E3 ligase [52]. Loss of function of WFS1 in Wolfram Syndrome causes pancreatic beta cell dysfunction, apoptosis and diabetes through dysregulated excess ATF6α activity [52]. ATF6α was also implicated in the transcriptional response to lipotoxicity leading to human beta cell death [55]. On the other hand, loss of Atf6α was reported to cause beta cell death in a type 1 diabetes model, and cell death was decreased by restoration of Atf6α expression [56]. Known mechanisms of pleiotropic pro-survival and/or pro-cell death Atf6α functions are reviewed below.

4. ATF6α PROMOTES CELL SURVIVAL

4.1. Atf6α promotes cell survival by adapting protein folding capacity during ER stress

As noted above, the primary function of Atf6α is as an ER membrane sensor, detecting misfolded proteins in the ER lumen and activating a transcriptional response to restore protein folding homeostasis. Efficient ER function requires the activity of many genes that Atf6α controls, including protein folding chaperones, foldases, [Ca^{2+}]-regulatory and -regulated ER proteins, redox regulators, as well as other miscellaneous genes with unclear roles in the UPR [2,4,13,14,57,58]. One of the earliest studies of Atf6α revealed that ER Ca^{2+}-ATPase inhibitor thapsigargin activates cleavage of Atf6α to induce protein folding chaperones [13]. Overexpressed ATF6α cooperates with general transcription factors NF-Y or YY1 to bind the ERSE and induce expression of ER chaperones GRP78, GRP94, and calreticulin, among many other genes later identified [14,47]. Conversely, deletion of Atf6α in MEFs severely reduced the ER-stress dependent induction of a suite of ER chaperone genes: Grp78, Grp94, Grp170, p58IPK, and Erdj3 [57]. In addition to chaperones, Atf6α also increases membrane phosphatidylcholine synthesis which may help to increase folding capacity by increasing ER volume [59].

Some Atf6α-dependent chaperones are critically important for cell survival; chaperone deletion may induce apoptosis despite activation of UPR [60–62]. In addition to chaperone, calcium and UPR-inhibitory actions, Grp78 directly binds and inhibits ER-resident Bik pro-apoptotic activity, preventing binding of Bcl2 [63,64]. Homozygous loss of chaperone expression can cause embryonic lethality or severe developmental defects. For example, deletion of Grp78 is lethal very early in development, around the time of embryo implantation into the

