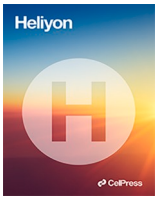
Heliyon 10 (2024) e25937

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Review article

Molecular mechanism of ATF6 in unfolded protein response and its role in disease

Yingying Lei [1], Hong Yu [1], Shaoxue Ding, Hui Liu, Chunyan Liu, Rong Fu [*]

Department of Hematology, Tianjin Medical University General Hospital, Tianjin, People's Republic of China

ARTICLE INFO

Keywords:
Proteostasis
Endoplasmic reticulum stress (ERS)
Unfolded protein response (UPR)
Activating transcription factor 6 (ATF6)

ABSTRACT

Activating transcription factor 6 (ATF6), an important signaling molecule in unfolded protein response (UPR), plays a role in the pathogenesis of several diseases, including diseases such as congenital retinal disease, liver fibrosis and ankylosing spondylitis. After endoplasmic reticulum stress (ERS), ATF6 is activated after separation from binding immunoglobulin protein (GRP78/BiP) in the endoplasmic reticulum (ER) and transported to the Golgi apparatus to be hydrolyzed by site 1 and site 2 proteases into ATF6 fragments, which localize to the nucleus and regulate the transcription and expression of ERS-related genes. In these diseases, ERS leads to the activation of UPR, which ultimately lead to the occurrence and development of diseases by regulating the physiological state of cells through the ATF6 signaling pathway. Here, we discuss the evidence for the pathogenic importance of ATF6 signaling in different diseases and discuss preclinical results.

1. Introduction

Throughout their life cycle, cells are subjected to a range of environmental stresses, such as hypoxia and pathogens, which can cause cell damage and even death. Genetic or environmental damage can lead to dysregulation of intracellular calcium homeostasis, oxidative stress, nutrient deficiencies, inhibition of glycosylation and protein misfolding, and disruption of endoplasmic reticulum (ER) function, inducing ER stress (ERS). The cell development process stimulates the production of proteins and lipids, create an environment conducive to ERS and unfold protein response (UPR) [1]. Three main branches of UPR are regulated by transmembrane protein sensors on ERS, namely activating transcription factor 6 (ATF6), protein kinase R (PKR)-like kinase (PERK) and inositol requiring enzyme 1(IRE1). Compared to other molecules of the UPR pathway, the importance of ATF6 in disease development has been overlooked compared to other molecules in the UPR pathway. Especially in inflammatory and autoimmune diseases, reviews in this area are missing. Therefore, this review summaries the role of ATF6 in disease onset and progression and adds the involvement of ERS in disease mechanisms.

2. Proteostasis and proteotoxicity

In all eukaryotic cells, the proteostasis network (PN) maintains the integrity of the proteome, and protein homeostasis includes

* Corresponding author. Department of Hematology, Tianjin Medical University General Hospital, No. 154, Anshan Road, Heping District, Tianjin, 300052, People's Republic of China.
E-mail address: furong8369@tmu.edu.cn (R. Fu).
[1] Yingying Lei and Hong Yu contributed equally to this work.

https://doi.org/10.1016/j.heliyon.2024.e25937
Received 1 November 2023; Received in revised form 4 February 2024; Accepted 5 February 2024
Available online 10 February 2024

protein synthesis, folding, transport and degradation [2]. Imbalances between these components can lead to protein misfolding, accumulation, and protein toxicity or protein disease [3]. Impaired PN has also been linked to a number of other pathological conditions, including heart disease, diabetes, fatty liver and neurodegenerative diseases [4,5]. In addition, the imbalance of protein homeostasis can also promote the process of aging, which is a mechanism of the aging process [6].

Protein misfolding and protein toxicity associated with disease and age have been found in many organs, and many researchers are committed to protein homeostasis research in the hope of finding potential therapeutic targets to reduce the adverse effects of protein toxicity on organ function. These studies show that structures exist in multiple parts of the cell to monitor newborn and mature proteins, as well as to recognize and deal with end-misfolded proteins [7]. Proteins with misfolded ends may be degraded by the ubiquitin proteasome system (UPS), which is located in a specific region of the cell [8]. It can also be degraded by autophagy in a non-proteasome manner [9]. Organelle and subcellular autophagy forms can also degrade end-misfolded proteins, such as mitotic phagocytosis and endoplasmic reticulum autophagy or reticular phagocytosis, all of which contribute to maintaining the integrity of the proteostasis network [10].

3. Endoplasmic reticulum stress and unfold protein response

In recent years, ERS has attracted increasing interest and attention. ER is an essential subcellular unit that performs diverse biochemical and metabolic operations. This tubular network facilitates lipid biosynthesis, calcium homeostasis, and biogenesis of autophagosomes and peroxidase bodies [11]. Thus, maintaining homeostasis of ER proteins (protein homeostasis) is a dynamic, intricate network [12]. Damage to any of these processes may lead to ERS and the accumulation of misfolded proteins in the endoplasmic network cavity or membrane [13]. For example, β-cells of the pancreas synthesize and transport so much insulin through the ER/Golgi secretory pathway that they are continuously under ERS [14].

When ERS occurs, proteins fail to fold correctly in the ER lumen, and cells use the three signaling pathways of UPR to improve the ability of proteins to fold correctly, inhibit the production and accumulation of proteins, accelerate the degradation of unfolded/misfolded proteins, cause the transcription of ERS-related genes and enhance the self-repair ability of the ER. Chronic and persistent ERS can activate the C/EBP homologous protein (CHOP) to initiate apoptosis [15].

Cells respond to ERS by activating and utilizing evolutionarily conserved UPR. When ERS is caused by changes in the ER environment, unfolded/misfolded proteins activate the UPR. Three main branches of UPR are regulated by transmembrane protein sensors on ERS, namely activating transcription factor 6 (ATF6), protein kinase R (PKR)-like kinase (PERK) and inositol requiring enzyme 1 (IRE1). IRE1 is a nuclease that splices X-box binding protein 1 (XBP1) mRNA to encode an active transcription factor called XBP1 splicing (XBP1s) [16]. PERK, a kinase that phosphorylates eIF2α at the translation initiation factor Ser-51, causes translation arrest in cells but allows continued translation of a selected subset of mRNAs encoding proteins required for the adaptive UPR [17]. ATF6 is a transcription factor, and many of the genes induced by XBP1s, as well as other events downstream of PERK, are originally intended to restore ER protein folding [18]. In the presence of the misfolded protein, ATF6 is displaced into the Golgi body and cleaved by the site 1 and site 2 proteases (S1p and S2p) to release the ATF6(N) transcription factor contained in its cytoplasmic tail. Together with XBP1s, ATF6(N) increases target transcription, expands ER size, increases its protein-folding capacity, and promotes cell survival. Activated

