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IRE1α-XBP1 signaling pathway, a potential therapeutic target in multiple myeloma

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ABSTRACT

Multiple myeloma (MM), which arises from the uncontrolled proliferation of malignant plasma cells, is the second most commonly diagnosed hematologic malignancy in the United States. Despite the development and application of novel drugs and autologous stem cell transplantation (ASCT), MM remains an incurable disease and patients become more prone to MM relapse and drug resistance. It is extremely urgent to find novel targeted therapy for MM. To date, the classic signaling pathways underlying MM have included the RAS/RAF/MEK/ERK pathway, the JAK-STAT3 pathway, the PI3K/Akt pathway and the NF-KB pathway. The IRE1α-XBP1 signaling pathway is currently emerging as an important pathway involved in the development of MM. Moreover, it is closely associated with the effect of MM treatment and its prognosis. All these findings indicate that the IRE1α-XBP1 pathway can be a potential treatment target. Herein, we investigate the relationship between the IRE1α-XBP1 pathway and MM and discuss the functions of IRE1α-XBP1-targeted drugs in the treatment of MM.

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1. The unfolded protein response (UPR) and IRE1α-XBP1 signaling pathway

Multiple stimuli and pathological conditions including hypoxia, oxidative injury, high-fat diet, hypoglycemia, inclusion body proteins and viral infections induce an accumulation of unfolded proteins in the endoplasmic reticulum (ER). To maintain ER homeostasis, cells initiate the activation of ER-associated protein degradation (ERAD), via cytosolic 26 s proteasomes, autophagy and the unfolded protein response (UPR). The UPR relieves the ER of the unfolded protein load by reducing protein synthesis and by restricting proteins from entering the ER and also accelerates protein folding by increasing the expression of ER stress-related molecular chaperones and folding enzymes [1–4]. During the differentiation of mature B cell to plasma cell, the significantly elevated production of immunoglobulin requires a massive expansion size of the ER. Herein, the efficient regulation of the ER is essential for plasma cell differentiation and cellular activities. Any conditions that interfere with ER function lead to an accumulation of unfolded proteins and ER stress. Persistent high-level antibody secretion in plasma cells and the inhibition of key apoptotic caspases in plasma cells temporarily act to block apoptotic signaling that is triggered by ER stress. If this ER stress persists or the adaptive response fails, cells initiate ER stress-induced apoptotic cell death through the activation of c-Jun amino-terminal kinases (JNKs), cell-autonomous and UPR-controlled activation of death receptor 5 (DR5). The ER stress-related apoptotic mechanisms remain elusive. The apoptotic pathway through ER stress-mediated leakage of calcium into the cytoplasm may be directly activated by ER and leads to the activation of death effectors. ER stress activates Bim (a proapoptotic member of the Bcl-2 family which is essential for ER stress-induced apoptosis) and DR5 transcription through C/EBP homologous protein (CHOP)-mediated transcriptional induction. Persistent ER stress drives ligand-independent DR5 activation and cell apoptosis via caspase-8. Persistent ER stress also suppress the synthesis of anti-apoptotic Bcl-2 and Bcl-x_L protein which is essential for protection from CHOP-dependent apoptosis during plasma cell differentiation [5–13].

MM is characterized by chronic ER stress induced by high production of monoclonal immunoglobulin [14]. Any strategies for MM cells returning to ER homeostasis are critical for the treatment of MM. Currently, the diagnosis of MM relies on serological or urine testing of monoclonal immunoglobulins or light chains [15]. The existing drugs for treating MM include vorinostat (HDAC inhibitor), bortezomib and clarithromycin. These drugs target the integrated networks of aggresome, proteasome and autophagy and induce efficient ER stress-mediated apoptosis in MM cells [16]. Myeloma cells comprise various subsets in differentiated phases and differentiation induction could be a potential therapeutic strategy for myeloma. Herein, UPR, which play crucial roles in terminal plasmacytic differentiation and maturation, can be an effective new therapeutics for myeloma [17]. In mammals, there are three UPR-related ER stress sensors, i.e., the ER transmembrane proteins inositol-requiring enzyme 1 (IRE1), PKR-like ER kinase (PERK) and activating transcription factor 6 (ATF6). These proteins function in response to ER stress through binding their ER-luminal domains to an ER chaperone 78 kDa glucose-regulated protein (GRP78), which is also called immunoglobulin binding protein (BiP). However, accumulated unfolded proteins also interact with GRP78, competitively inhibiting the interaction between GRP78 and the ER stress sensors, leading to dissociated but activated sensors [18]. Activated PERK inhibit the initiation step of mRNA translation by phosphorylating eukaryotic initiation factor 2α (eIF2α). Activated ATF6 translocate to the Golgi complex, where it regulates the expression of molecules involved in protein quality control and ERAD. In addition, ATF6 promote IRE1a-mediated splicing of X-box binding protein 1 (XBP1) and increase its expression. In addition, activated ATF6 and XBP1 bind to the ER stress response element (ERSE) and the UPR element (UPRE), leading to up-regulated expression levels of target genes such as GRP78.