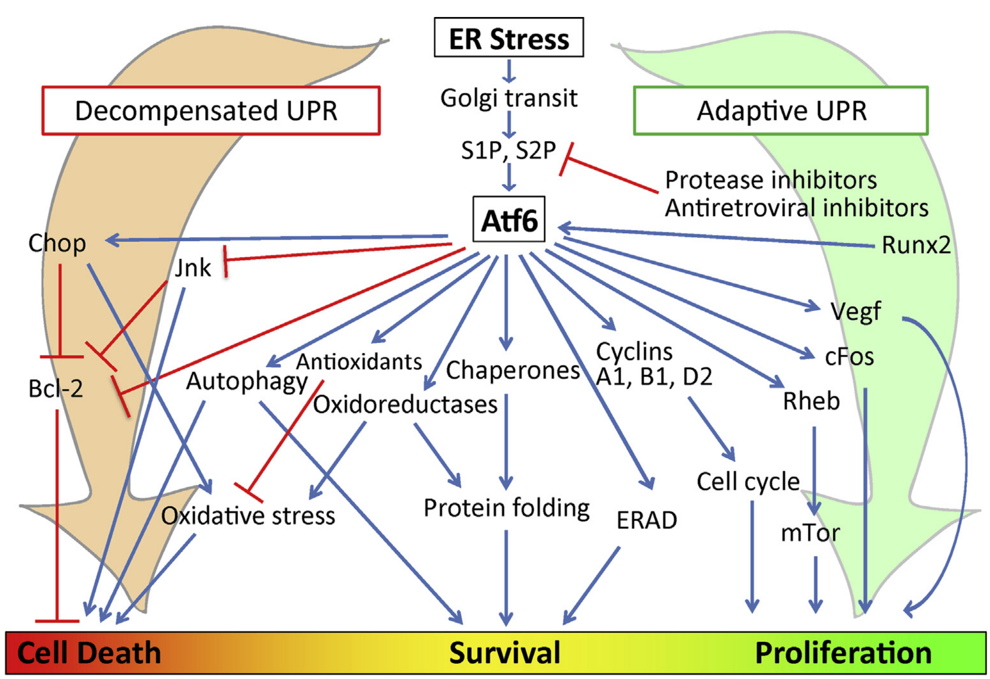

Figure 2: Summary of Atf6α-regulated pathways regulating cell fate decisions leading to cell death, cell survival or proliferation. S1P, site 1 protease. S2P, site 2 protease. Chop, C/EBP homologous protein. Jnk, c-Jun N-terminal kinase. Runx2, Runt-related transcription factor 2. Bcl-2, B-cell lymphoma 2. Vegf, Vascular endothelial growth factor. cFos, human homolog of Finkel–Biskis–Jinkins murine osteogenic sarcoma virus oncogene. Rheb, Ras homolog, mTor binding. ERAD, ER associated degradation. mTor, mammalian target of rapamycin. Please see the text for citations.

uterine wall, with excess apoptosis in the inner cell mass [60]. Loss of function in chaperone p58IPK causes diabetes and neurodegenerative disorders in mice and is linked to a similar syndrome in rare familial cases [65]. Intriguingly, in addition to ER-resident chaperone expression, Atf6α may also control extracellular protein folding via increased transcription and secretion of chaperone ERdj3, which functions both intracellularly and extracellularly to prevent aggregation of unfolded proteins [66]. Overexpressed ERdj3 reduced extracellular amyloid beta aggregation, and secreted ERdj3 in conditioned media prevented vacuolization in a neuroblastoma line treated with toxic prion protein. As such, Atf6α-mediated induction of chaperones may be important for both intracellular and extracellular proteostasis.

4.2. Atf6α influences ER redox status

Atf6α pro-survival functions also include maintenance of healthy ER redox status. Atf6α controls the expression of several ER-resident proteins that catalyze the formation and breakage of disulfide bonds during protein folding [67], such as Erp72, p5, & Ero1beta [42,57]. These oxidoreductases are oxygen-dependent enzymes that that may link hypoxia to UPR activation [68]. Atf6α has a well-supported role in promoting adaptation to hypoxic stress. Atf6α knock-in reduced necrosis and apoptosis and improved heart function after ischemia/reperfusion injury [69]. Conversely DN-Atf6α or siAtf6α increased apoptosis in response to ischemia/reperfusion in cardiac myocytes [70]. Pdia6 is an Atf6α target that promotes chemotherapeutic resistance in cancer and protects against ischemia/reperfusion injury in cardiomyocytes when overexpressed [71,72]. Atf6α-dependent induction of antioxidant genes has also been reported to be protective in cardiac ischemic/reperfusion injury [73] but an antioxidant function of Atf6α has not been confirmed in other studies. Besides the heart, Atf6α also appears protective against ischemia/reperfusion injury in the brain. In a surgically-induced murine stroke model, overexpressed Atf6α reduced infarct size and improved cognition, associated with upregulated Bcl2 and accelerated induction of autophagy [74]. Interestingly, the usually pro-apoptotic Atf6α target Chop may actually be protective in hypoxic neurons [75].

4.3. Atf6α targets improve clearance of ER misfolded proteins

Atf6α also promotes cell survival by transcriptionally activating ER-associated degradation pathways (ERAD) that clear misfolded proteins from the ER. Atf6α and Xbp1 knockout MEFs show an inability to induce canonical ERAD genes HerpUD1, Edem, and Hrd1 in response to ER stress, along with a decrease in viability compared to wild type cells [42]. ATF6α also induces Derlin-3, an important ERAD component that facilitates extrusion of misfolded proteins into the cytosol for proteasomal degradation [76,77]. Derlin-3 improved clearance of misfolded protein from the ER and was necessary and sufficient to reduce apoptosis in rat cardiomyocytes that underwent simulated ischemia/reperfusion injury [76].