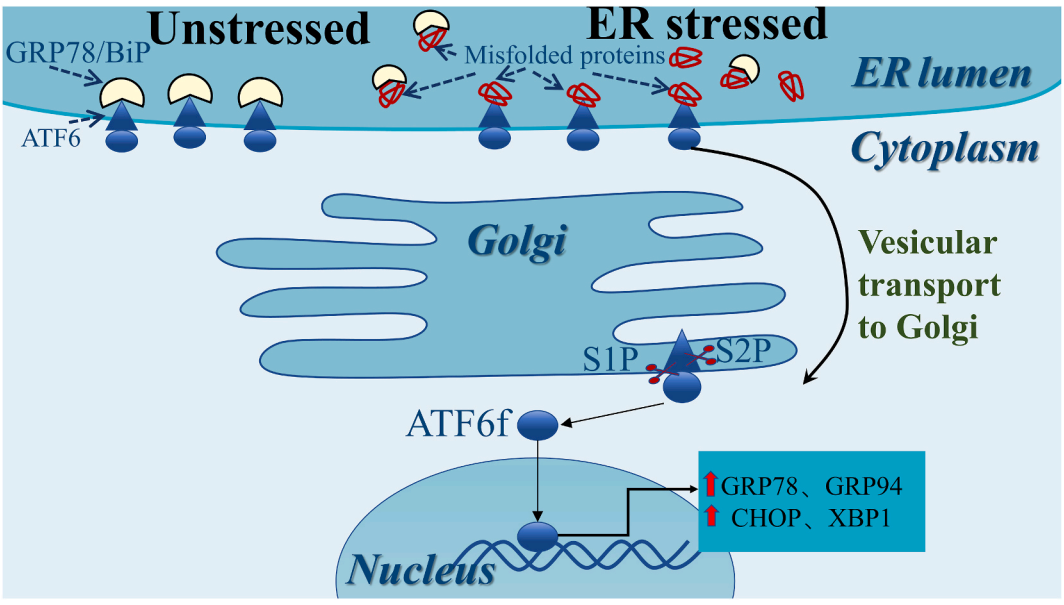


Fig. 1. ATF6 arm of unfolded protein response
(GRP78/BiP: binding immunoglobulin protein; ATF6: Activating transcription factor 6; S1P/S2P: site 1/site 2 proteases 2; ATF6f: ATF6 fragment).

ATF6 transcription factor induces the transcription and expression of GRP78, GRP94 , CHOP and XBP1 (Fig. 1).

ATF6, IRE1 and PERK axis coordinate downstream components and play a role of cell protection in the initial stage. However, in the presence of chronic and persist stress, apoptotic mechanisms prevail to eliminate stressed cells [19]. With the further study of UPR, ERS response mediators are also involved in regulating other processes, such as cell differentiation and maturation. In addition, UPR disorders are associated with a variety of pathological conditions, including neurodegeneration, and immune disorders [20].

4. ATF6 is an adaptive response factor to ERS

4.1. Molecular structure and mechanism of ATF6 activation during ERS

ATF6 is a type 2 ER transmembrane protein. The C-terminus of the ATF6 isoform protrudes into the endoplasmic network lumen, while the N-terminus faces the cytosol [21]. The cytoplasmic portion of ATF6 includes the basic region/leucine zipper motif (bZIP domain) DNA binding region and transactivation domain, followed by a 20-amino acid transmembrane region. Mammals express two homologous ATF6 proteins, ATF6α (670 amino acids) and ATF6β (703 amino acids), however, the fragment at the N-terminal end of ATF6α contains an 8-amino acid sequence, termed VN8, which has high transcriptional activity and rapid degradation (Fig. 2). ATF6α is an effective transcriptional activator, which is responsible for regulating the expression of ERS response gene, and the physiological activity of ATF6α is stronger than ATF6β [22]. The latter may inhibit ATF6α activation as an endogenous inhibitor of ATF6α and fine-tune the intensity and duration of ATF6α signaling during ERS [23,24].

After dissociation of ERS induced ATF6α from binding immunoglobulin protein (GRP78/BiP), two Golgi localization sequences (GLS1 and GLS2) were exposed in the ER domain of ATF6α, which were translocated to the Golgi apparatus and cleaved by two of these enzymes [25]. S1p and S2p remove the lumen domain and transmembrane anchor, respectively, to mobilize a 50 kDa amino terminal cytoplasmic fragment (ATF6f). The released ATF6f transcription factor enters the nucleus and binds to ERS response elements [26] (Fig. 3). ATF6α induces the expression of chaperones and UPR mediators, including BiP and X-box binding protein 1 (XBP1), which contribute to protein stabilization and increased output of IRE1 arm regulation, respectively. In addition, ATF6α plays a role in cell protection and growth regulation [27].

In the absence of ERS, ATF6 remains in the ER in the form of disulfide bonded oligomers and binds to the ER chaperone protein

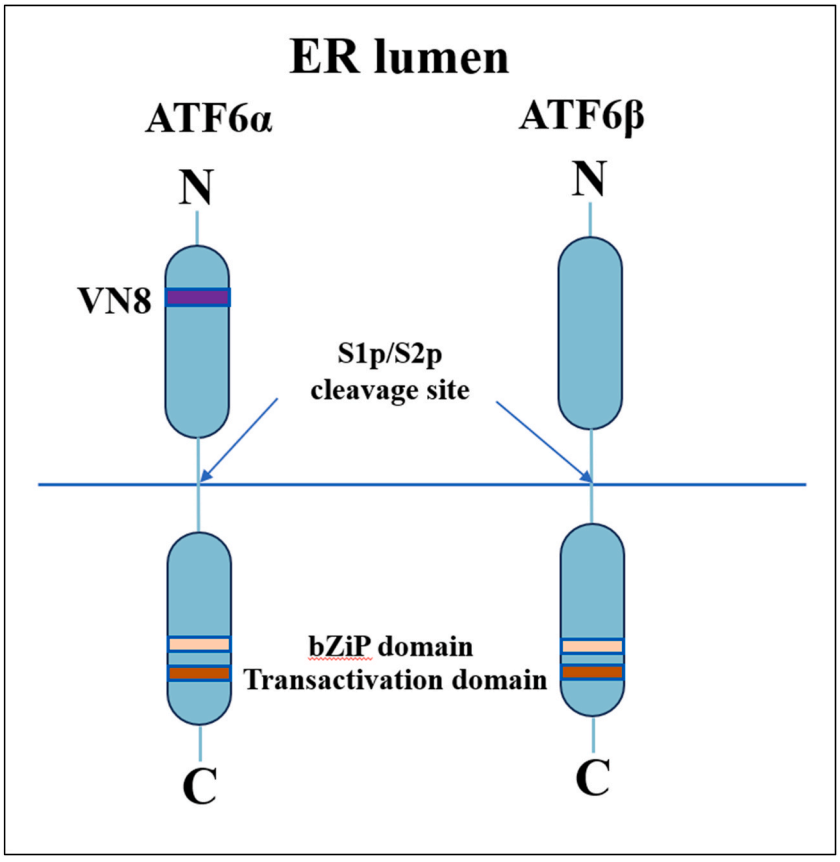


Fig. 2. The molecular structure of activating transcription factor 6 (ATF6)
(S1P/S2P: site 1/site 2 proteases 2; VN8: 8-amino acid sequence).