IRE1P is the yeast homologue of human IRE1. In yeast, the transmembrane protein IRE1P activates HAC1 mRNA, and the product of HAC1 mRNA activates the UPR. In mammals, ATF6-induced IRE1 activation induce the splicing of XBP1, and only the spliced form of XBP1 (XBP1s) can activate the UPR effectively [19,20]. IRE1 is a highly conserved type I ER transmembrane protein that contains a kinase domain and an endoribonuclease domain. Misfolded protein-mediated dissociation between IRE1 and GRP78 during ER stress lead to the autophosphorylation of the cytoplasmic kinase domain of IRE1a and its subsequent oligomerization and ultimate activation of its RNase activity. Additionally, the kinase domain of IRE1a activate the JNK and NF-kB signaling pathways by recruiting different molecules, leading to apoptotic cell death [18]. The RNase activity of IRE1, however, can cut off an intron from the unspliced-X-box-binding protein 1 (XBP1u) mRNA with the help of an RNA ligase, resulting in spliced-X-box-binding protein 1 (XBP1s) — the active form of XBP1. XBP1s detaches from the membrane (XBP1u) and then transfers into the cytosol and nucleus of cells and acts as a transcription factor. XBP1s can regulate the transcription of genes involved in ER membrane biosynthesis, protein transportation, chaperoning, ERAD, secretory machinery of exocrine glands and hepatic lipogenesis [21–24]. Additionally, XBP1, together with the interferon regulatory factor 4 (IRF4) and the transcriptional repressor B lymphocyte-induced maturation protein 1(BLIMP1), plays an important role in plasmacytic differentiation. Signals involved in plasma cell differentiation, specifically interleukin-4, control the transcription of XBP1. Moreover, XBP1 regulates the expression of interleukin-6, a cytokine critical for driving B cells into immunoglobulin-secreting plasma cells and plasma cells survival [25–27]. Todd et al. [28] showed that $XBP1^{CD19}$ mice (XBP1 deficiency mice) were protected from disease in an autoantibody-mediated mouse lupus model. Cells lacking XBP1 and ATF6 showed an impaired ability to produce UPR target genes and activate ERSE. XBP1 and ATF6 might be directly downstream of XBP1 are ERdj3 and OBF-1[29]. XBP1 and ATF6 might have other redundant functions [30]. In addition to plasma and MM cells, XBP1s also be produced by bone marrow stromal cells (BMSCs), a key microenvironmental support for MM. High expression levels of XBP1s in healthy human BMSCs promoted MM cell growth and osteoclast formation in vitro and in vivo. Conversely, XBP1s deficiency in healthy donor BMSCs had no such effect. Therefore, knock-down of XBP1 in BMSCs of MM patients can be a good choice for the treatment of MM [31].

2. IRE1-XBP1 signaling pathway and MM

One supervised analysis identified 263 genes to be differentially expressed between normal and monoclonal gammopathy of undetermined significance (MGUS) groups, 380 differentially expressed genes between normal and MM groups, and 197 genes overlapping between the groups. Only 74 genes were differentially expressed between the MGUS and MM groups, indicating a close association between the groups. XBP1s was one of those differentially expressed genes shared by MGUS and MM [32]. In addition, there were 34 up-regulated and 18 down-regulated genes in myeloma cells compared with non-myeloma cell lines. These genes included syndecan, BCMA, PIM2, MUM1/IRF4 and XBP1 [33]. However, IRE1α was expressed in all MM cell lines, although at different protein levels. XBP1u existed in all MM cell lines, whereas XBP1s could only be detected in a subset of MM cell lines. RT-PCR analysis demonstrated the presence of XBP1s in RPMI 8226 and LR5 cell lines. The