4.4. Atf6α influences autophagy

ATF6α may also improve cell survival by inducing autophagy, clearing misfolded proteins and damaged organelles. As noted in *4.2*, overexpression of nuclear Atf6α protected mice against stroke, with early induction of autophagy [74]. Ormld3 knockout splenic B cells had decreased Atf6α and Beclin1 expression, with reduced survival; overexpression of ATF6α rescued Beclin1 expression, autophagy, and survival [78]. Atf6α can also interact with C/EBP-beta to trigger autophagy through induction of Dapk1 in response to bacterial insult or IFNγ. In support of the importance of this observation, Atf6αKO mice are susceptible to death from bacterial infection [79]. Phosphorylation of Atf6α by Ask1/Mkk3-p38Mapk pathway was necessary for its activation and subsequent interaction with C/EBP-beta to mediate IFNγ induced Dapk1 [28]. Similarly, in the mouse neuroblastoma line Neuro2, Japanese encephalitis virus infection induced Atf6α and Xbp1-dependent autophagy, preventing apoptosis [80]. In this model system Xbp1, but not Atf6α, was necessary for Beclin-1 induction, while Atg3 was Atf6α-dependent. An intriguing hypothesis is that Atf6α could have evolved in part as a defense mechanism against pathogen-induced ER stress. On the other hand, ER-stress induced autophagy was unaffected by knockdown of Atf6α in the human neuroblastoma line SK-N-SH but was instead dependent on the Ire1-Jnk pathway [81], and siAtf6α had no effect on Dengue-virus induced autophagy [82].

4.5. Atf6α may affect survival through activation of mTor

Atf6α was required for mTor activation in a *Drosophila* cell line [83]. Atf6α promoted chemotherapeutic resistance of dormant squamous carcinoma through Akt-independent mTor activation via transcriptionally inducing mTor-activator Rheb [84]. Furthermore, in endothelial cells, Vegf induced Atf6α was required for pro-survival Akt phosphorylation by mTor [85].

4.6. Atf6α has a limited role under unstressed conditions

Surprisingly, considering the implied importance of this supposedly critical UPR component, under unstressed conditions Atf6α-null mice are remarkably normal. Individual Atf6α or Atf6β-null mice appear viable and healthy, but deletion of both genes results in embryonic lethality, suggesting that Atf6α and Atf6β have redundant functions such that Atf6β can replace Atf6α under basal conditions [42,44]. One cell type that may require Atf6α under unstressed conditions is the pancreatic beta cell; in normoglycemic conditions, anti-Atf6α siRNA-treated insulinoma cells had a JNK-dependent increase in apoptosis [86]. Although Atf6α knockdown in these cells reduced Atf6α protein by only around 60%, this reduction was sufficient to reduce Grp78 mRNA and protein expression under basal conditions. Other Atf6α targets Grp94 and ERAD component Herp were only blunted during induction of ER stress. On the other hand, whole body Atf6α-null mice had no discernible impairment in glucose metabolism except under insulin-demand stress conditions [87].

4.7. Atf6α is required for resilience in the face of stress

When exposed to stress conditions, Atf6α-null cells have impaired stress resistance. Although Atf6α knockout MEFs had no significant difference in chaperone expression or viability when cultured in normal growth medium, induction of chaperones was blunted after treatment with ER stress-inducing drugs, and viability was decreased [44]. Atf6α is also critical for the acute adaptive response to ER stress in vivo. Challenging Atf6α-null mice with intraperitoneal tunicamycin resulted in macroscopic liver damage and a dramatic 80% mortality (compared to 0% in wild type mice), along with reduced and delayed induction of ER-chaperone and ERAD genes. Pancreatic beta cells in Atf6α-null mice also showed impaired function under insulin demand stress [87]. Taken together, it seems the impact of Atf6α depletion requires acute stress to be revealed [44].

In contrast, it has been reported that Atf6α is not required for induction of UPR genes by ER stress in stable anti-Atf6α siRNA-expressing MEFs [31]. The authors postulated that transcription factors related to Atf6α (Atf6β or other family members) may compensate for Atf6α loss. Although the authors reported that residual Atf6α activity was unlikely, due to undetectable Atf6α expression in the Atf6α knockdown cells, nuclear Atf6α is a potent and short-lived transcription factor [16].

Therefore, it is possible that some Atf6α may have been present but not detected. This is consistent with another study using Atf6α siRNA in liver Kupffer cells that showed Tm-induced upregulation of Xbp1, Chop, and Grp78 was unaffected by Atf6α KD in which p50-Atf6α was decreased but still detectable after knockdown [88].

5. IN OTHER CONTEXTS, ATF6α INCREASES APOPTOSIS

Contradictory to its reported pro-survival role, in certain contexts Atf6α has been shown to activate the intrinsic mitochondrial apoptosis pathway, possibly related to supra-physiological Atf6α activation. Ectopically expressed Atf6α directly bound an ERSE in the Bcl-2 promoter to repress its expression [89]. Overexpressed Atf6α decreased viability of vascular endothelial cells exposed to thapsigargin [90]. Atf6α may also regulate intrinsic apoptosis through downregulation of E2f1 expression, the loss of which was sufficient to increase expression of Puma and Noxa [91]. In mouse granulosa cells, knockdown of Atf6α decreased p53 and apoptosis [92]. In contrast, knockdown of Xbp1 increased apoptosis [93]. Overexpression of nuclear Atf6α in differentiating myoblasts upregulated a WW-domain binding protein (Wbp1) and downregulated anti-apoptotic Mcl-1, which was sufficient to increase apoptosis [94].