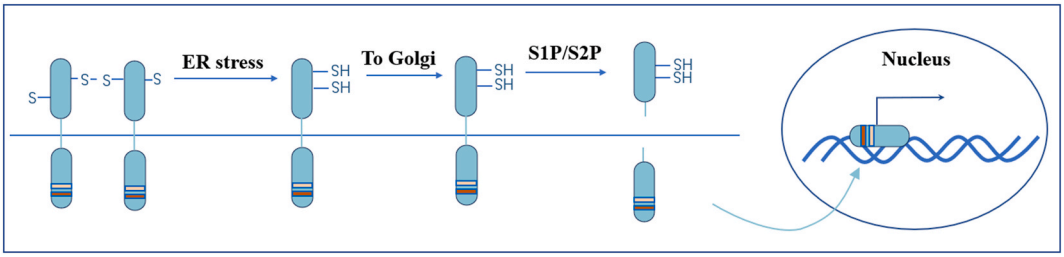


Fig. 3. ATF6 is activated in response to endoplasmic reticulum stress
(-S: sulfur ion; –SH: sulfhydryl; -S-S-: disulfide bond).

GRP78/Bip, which helps to fix ATF6 in the ER and prevent its transport to the Golgi apparatus [28]. The transcription factor ATF6 is activated after ERS. ATF6 promotes the adaptive UPR response and early ATF6 induces ER host proteins and folding proteins such as chaperone [29]. Many studies have elucidated the activation mechanism of ATF6. In the absence of ERS, inactivated ATF6 is a 90kD ER transmembrane protein. GRP78/Bip binds to the ER lumen domain of ATF6 and is anchored in the ER by ER retention sequence at the C-terminal of GRP78 [30]. When ERS occurs, ATF6 senses the accumulation of misfolded proteins in ER through GRP78, and GRP78 dissociates from ATF6, thus releasing ATF6 and relocating it to Golgi apparatus [31]. In Golgi apparatus, ATF6 is decomposed by S1p and S2p [32]. The 50kD N-terminal domain of the cytoplasmic side of ATF6 is released, allowing it to locate in the nucleus as a transcription factor regulating the expression of stress response genes (e.g., Bip) [33].

At ERS, disulfide bonds in ATF6 are reduced, which promotes dissociation of ATF6 into reduced monomer. Protein disulfide isomerases (PDIs), such as PDIA5, are associated with ERS-dependent reduction of ATF6 disulfide bonds [34], and PDI plays a key role in ATF6 transport. In addition, other mechanisms are also involved in the activation of this UPR signaling pathway. For example, GRP78/Bip dissociation from the ATF6 lumen domain or changes in ATF6 N junction glycosylation are associated with ERS-dependent ATF6 activation and may be involved in the regulation of ATF6 activation during ERS [35].

ATF6 plays a central role in the composition of biological pathways that regulate different functions, including ER protein stabilization, protein degradation, and cellular REDOX regulation [36,37]. ATF6 mainly plays a role in "adaptive UPR", which is designed to promote protective, adaptive remodeling of cell physiology and recovery after acute physiological and pathological injury. As part

Table 1
The role of ATF6 in disease development.

Diseases	mechanisms	Reference
AS	1. Macrophages in joints express high levels of GRP78 and chondrocytes in the femoral head have high levels of GRP78 and ATF6, indicating elevated levels of ERS. 2. In chondrocytes, mRNA levels of FGF2 were reduced following ATF6 knockdown or inhibition 3. 3. Inhibition of angiogenic bone coupling by Ceapin-A7, an ATF6α-specific inhibitor, delays the pathological progression of osteogenesis	[53,54]
SAP	1. One of the main pathogenic mechanisms of SAP is ERS 2. Apoptosis mediated by the ATF6-P53-AIFM2 pathway regulates multi-organ damage in the SAP disease process 3. Silencing of the ATF6 gene, down-regulation of AIFM2 expression, reduced apoptosis and inflammation.	[55,56]
Liver fibrosis	1. ATF6 is involved in macrophage activation and also binds directly to the IL-6 and TNF-α promoters to promote macrophage secretion of IL-6 and TNF-α. 2. In the early stage of acute liver injury, silencing of ATF6 can reduce the secretion of various cytokines by macrophages. It also inhibits the formation of hepatic fibrosis after acute liver injury 3. After acute liver injury, ATF6 stimulates macrophages to secrete a variety of pro-inflammatory factors, thereby promoting the formation of hepatic fibrosis, and IL-1α is the main cytokine involved in this process.	[57–60]
CRC	1. ATF6 is recognised as a marker of early dysplasia in UC and non-UC associated CRCs 2. ATF6 activity creates favorable conditions for bacterial-mediated tumorigenesis.	[78.81]
PSS	1. 1. GRP78-ATF6 signaling is over-activated in the lacrimal gland of PSS patients and is involved in apoptosis via activation of CHOP 2. Inhibition of the GRP78-ATF6-CHOP pathway significantly improves symptoms in PSS mice 3. ERS-triggering IFN-α is highly expressed in the serum and salivary glands of patients with PSS. 4. β-arrestin 2 deletion significantly inhibited the GRP78-ATF6-CHOP apoptosis signaling pathway and reduced the rate of IFN-α-induced apoptosis, thereby attenuating ERS response.	[61,62, 63–65]
ACHM	1. Mutations in the ATF6a gene are associated with congenital retinal color blindness but are not involved in the pyranosome phototransduction pathway 2. ATF6 activating compounds (N-(2-hydroxy-5-methylphenyl)-3-phenylpropanamide activator [AA147]) may be useful in correcting vision loss disorders caused by ATF6 mutations	[42–44]
Neurodegeneration disease	1. UPR (via ATF6) decreases as ALS progresses in older patients 2. ERS was detected in postmortem brains of AD patients and in an animal model of AD, and ATF6 significantly reduced Aβ1 levels in LN229 (brain neuroblastoma cell line) through the amyloid pathway, which includes APP, ADAM17 and BACE1 proteins.	[66,67]

(AS: Ankylosing spondylitis; SAP: Severe acute pancreatitis; CRC: colorectal cancer; PSS: Primary Sjogren's syndrome; ACHM: Achromatopsia; ALS: Amyotrophic lateral sclerosis; AD: Alzheimer's disease).

of adaptive UPR, ATF6 integrates with multiple other stress response signaling pathways, enabling the cell physiology to adapt to different types of ER injury.

4.2. ATF6 degrades rapidly upon activation

It has been found that the active form of ATF6 is rapidly degraded and it is difficult to find the active form of ATF6 by western blotting unless proteasome inhibitors are used [38]. Therefore, the activity of ATF6 is transient [39]. The mapping of cell lines showed that there were eight amino acid extensions in the N-terminal transcriptional activation region of ATF6, whose sequences were very similar to those found in the rapidly degrading viral transcription factor VP16 [40]. In VP16, these 8 amino acid regions are responsible for its strong transcriptional activity and rapid degradation. This area of ATF6 has the same function. Further studies have shown that ATF6 degrades rapidly only when it is actively involved in transcriptional activation, and that any mutated form of ATF6 reduces its transcriptional activity and increases its half-life. However, ATF6β, which is activated in response to ERS, has no VN8 region, and its transcription factor activity is very low and degradation is slow. Since ATF6α can form a dimer with ATF6β, the stability of ATF6α is increased [41]. Transcription factor activity and dimer stability were found to decrease in a coordinated manner in the following order: ATF6α- ATF6α > ATF6α - ATF6β > ATF6β- ATF6β [42].