5.1. Atf6α increases expression of Chop

The most widely supported pro-death signal downstream of Atf6α is the transcription factor Chop (Ddit3, Gadd153). Atf6α cooperates with the Perk/Atf4 pathway to induce maximal expression of Chop in response to ER stress [95]. Chop knockout MEFs have delayed apoptosis after exposure to tunicamycin [96]. Similarly, tunicamycin-induced apoptosis was reduced, but not eliminated, in the kidney proximal tubular epithelium of Chop-null mice. Chop loss of function is protective in models of diabetes [97—100], neurodegenerative disease [101,102], renal injury [103—107], and sepsis [108].

Chop induces cell death through several mechanisms. Like Atf6α, Chop directly controls expression of components of the intrinsic apoptosis pathway. It is reported to downregulate pro-survival Bcl2 [109] and increase expression of pro-apoptotic Puma and Bim [110]. Via induction of Gadd34, Chop antagonizes the p-eIF2α-mediated translation block to increase protein synthesis even though the protein folding capacity may not have been adequately restored [103,111]. Furthermore, Ero1α is activated by Chop and contributes to oxidative stress in the ER which sensitizes cells to undergo apoptosis [103,111]. The Atf4/Chop pathway could define a switch from anti-apoptotic to pro-apoptotic signaling with longer stress duration, with the short half-life of pro-apoptotic mRNAs providing protection against cell death early during adaptive UPR [112].

5.2. Atf6α-induced autophagy promotes cell death

As described above, Atf6α-dependent autophagy can be protective in some cases but leads to autophagic cell death in other contexts. In MCF7 cells, siRNA silencing of ATF6α, IRE1, or dnPERK, inhibited doxorubicin-induced autophagy and apoptosis [113]. Knockdown of ATF6α also prevented berberine-induced elevation of GRP78 in cancer cell lines, which was required for induction of autophagy and cell death [114].

5.3. Atf6α leads to inflammation

In addition to the well-studied effects on Chop and intrinsic apoptosis pathways, Atf6α also modulates inflammatory and immunogenic cell death. Atf6α promoted NF-kB activation and pro-inflammatory cytokine expression in liver Kupffer cells to promote liver damage during ischemia/reperfusion injury [88]. On the other hand, Atf6α-induced sXbp1 prevents Tnf-a induced apoptosis in osteoarthritic cartilage [115], and Atf6α was necessary for suppression of Tnfa-induced NF-kB activation via upregulation of C/EBPβ and activation of mTor, which prevented Akt phosphorylation [116].

5.4. How can Atf6α be both pro- and anti-cell survival?

The many seemingly contradictory findings with regard to the downstream effects of Atf6α may have multiple explanations. Heterodimerization with other transcription factors could provide cell-type specificity for Atf6α target genes, leading to different results in different cell types. Post-translational modifications may also provide context-specificity of Atf6α activity. Cell-type specific epigenetic landscapes could prime or block activation of Atf6α target genes. In addition, the ability of Atf6β to compensate for Atf6α loss may vary by cell type. Secretory cells such as pancreatic beta cells may be especially dependent on Atf6α to cope with the high basal ER function requirement inherent in synthesizing proteins for systemic use. The duration and intensity of Atf6α activation may clearly play a role in the switch between pro-survival and pro-apoptotic UPR signaling, and some differences in results may be due to excess overexpression. Specific underlying mechanisms explaining divergent effects of Atf6α require further study.

6. ATF6α ALSO MODULATES CELL PROLIFERATION

In addition to the canonical Atf6α downstream response leading to expanded ER proteosynthetic capacity, and the extensive evidence that Atf6α modulates cell survival, some studies have found that Atf6α action also influences the decision to enter the cell cycle. Some of the work implicating Atf6α in proliferation has been performed in cancer or cancer cell lines [117—122]; other observations are in primary tissues such as pancreatic beta cells, ovarian cells, chondrocytes and cardiomyocytes [46,92,123—125]. In most cases, Atf6α activation increased cell cycle entry, whether as part of healthy tissue growth and adaptation or as a maladaptive response to disease. Some data show a role for Atf6α in tissue hypertrophy without hyperplasia [125—127]. An anti-proliferative effect has been described as well [128]. Since proliferation of normal tissues may be part of healthy adaptation or maladaptation, and proliferation of cancer cells leads to disease, Atf6α roles in proliferation defy categorization as uniformly beneficial or harmful. What little is known of the mechanisms by which Atf6α activation influences cell proliferation is summarized below.

6.1. Decreasing Atf6α signaling inhibits cancer cell proliferation

Endoplasmic reticulum stress, and the UPR, are well-established features of cancer biology related to insults such as hypoxia, poor nutrient availability relative to metabolic demand, and oxidative stress [129]. Although the majority of studies investigating ATF6α in cancer cells have focused on oncogenic cell survival in the face of ER stress, there is evidence that ATF6α promotes proliferation as well. ATF6α, known to be a tumorigenic factor in hepatocellular carcinoma [130], drives proliferation and BrdU incorporation in hepatoma cells in a proteostasis-stress dependent manner [118]. Treating cells with a proteasome inhibitor oprozomib decreased proliferation by inhibiting regulated intramembrane proteolysis, thus reducing ATF6α cleavage and decreasing ATF6α target gene activation [118]. Similarly, the antiretroviral protease inhibitor nelfinavir was found to have anti-proliferative effects in prostate cancer and liposarcoma through an off-target inhibition of S1P/S2P activation of ATF6α [121,122]. In addition, knockdown of *ATF6α* in glioblastoma cells reduced

proliferation, although the observation was weakened by use of a nonspecific viability assay to quantify proliferation [120]. These studies suggest that decreasing ATF6α expression or activation reduced proliferation, supporting a pro-proliferative role for ATF6α in human cancers, although downstream mechanisms were not tested.

6.2. Increasing Atf6α signaling drives cancer cell proliferation

ATF6α is implicated in the pathogenesis of hepatocellular carcinoma, and overexpression of nATF6α in an HCC cell line increased gene expression of cell cycle associated genes [131]. In two colorectal cancer tumor banks, increased *ATF6α* expression was associated with reduced disease-free survival [117]. To explore the mechanism, a mouse model was generated with tissue specific overexpression of active nuclear nAtf6α in intestinal epithelial cells. These mice developed spontaneous colon cancer by 12 weeks of age, with increased proliferation of epithelial cells [117]. The mechanism was determined to be through an increase in gut permeability leading to inflammatory bacterial penetration into the gut wall, which activated Stat3 and led to cancer [117]. In endothelial cells, ATF6α was found to activate a novel target, αB-crystallin, which was pro-proliferative via a mechanism involving VEGF [119].

6.3. Atf6α influences cell cycle entry in non-transformed cells

Emerging evidence suggests that UPR pathways in general, and Atf6α specifically, have previously unrecognized roles in normal organ development and function [1]. Deletion of both Atf6α and Atf6β is embryonic lethal [42]. To date, most evidence implicating Atf6α in proliferation in normal tissues comes from neuro-endocrine type cells such as neurons, ovarian granulosa cells and pancreatic beta cells, or mesenchymal cells such as cartilage, vascular smooth muscle and cardiomyocytes. The involvement of Atf6α in expansion of tissue cell number in response to tissue load stress is an interesting paradigm linking organ structure with function [123]. In each case, tissue growth may be beneficial or maladaptive.

6.4. Atf6α promotes proliferation in endocrine cells and neurons

Unresolved ER stress contributes to diabetic decompensation, both through tissue insulin resistance in type 2 diabetes [132] and impaired beta cell insulin secretory capacity in type 1 and type 2 diabetes [2]. ER stress negatively impacts insulin production capacity through both impaired insulin synthesis and increased beta cell death [2]. However, modest physiological levels of ER stress may play a role in the adaptive increase in beta cell number that occurs in response to insulin demand [123,133]. During increased insulin demand in various physiological conditions (misfolding of pro-insulin, high fat feeding, hyperglycemia) beta cells showing activation of the UPR were more likely to enter the cell cycle [123]. Stress-associated beta cell proliferation was lost if ER stress was reduced using molecular chaperones, or by chemical inactivation or gene knockdown of Atf6α [123]. Conversely, overexpression of Atf6α was sufficient to drive proliferation in glucose-permissive conditions [123]. The mechanism by which Atf6α promotes proliferation in beta cells is not yet known, but a proliferative role for Atf6α has been observed in other endocrine cells as well. In ovarian granulosa cells, knockdown of Atf6α arrested cells in S-phase, and caused a reduction in mRNA of cell cycle drivers cyclin A1, cyclin B1 and cyclin D2 [92]. Atf6α may also play an intriguing toxic-proliferation role in the Huntington's neurodegenerative disorder. Neurons are post-mitotic and cannot tolerate cell cycle entry. In both mouse models and human disease, Atf6α processing was found to be altered, leading to accumulation of full length Atf6α, loss of the small GTPase Rheb, and inappropriate accumulation of cell cycle drivers which resulted in neuronal cell death [124].