5. The role of ATF6 signaling molecules in tissue homeostasis and disease

Recently, there is increasing evidence that ATF6 plays a role in specific cellular and tissue environments, and that abnormalities in ATF6 signaling may contribute to the development of a variety of diseases [42–52]. Below, we provide detailed information about the important role of ATF6 in inflammatory, autoimmune and cancer diseases (Table 1).

5.1. Ankylosing spondylitis

Ankylosing spondylitis (AS) is a rheumatic disease characterized by chronic and repeated inflammation, which mainly affects the axial bones and joints. Nearly 40% of patients developed functional malformations, including joint malformations and spinal stiffness [68,69]. Macrophages in peripheral joints of patients with AS were found to express high levels of GRP78 and elevated levels of GRP78 and ATF6 in chondrocytes of the femoral head, which may be induced by widespread inflammation [53,54]. Many studies have focused on the mechanisms by which ERS regulates angiogenic activity, and the expression of the key angiogenic factor VEGF is regulated by XBP-1, ATF4 and ATF6 [70]. Fibroblast growth factor 2 (FGF2) is a widely studied peptide that plays a role in angiogenesis, tissue regeneration, and neuroprotection [71]. FGF2 may play an important role in pathological osteogenesis by promoting vascular growth. FGF2 mRNA levels in chondrocytes were decreased after ATF6 knockdown or inhibition. In addition, the ATF6α--specific inhibitor Ceapin-A7 was found to slow down the pathological progression of osteogenesis by inhibiting angiogenic bone coupling [54]. These results suggest that ATF6-mediated FGF2 transcription is an important pathway for the regulation of angiogenic activity in ERS. Taken together, we conclude that ATF6 is a key positive regulator of angiogenic-osteogenic coupling in AS, and that targeted inhibition of ATF6 in chondrocytes may be a promising therapeutic tool for the treatment of AS.

5.2. Acute pancreatitis

Severe acute pancreatitis (SAP) is often characterized by persistent single or multiple organ failure (MOF) and/or local pancreatic complications. The main pathogenesis is premature activation of trypsinogen, ERS and apoptosis [72]. Apoptosis-inducing factor mitochondria-associated 2 (AIFM2), also known as apoptosis-inducing factor-like mitochondrion-associated inducer of death (AMID) or PRG3, located in the outer membrane of mitochondria or freely distributed in the cytoplasm [55,73], it is an important downstream regulator of ATF6, located on human chromosome 10 [74,75], and apoptosis induced by AMID is regulated by P53 [76]. When ATF6 is activated, AIFM2 protein expression is up-regulated and the activity of ERS-induced apoptosis signaling pathway is enhanced. The ATF6-P53-AIFM2 pathway is a key factor in endoplasmic reticulum-induced apoptosis during SAP development. In contrast, when ATF6 is silenced, AIFM2 expression is down-regulated, which is accompanied by decreased apoptosis and inflammation. In addition, ATF6 promotes the transcription of P53 and AIFM2, thereby inducing the apoptosis of SAP acinar cells. These results suggest for the first time that AIFM2 regulates SAP multiorgan damage through ATF6/P53-mediated apoptosis [56]. ATF6 also promotes inflammation during the progression of chronic pancreatitis (CP) and plays an important role in trypsin-induced acinar ERS and apoptosis. In CP, P53, as the main regulator of apoptosis, can mediates ATF6-induced apoptosis of acinar cells. In the pathogenesis of CP, in addition to the increased mRNA and protein expression levels of ATF6, XBP1 and CHOP, the apoptosis rate of acinar cells is also significantly increased, along with the upregulation of P53. Inhibition of ATF6 or P53 can reduce the expression of inflammatory cytokines in mouse models [77]. These results suggest that the expression of P53 is regulated by the ATF6/XBP1/CHOP axis. These findings provide new insights into ATF6-triggered signaling as a promising targeted therapy for pancreatitis.

5.3. Liver fibrosis

Macrophages promote the occurrence and repair of acute liver injury by secreting a series of cytokines [78,79]. Previous studies have shown that depletion of macrophages can alleviate acute liver injury, but also delay the repair of acute liver injury [80,81]. Hepatic fibrosis is the early manifestation of liver injury repair. Studies have shown that when macrophages are depleted, liver fibrosis

is weakened and liver tissue inflammation cannot be timely recovered [82,83]. ERS signals are involved in the activation of macrophages in the early stage of hepatic ischemia-reperfusion injury. ATF6 not only participates in the activation of macrophages, but also directly binds to IL-6 and TNF-α promoters to promote the secretion of IL-6 and TNF-α by macrophages. Silencing of ATF6 may Silencing ATF6 can reduce the secretion of various cytokines by macrophages [57–59]. It also inhibits the formation of hepatic fibrosis after acute liver injury [60]. After the occurrence of acute liver injury, ATF6 stimulates macrophages to secrete a variety of pro-inflammatory factors, thus promoting the formation of liver fibrosis, and IL-1α is the main cytokine involved in this process.

Some studies have found that depletion of macrophages attenuates acute liver injury, but at the same time makes it difficult for inflammation to dissipate in the liver tissue after acute liver injury, ultimately leading to exacerbation of liver injury [84].

5.4. Colorectal cancer

ERS and UPR activation is associated with clinically relevant enteritis. ATF6 is recently considered as a marker for early dysplasia of both ulcerative colitis (UC) and non-UC-associated colorectal cancer (CRC) [85]. Analysis of CRC patients in the Cancer Genome Atlas dataset identified ATF6 mutations as the only clinically relevant UPR signaling protein. About 11% of CRC patients overexpress ATF6, i.e., ATF6 is a novel and clinically relevant tumor risk gene, and ATF6 activation may be a risk factor for oncogenic transformation in these patients. UPR in the ATF6-activated epithelium requires the presence of gut microbes in order to form tumors. Microbial dysregulation is positively correlated with the pathogenesis of colon cancer [86,87]. Second, sustained ATF6 signaling and downstream gene targets promote a clinically relevant and most likely cellular autonomy state that triggers microbial dysregulation and TRIF-mediated STAT3 signaling, leading to focal dysplasia of the colonic epithelium [88]. After antibiotic treatment, STAT3 phosphorylation was completely eliminated and tumor development was inhibited, indicating that ATF6 activity created favorable conditions for bacteria-mediated tumorigenesis. Therefore, ATF6 continuously stimulates intestinal activation in the colon to promote dysregulation and microbial-dependent tumorigenesis.