6.5. Atf6α promotes proliferation in mesenchymal cells such as cartilage and smooth muscle

Atf6α and Atf6β are expressed throughout the proliferating and hypertrophic zones of cartilage development [125]. Metaphyseal chondrodysplasia type Schmid (MCDS) is an ER stress-associated dwarfism syndrome caused by mutations in type X collagen [46]. Overexpression of mutant collagen increased both Atf6α and Atf6β activation in HeLa cells. Ablation of Atf6α in vitro diminished cellular transcriptional response to stress, and ablation of Atf6α in vivo in MCDS mice worsened the disease phenotype, with expansion of the growth plate hypertrophic zone, decreased bone growth and increased Ire1 and Perk signaling [46]. On the other hand, ablation of Atf6β in MCDS mice decreased ER stress markers and decreased the proliferation rate of growth plate chondrocytes [46]. Runx2, a transcription factor important for cartilage development, transcriptionally activates the Atf6α gene [127]. Atf6α was found to physically interact with Runx2, and Atf6α overexpression promoted bone length increase in a long term hMSC culture model [125,127]. On the other hand, in two cell transformed chondrocyte cell lines, overexpression of Atf6α decreased cell cycle entry as determined by a flow cytometry assay [128]. In human mesenchymal stem cells, CRISPR-mediated deletion of ATF6α decreased population doubling, Ki67 levels, and percent of cells in S-phase, while increasing senescence markers [61]. RNAseq demonstrated loss of a number of cell-cycle promoting genes, including the protooncogene FOS [61]. Surprisingly, knockdown of FOS recapitulated many of the effects of ATF6α deletion in hMSCs [61].

Maladaptive smooth muscle proliferation in pulmonary arterial hypertension was found to be mediated by Atf6α [134]. Mild hypoxic stress activated Atf6α; interventions that decreased Atf6α cleavage and target activation suppressed proliferation in smooth muscle cells both in vitro and in vivo [134]. In addition, ER stressors that increased nuclear Atf6α in pulmonary artery smooth muscle cells increased proliferation as measured by nucleoside analog or Ki67, an effect that might be due to increased accumulation of intracellular iron [135].

6.6. Atf6α can also drive tissue growth through cellular hypertrophy

Beyond increase in cell number, Atf6α may also increase tissue mass by inducing cellular hypertrophy in chondrocytes and cardiomyocytes. In mice, Atf6α deletion in the chondrodysplasia model described above resulted in reduced bone growth related, in part, to loss of cell height in the hypertrophic chondrocytes [46]. Atf6α signaling was found to be markedly induced in two different cardiac hypertrophy models: pressure overload, by transverse aortic constriction, and hypertrophy in response to free-wheel exercise [126]. Conditional deletion of Atf6α in cardiac myocytes decreased the hypertrophic response and caused cardiac dysfunction in both models; the mechanism was found to be through Atf6α induction of mTor activator Rheb [126].

7. SUMMARY AND CONCLUSIONS

Atf6α is an important stress response protein, sensing luminal ER stress and transmitting a nuclear signal that has many cellular effects. Canonically, in concert with other UPR pathways, Atf6α activates gene expression of numerous ER resident proteins, resulting in enhanced protein folding capacity, resilience to oxidative/reductive stress, and degradation of ER luminal misfolded proteins. Activation of Atf6α can have both pro-survival and pro-death outcomes, depending on the cell

type and other contextual cues that largely remain to be clarified. Atf6α is also implicated in driving tissue growth, through both proliferative and hypertrophic responses, which can be beneficial or maladaptive depending on the context. The literature contains numerous conflicting conclusions and unanswered questions that require further experimental investigation.

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CONFLICT OF INTEREST

None declared.

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