5.5. Primary Sjogren's syndrome

Primary Sjogren's syndrome (PSS) is a chronic autoimmune disease characterised by lymphocyte infiltration of exocrine glands, leading to dryness of the eyes and mouth, belonging to epithelial inflammatory diseases [89,90]. The epithelial cells of the submandibular gland, as the main epithelial cells of the secretory glands, have a relatively strong endoplasmic reticulum system and are susceptible to endoplasmic reticulum stress caused by external factors, such as IFN-α or viruses [91]. Subsequently, the IRE1α, PERK and ATF6 signaling pathways are activated to restore endoplasmic reticulum homeostasis, and a chronic, persistent stress response can lead to apoptosis [92], which may be related to the pathological mechanisms of PSS. It was found that GRP78-ATF6 signaling was over-activated in the labial glands of pSS patients and was involved in apoptosis through activation of CHOP [61], and inhibition of this signaling pathway significantly ameliorated the symptoms in Sjogren's syndrome mice [62]. In addition, IFN-α, which triggers ERS, is highly expressed in the serum and salivary glands of PSS patients [93]. β-arrestin 2 is a key protein that mediates the desensitization and internalization of G protein coupled receptors (GPCRs), which are involved in inflammatory and immune responses and mediate apoptosis in autoimmune diseases. β-arrestin2 deletion significantly inhibited the GRP78-ATF6-CHOP apoptosis signaling pathway and reduced IFN-α-induced apoptosis rate, thereby alleviating the ERS response. Therefore, when β-arrestin2 was inhibited, the activation of cell signaling pathways was weakened, while the loss of β-arrestin2 inhibited the activation of downstream signaling pathways of GRP78, reducing the generation of apoptosis, thereby increasing salivary secretion, reducing lymphocyte infiltration, and the histopathological score of salivary glands [63–65]. In conclusion, IFN-α-induced ERS apoptotic signaling pathway, namely GRP78-ATF6-CHOP, is involved in the pathogenesis of PSS, and inhibition of GRP78-ATF6-CHOP apoptotic signaling can reduce ERS and apoptosis. Loss of β-arrestin2 alleviates inflammatory induced epithelial apoptosis and improves symptoms through the GRP78ATF6-CHOP apoptotic signaling pathway, which is dependent on the interaction of β-arrestin2 with GRP78.

5.6. Achromatopsia

Achromatopsia (ACHM) is an autosomal recessive genetic disease caused by selective dysfunction of cone photoreceptor cells. It mainly has cone dysfunction and is manifested as vision loss, photophobia, nystagmus and poor color vision in infancy. Recent studies have found that mutations in the ATF6a gene is associated with congenital retinal color blindness. Unlike other ACHM genes, it does not participate in the pyramic light transduction pathway [41]. To date, 11 different mutation types of ATF6 disease alleles have been identified in ACHM patients, including missense, nonsense and insertion mutations or splice point changes and single nucleotide mutations [42,44]. These mutations result in loss of ATF6 function by disrupting the DNA-binding domain of the ATF6 amino-terminal transcription activator/bZIP or by disrupting the carboxy-terminal ER-to-Golgi protein transport domain. In situ immunohybridisation showed that ATF6 is widely expressed not only in the cones but also in all l retinal layers [94]. ATF6 mutations lacking both exons completely lose transcriptional activation. These findings further emphasize that all ACHM-associated ATF6 mutations identified to date impair transcriptional activity. In vitro studies have shown that ERS induces ATF6 expression in retinal cells such as retinal ganglion cells [95]. ATF6 plays an important role in regulating ERS in all retinal neurons. ATF6 mutations associated with retinal developmental diseases are due to the loss of ATF6 transcriptional activity, which in turn is caused by defects in different steps of ATF6 activation [47]. Based on these findings, ATF6-activating compounds may help correct vision loss disorders in patients due to ATF6 mutations. Especially in patients with functional loss due to the ER resident protein ATF6, ATF6(N-(2-hydroxy-5-methylphenyl)-3-phenylpropanamide activator [AA147]) may contribute to the restoration of activity by promoting ATF6

transport to the Golgi apparatus [43].

5.7. Neurodegeneration disease

Amyotrophic lateral sclerosis (ALS) is a chronic, progressive degenerative disease involving upper and lower motor neurons and their innervated trunk, limbs, and head and facial muscles [66]. ALS patients have immunophenotypic changes in peripheral blood mononuclear cells (PBMCs), decreased mtDNA gene expression, decreased nitrative stress and calcium. expression, decreased mtDNA gene expression, increased nitrative stress and calcium. Recent studies have shown that ERS is involved in the pathogenesis of ALS. Prell et al. demonstrated that the UPR pathway of ATF6 is activated in PBMC. There was no correlation between the expression level of active ATF6 and disease progression. However, the UPR (via ATF6) is reduced as ALS progresses in older patients [67].

Another neurodegenerative disease, Alzheimer's disease (AD), which is characterised by the accumulation of β-amyloid (Aβ) plaques, the breakdown of Aβ into a-secretase and b-secretase enzymes by a-secretase and b-secretase enzymes, and the elevated expression of APP leading to amyloid toxicity. plays a key role in the pathogenesis of AD. ERS was detected in postmortem brains of AD patients and animal models of AD [96], and ATF6 significantly reduced Aβ1 levels in LN229 (brain neuroblastoma cell line) through the amyloid pathway, which consists of APP, ADAM17 and BACE1 proteins. Our findings clearly demonstrate that ATF6 expression is reduced in APP/PS1 mice and that ATF6 can inhibit Ab levels by downregulating BACE1 promoter activity. In addition, ATF6 has a protective effect on spatial memory retention in AD model mice [97].

5.8. Other diseases

ATF6 is a challenging target protein that can be used as a small molecule binding site for pharmacological targets. As an inhibitor of ERS, 4-phenylbutyric acid (4-PBA) can restore endoplasmic reticulum function and promote protein synthesis [98]. Previous studies have shown that 4-PBA can significantly inhibit GRP78-ATF6-CHOP apoptosis signaling pathway. 4-PBA inhibits lipopolysaccharids-induced GRP78 and CHOP expression in human umbilical vein endothelial cells [99]. In hypothalamic diseases, the GRP78-ATF6-CHOP apoptotic signaling pathway was significantly down-regulated after administration of 4-PBA [100].

6. Conclusion

Protein homeostasis is a prerequisite for maintaining normal physiological activities of cells, and about 40% of proteins are synthesized in the endoplasmic reticulum. When cells are subjected to genetic or environmental changes, such as hypoxia, pathogens, etc., the function of the ER will be damaged and cause ERS. A large number of unfolded/misfolded proteins accumulate in the ER, inducing the unfolded protein response, improving the correct folding ability of proteins through three signaling pathways, accelerating the degradation of unfolded/misfolded proteins, and enhancing the self-repair ability of the ER. ATF6 is an adaptive response factor to ERS. ATF6 is activated after ERS, separated from GRP78 and localized in the Golgi apparatus. ATF6 is decomposed by S1P and S2P proteases in the Golgi apparatus into a 50kD N-terminal domain, which is transported to the nucleus as a transcription factor to regulate the expression of stress response genes. The active form of ATF6 is then rapidly degraded. ATF6 has been implicated in the pathogenesis of many human diseases, but there are still discrepancies between some of the theories, and targeting ATF6 molecules to treat diseases is still unfulfilled and must be explored through further research.

Funding statement

We thank the staffs of Department of Hematology, Tianjin Medical University General Hospital for their support. This work was supported by the Tianjin Medical Health Association (TJSYLJKXH005).

Availability of supporting data

There is no **additional data** available for this study.

Ethical statement

This manuscript does not involve any ethical issues.

CRediT authorship contribution statement

Yingying Lei: Writing – original draft. **Hong Yu:** Writing – original draft, Methodology. **Shaoxue Ding:** Methodology, Conceptualization. **Hui Liu:** Funding acquisition, Conceptualization. **Chunyan Liu:** Validation, Supervision. **Rong Fu:** Supervision, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to

influence the work reported in this paper.

References

[1] J.D. Godin, C. Creppe, S. Laguesse, et al., Emerging roles for the unfolded protein response in the developing Nervous system, Trends Neurosci. 39 (2016) 394–404.
[2] A.J. Sala, L.C. Bott, R.I. Morimoto, Shaping proteostasis at the cellular, tissue, and organismal level, J. Cell Biol. 216 (2017) 1231–1241.
[3] P.M. Douglas, D.M. Cyr, Interplay between protein homeostasis networks in protein aggregation and proteotoxicity, Biopolymers 93 (2010) 229–236.
[4] C. Hetz, S. Saxena, ER stress and the unfolded protein response in neurodegeneration, Nat. Rev. Neurol. 13 (2017) 477–491.
[5] V. Valenzuela, K.L. Jackson, S.P. Sardi, et al., Gene therapy strategies to restore ER proteostasis in disease, Mol. Ther. 26 (2018) 1404–1413.
[6] M.S. Hipp, P. Kasturi, F.U. Hartl, The proteostasis network and its decline in ageing, Nat. Rev. Mol. Cell Biol. 20 (2019) 421–435.
[7] J. Labbadia, R.I. Morimoto, The biology of proteostasis in aging and disease, Annu. Rev. Biochem. 84 (2014) 435–464.
[8] C. Pohl, I. Dikic, Cellular quality control by the ubiquitin-proteasome system and autophagy, Science 366 (2019) 818–822.
[9] R.H. Chen, Y.H. Chen, T.Y. Huang, Ubiquitin-mediated regulation of autophagy, J. Biomed. Sci. 26 (2019) 80.
[10] S. Wilkinson, ER-phagy: shaping up and destressing the endoplasmic reticulum, FEBS J. 286 (2019) 2645–2663.
[11] S. Ghaemmaghami, W.K. Huh, Bower, et al., Global analysis of protein expression in yeast, Nature 425 (2003) 737–741.
[12] I. Braakman, N.J. Bulleid, Protein folding and modification in the mammalian endoplasmic reticulum, Annu. Rev. Biochem. 80 (2011) 71–99.
[13] D.T. Rutkowski, R.J. Kaufman, A trip to the ER: coping with stress, Trends Cell Biol. 14 (2004) 20–28.
[14] I. Hodish, A. Absood, L. Liu, et al., In vivo misfolding of proinsulin below the threshold of frank diabetes, Diabetes 60 (2011) 2092–2101.
[15] H. Hu, M. Tian, C. Ding, et al., The C/EBP homologous protein (CHOP) transcription factor functions in endoplasmic reticulum stress-induced apoptosis and microbial infection, Front. Immunol. 9 (2018) 3083.
[16] F. Urano, A. Bertolotti, D. Ron, IRE1 and efferent signaling from the endoplasmic reticulum, J. Cell Sci. 113 (2000) 3697–3702.
[17] M. Schroder, R.J. Kaufman, Divergent roles of IRE1alpha and PERK in the unfolded protein response, Curr. Mol. Med. 6 (2006) 5–36.
[18] C.C. Glembotski, Roles for ATF6 and the sarco/endoplasmic reticulum protein quality control system in the heart, J. Mol. Cell. Cardiol. 71 (2014) 11–15.
[19] M. Schroder, R.J. Kaufman, ER stress and the unfolded protein response, Mutat. Res. 569 (2005) 29–63.
[20] C. Hetz, The unfolded protein response: controlling cell fate decisions under ER stress and beyond, Nat. Rev. Mol. Cell Biol. 13 (2012) 89–102.
[21] M. Hong, S. Luo, P. Baumeister, et al., Underglycosylation of ATF6 as a novel sensing mechanism for activation of the unfolded protein response, J. Biol. Chem. 279 (2004) 11354–11363.
[22] K. Haze, T. Okada, H. Yoshida, et al., Identification of the G13 (cAMP-response-element-binding protein-related protein) gene product related to activating transcription factor 6 as a transcriptional activator of the mammalian unfolded protein response, Biochem. J. 355 (2001) 19–28.
[23] M. Forouhan, K.R.P. Mori, Boot-Handford, Paradoxical roles of ATF6alpha and ATF6beta in modulating disease severity caused by mutations in collagen X, Matrix Biol. 70 (2018) 50–71.
[24] L.A. Pieper, M. Strotbek, T. Wenger, et al., ATF6beta-based fine-tuning of the unfolded protein response enhances therapeutic antibody productivity of Chinese hamster ovary cells, Biotechnol. Bioeng. 114 (2017) 1310–1318.
[25] C. Mao, W.C. Tai, Y. Bai, et al., In vivo regulation of Grp78/BiP transcription in the embryonic heart: role of the endoplasmic reticulum stress response element and GATA-4, J. Biol. Chem. 281 (2006) 8877–8887.
[26] J. Shen, E.L. Snapp, J. Lippincott-Schwartz, et al., Stable binding of ATF6 to BiP in the endoplasmic reticulum stress response, Mol. Cell Biol. 25 (2005) 921–932.
[27] S. Nadanaka, T. Okada, H. Yoshida, et al., Role of disulfide bridges formed in the luminal domain of ATF6 in sensing endoplasmic reticulum stress, Mol. Cell Biol. 27 (2007) 1027–1043.
[28] D.M. Schewe, J.A. Aguirre-Ghiso, ATF6alpha-Rheb-mTOR signaling promotes survival of dormant tumor cells in vivo, Proc Natl Acad Sci U S A 105 (2008) 10519–10524.
[29] M.D. Shoulders, L.M. Ryno, J.C. Genereux, et al., Stress-independent activation of XBP1s and/or ATF6 reveals three functionally diverse ER proteostasis environments, Cell Rep. 3 (2013) 1279–1292.
[30] R. Asada, S. Kanemoto, S. Kondo, et al., The signalling from endoplasmic reticulum-resident bZIP transcription factors involved in diverse cellular physiology, J. Biochem. 149 (2011) 507–518.
[31] D.J. Thuerauf, L.E. Morrison, H. Hoover, et al., Coordination of ATF6-mediated transcription and ATF6 degradation by a domain that is shared with the viral transcription factor, VP16, J. Biol. Chem. 277 (2002) 20734–20739.
[32] F. Geng, S. Wenzel, W.P. Tansey, Ubiquitin and proteasomes in transcription, Annu. Rev. Biochem. 81 (2012) 177–201.
[33] C.C. Glembotski, J.D. Rosarda, R.L. Wiseman, Proteostasis and beyond: ATF6 in ischemic disease, Trends Mol. Med. 25 (2019) 538–550.
[34] J.K. Jin, E.A. Blackwood, K. Azizi, et al., ATF6 decreases myocardial ischemia/reperfusion damage and links ER stress and oxidative stress signaling pathways in the heart, Circ. Res. 120 (2017) 862–875.
[35] Z. Yu, H. Sheng, S. Liu, et al., Activation of the ATF6 branch of the unfolded protein response in neurons improves stroke outcome, J. Cerebr. Blood Flow Metabol. 37 (2017) 1069–1079.
[36] D. Kezuka, M. Tkarada-Iemata, T. Hattori, et al., Deletion of Atf6alpha enhances kainate-induced neuronal death in mice, Neurochem. Int. 92 (2016) 67–74.
[37] J.R. Naranjo, H. Zhang, D. Villar, et al., Activating transcription factor 6 derepression mediates neuroprotection in Huntington disease, J. Clin. Invest. 126 (2016) 627–638.
[38] A. Cinaroglu, C. Gao, D. Imrie, et al., Activating transcription factor 6 plays protective and pathological roles in steatosis due to endoplasmic reticulum stress in zebrafish, Hepatology 54 (2011) 495–508.
[39] J. Aboshiha, A.M. Dubis, J. Carroll, et al., The cone dysfunction syndromes, Br. J. Ophthalmol. 100 (2016) 115–121.
[40] N. Hirji, J. Aboshiha, M. Georgiou, et al., Achromatopsia: clinical features, molecular genetics, animal models and therapeutic options, Ophthalmic Genet. 39 (2018) 149–157.
[41] S. Kohl, D. Zobor, W.C. Chiang, et al., Mutations in the unfolded protein response regulator ATF6 cause the cone dysfunction disorder achromatopsia, Nat. Genet. 47 (2015) 757–765.
[42] M. Ansar, R.L. Santos-Cortez, M.A. Saqib, et al., Mutation of ATF6 causes autosomal recessive achromatopsia, Hum. Genet. 134 (2015) 941–950.
[43] R.R. Mastey, M. Georgiou, C.S. Langlo, et al., Characterization of retinal structure in ATF6-associated achromatopsia, Invest. Ophthalmol. Vis. Sci. 60 (2019) 2631–2640.
[44] M. Xu, V. Gelowani, A. Eblimit, et al., ATF6 is mutated in early onset photoreceptor degeneration with macular involvement, Invest. Ophthalmol. Vis. Sci. 56 (2015) 3889–3895.
[45] A. Skorczyk-Werner, W.C. Chiang, A. Wawrocka, et al., Autosomal recessive cone-rod dystrophy can be caused by mutations in the ATF6 gene, Eur. J. Hum. Genet. 25 (2017) 1210–1216.
[46] W.C. Chiang, P. Chan, B. Wissinger, et al., Achromatopsia mutations target sequential steps of ATF6 activation, Proc Natl Acad Sci U S A 114 (2017) 400–405.
[47] E.J. Lee, W.J. Chiang, H. Kroeger, et al., Multiexon deletion alleles of ATF6 linked to achromatopsia, JCI Insight 5 (2020).
[48] H. Miyagi, S. Kanemoto, A. Saito, et al., Transcriptional regulation of VEGFA by the endoplasmic reticulum stress transducer OASIS in ARPE-19 cells, PLoS One 8 (2013) e55155.
[49] J. Wu, P. Sun, X. Zhang, et al., Inhibition of GPR40 protects MIN6 beta cells from palmitate-induced ER stress and apoptosis, J. Cell. Biochem. 113 (2012) 1152–1158.

[50] T. Yoshikawa, N. Ogata, H. Izuta, et al., Increased expression of tight junctions in ARPE-19 cells under endoplasmic reticulum stress, Curr. Eye Res. 36 (2011) 1153–1163.
[51] C.M. Gallagher, C. Garri, E.L. Cain, et al., Ceapins are a new class of unfolded protein response inhibitors, selectively targeting the ATF6alpha branch, Elife 5 (2016).
[52] I. Das, A. Krzyzosiak, K. Schneider, et al., Preventing proteostasis diseases by selective inhibition of a phosphatase regulatory subunit, Science 348 (2015) 239–242.
[53] W. Dong, Y. Zhang, M. Yan, et al., Upregulation of 78-kDa glucose-regulated protein in macrophages in peripheral joints of active ankylosing spondylitis, Scand. J. Rheumatol. 37 (2008) 427–434.
[54] M. Ma, H. Li, P. Wang, et al., ATF6 aggravates angiogenesis-osteogenesis coupling during ankylosing spondylitis by mediating FGF2 expression in chondrocytes, iScience 24 (2021) 102791.
[55] Y. Ohiro, I. Garkavtsev, S. Kobayashi, et al., A novel p53-inducible apoptogenic gene, PRG3, encodes a homologue of the apoptosis-inducing factor (AIF), FEBS Lett. 524 (2002) 163–171.
[56] J.H. Tan, R.C. Cao, L. Zhou, et al., ATF6 aggravates acinar cell apoptosis and injury by regulating p53/AIFM2 transcription in Severe Acute Pancreatitis, Theranostics 10 (2020) 8298–8314.
[57] J. Grootjans, A. Kaser, R.J. Kaufman, et al., The unfolded protein response in immunity and inflammation, Nat. Rev. Immunol. 16 (2016) 469–484.
[58] J. Rao, S. Yue, Y. Fu, et al., ATF6 mediates a pro-inflammatory synergy between ER stress and TLR activation in the pathogenesis of liver ischemia-reperfusion injury, Am. J. Transplant. 14 (2014) 1552–1561.
[59] X. Xu, T. Lei, W. Li, et al., Enhanced cellular cholesterol efflux by naringenin is mediated through inhibiting endoplasmic reticulum stress - ATF6 activity in macrophages, Biochim. Biophys. Acta Mol. Cell Biol. Lipids 1864 (2019) 1472–1482.
[60] Q. Wang, X. Zhu, Z. Li, et al., ATF6 promotes liver fibrogenesis by regulating macrophage-derived interleukin-1 alpha expression, Cell. Immunol. 367 (2021) 104401.
[61] M.J. Barrera, S. Aguilera, I. Castro, et al., Pro-inflammatory cytokines enhance ERAD and ATF6alpha pathway activity in salivary glands of Sjogren's syndrome patients, J. Autoimmun. 75 (2016) 68–81.
[62] L. Huang, Q. Liu, Q.T. Zhou, et al., Deficiency of beta-arrestin 2 alleviates apoptosis through GRP78-ATF6-CHOP signaling pathway in primary Sjogren's syndrome, Int. Immunopharm. 101 (2021) 108281.
[63] H. Fan, A. Bitto, B. Zingarelli, et al., Beta-arrestin 2 negatively regulates sepsis-induced inflammation, Immunology 130 (2010) 344–351.
[64] P. Li, J.A. Cook, G.S. Gilkeson, et al., Increased expression of beta-arrestin 1 and 2 in murine models of rheumatoid arthritis: isoform specific regulation of inflammation, Mol. Immunol. 49 (2011) 64–74.
[65] H.L. Nichols, M. Saffeddine, B.S. Theriot, et al., beta-Arrestin-2 mediates the proinflammatory effects of proteinase-activated receptor-2 in the airway, Proc Natl Acad Sci U S A 109 (2019) 16660–16665.
[66] T. Prell, B. Stubendorff, T.T. Le, et al., Reaction to endoplasmic reticulum stress via ATF6 in amyotrophic lateral sclerosis deteriorates with aging, Front. Aging Neurosci. 25 (2019) 5.
[67] M. Haniu, P. Denis, Y. Young, et al., Characterization of Alzheimer's beta -secretase protein BACE, A pepsin family member with unusual properties, J. Biol. Chem. 275 (2000) 21099–21106.
[68] F. Binet, P. Sapieha, ER stress and angiogenesis, Cell Metab 22 (2015) 560–575.
[69] R.F. Hillary, U. FitzGerald, A lifetime of stress: ATF6 in development and homeostasis, J. Biomed. Sci. 25 (2018) 48.
[70] M. De Palma, D. Biziato, T.V. Petrova, Microenvironmental regulation of tumour angiogenesis, Nat. Rev. Cancer 17 (2017) 457–474.
[71] M.R. Akl, P. Nagpal, N.M. Ayoub, et al., Molecular and clinical significance of fibroblast growth factor 2 (FGF2/bFGF) in malignancies of solid and hematological cancers for personalized therapies, Oncotarget 7 (2016) 44735–44762.
[72] R.P. Sah, P. Garg, A.K. Saluja, Pathogenic mechanisms of acute pancreatitis, Curr. Opin. Gastroenterol. 28 (2012) 507–515.
[73] M. Wu, L.G. Xu, T. Su, et al., AMID is a p53-inducible gene downregulated in tumors, Oncogene 23 (2004) 6815–6819.
[74] R. Bilyy, Y. Kit, U. Hellman, et al., AMID: new insights on its intracellular localization and expression at apoptosis, Apoptosis 13 (2008) 729–732.
[75] M. Wu, L.G. Xu, X. Li, et al., AMID, an apoptosis-inducing factor-homologous mitochondrion-associated protein, induces caspase-independent apoptosis, J. Biol. Chem. 277 (2002) 25617–25623.
[76] M. Varecha, J. Amrichová, M. Zimmermann, et al., Bioinformatic and image analyses of the cellular localization of the apoptotic proteins endonuclease G, AIF, and AMID during apoptosis in human cells, Apoptosis 12 (2007) 1155–1171.
[77] L. Zhou, J.H. Tan, R.C. Cao, et al., ATF6 regulates the development of chronic pancreatitis by inducing p53-mediated apoptosis, Cell Death Dis. 10 (2019) 662.
[78] Z. Shan, C. Ju, Hepatic macrophages in liver injury, Front. Immunol. 11 (2020) 322.
[79] S. Wen, X. Li, Y. Ling, et al., HMGB1-associated necroptosis and Kupffer cells M1 polarization underlies remote liver injury induced by intestinal ischemia/reperfusion in rats, FASEB J 34 (2020) 4384–4402.
[80] W. Alazawi, P.A. Knolle, Interfering with Kupffer cell replenishment: new insights into liver injury, J. Hepatol. 68 (2018) 635–637.
[81] S. Yang, G. Kuang, L. Zhang, et al., Mangiferin attenuates LPS/D-GalN-Induced acute liver injury by promoting HO-1 in kupffer cells, Front. Immunol. 11 (2020) 285.
[82] M. Feng, J. Ding, M. Wang, et al., Kupffer-derived matrix metalloproteinase-9 contributes to liver fibrosis resolution, Int. J. Biol. Sci. 14 (2018) 1033–1040.
[83] L. Zhang, M.B. Bansal, Role of kupffer cells in driving hepatic inflammation and fibrosis in HIV infection, Front. Immunol. 11 (2020) 1086.
[84] F. Yang, S. Wang, Y. Liu, et al., IRE1alpha aggravates ischemia reperfusion injury of fatty liver by regulating phenotypic transformation of kupffer cells, Free Radic. Biol. Med. 124 (2018) 395–407.
[85] M. Hanaoka, T. Ishikawa, M. Ishiguro, 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. 53 (2018) 631–641.
[86] Q. Feng, S. Liang, H. Jia, et al., Gut microbiome development along the colorectal adenoma-carcinoma sequence, Nat. Commun. 6 (2015) 6528.
[87] G. Zeller, J. Tap, A.Y. Voigt, et al., Potential of fecal microbiota for early-stage detection of colorectal cancer, Mol. Syst. Biol. 10 (2014) 766.
[88] O.I. Coleman, E.M. Lobner, S. Bierwirth, et al., Activated ATF6 induces intestinal dysbiosis and innate immune response to promote colorectal tumorigenesis, Gastroenterology 155 (2018) 1539–1552, e12.
[89] C.P. Mavragani, H.M. Moutsopoulos, The geoepidemiology of Sjogren's syndrome, Autoimmun. Rev. 9 (2010) A305–A310.
[90] R.I. Fox, Sjogren's syndrome, Lancet 366 (2005) 321–331.
[91] S. Katsiougiannis, R. Tenta, F.N. Skopouli, Endoplasmic reticulum stress causes autophagy and apoptosis leading to cellular redistribution of the autoantigens Ro/Sjogren's syndrome-related antigen A (SSA) and La/SSB in salivary gland epithelial cells, Clin. Exp. Immunol. 181 (2015) 244–252.
[92] A. Fernández, R. Ordóñez, R.J. Reiter, et al., Melatonin and endoplasmic reticulum stress: relation to autophagy and apoptosis, J. Pineal Res. 59 (2015) 292–307.
[93] U. Båve, G. Nordmark, T. Lövgren, et al., Activation of the type I interferon system in primary Sjogren's syndrome: a possible etiopathogenic mechanism, Arthritis Rheum. 52 (2005) 1185–1195.
[94] J. Aboshiha, A.M. Dubis, J. Cowing, et al., A prospective longitudinal study of retinal structure and function in achromatopsia, Invest. Ophthalmol. Vis. Sci. 55 (2015) 5733–5743.
[95] M.A. Genead, G.A. Fishman, J. Rha, et al., Photoreceptor structure and function in patients with congenital achromatopsia, Invest. Ophthalmol. Vis. Sci. 52 (2011) 7298–7308.
[96] Y. Du, X. Liu, X. Zhu, et al., Activating transcription factor 6 reduces Aβ1-42 and restores memory in Alzheimer's disease model mice, Int. J. Neurosci. 130 (2020) 1015–1023.
[97] P. Nagar, P. Sharma, R. Dhapola, et al., Endoplasmic reticulum stress in Alzheimer's disease: molecular mechanisms and therapeutic prospects, Life Sci. 330 (2023) 121983.

[98] P.S. Kolb, E.A. Ayaub, W. Zhou, et al., The therapeutic effects of 4-phenylbutyric acid in maintaining proteostasis, Int. J. Biochem. Cell Biol. 61 (2015) 45–52.
[99] J. Chen, M. Zhang, M. Zhu, et al., Paeoniflorin prevents endoplasmic reticulum stress-associated inflammation in lipopolysaccharide-stimulated human umbilical vein endothelial cells via the IRE1alpha/NF-kappaB signaling pathway, Food Funct. 9 (2018) 2386–2397.
[100] Z. Wu, J. Niu, H. Xue, et al., Sodium 4-phenylbutyrate protects hypoxic-ischemic brain injury via attenuating endoplasmic reticulum stress in neonatal rats, Front. Behav. Neurosci. 15 (2021) 632143.