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The Role of Endoplasmic Reticulum Stress Sensor Protein CREB3L2 in the Development of Tissues and Tumors

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Abstract: The endoplasmic reticulum plays an extremely important role in the process of cellular protein secretion. The cyclic AMP-responsive element-binding protein 3 (CREB3) transcription factor family is closely associated with the secretion and transport of proteins within the endoplasmic reticulum. As a member of the CREB3 transcription factor family, cyclic AMP-responsive element-binding protein 3-like protein 2 (CREB3L2) stands out as a non-classical sensor within the endoplasmic reticulum. CREB3L2 can detect and regulate endoplasmic reticulum pressure, exert control over the processes of protein transport and secretion, participate in the development of tumor cells, and is also closely linked to the development of certain human tissues and organs. This article aims to review the role of CREB3L2 in tissue development and disease, shedding light on the related mechanisms of CREB3L2 in cancer development. The goal is to provide insights and directions for further analysis of CREB3L2.

Keywords: CREB3L2; Endoplasmic reticulum stress sensor; CREB3

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1. Introduction to endoplasmic reticulum stress sensors

The endoplasmic reticulum (ER) assumes a crucial role in cellular life activities, particularly in the context of protein secretion, which is intricately linked to the ER [1-6]. Most proteins undergo initial entry into the ER, where they undergo storage, folding, and assembly processes. Only correctly assembled proteins proceed from the ER to the cell surface, emphasizing the significance of quality control within the ER. This quality control mechanism ensures that accurately folded proteins are packaged into ER exit vesicles and transported to the cell surface, while misfolded proteins are retained in the ER and subsequently degraded by the cytoplasmic proteasome – an event recognized as ER-associated degradation (ERAD) [7,8].

Throughout these processes, cells dynamically regulate the folding capacity of proteins in the ER as

required. The ER responds to the burden of unfolded proteins in its lumen, known as ER stress, by activating intracellular signal transduction pathways collectively termed the unfolded protein response (UPR). The canonical UPR consists of three branches, with distinct signal transduction mechanisms, that collectively regulate the expression of numerous genes to maintain ER homeostasis. Alternatively, they induce apoptosis in instances where ER stress remains unresolved [9,10]. The UPR signal sensors on these branches include protein kinase RNA-like endoplasmic reticulum kinase (PERK), inositol requiring enzyme 1 (IRE1), and activating transcription factor 6 (ATF6). These three signal transduction families sense protein folding conditions in the ER lumen and transmit this information. This leads to the production of basic leucine zipper transcription factors (bZIP), which enter the nucleus and drive the transcription of UPR target genes. The distinct pathways employ varied signal transduction mechanisms: ATF6 regulates proteolysis, PERK controls the translation process, and IRE1 regulates non-spliced messenger ribonucleic acid (mRNA). Both PERK and IRE1 reduce ER folding load by down-regulating translation and degrading ER-bound mRNAs respectively [11-14].

The cyclic adenosine 3',5'-monophosphaste (cAMP)-responsive element-binding protein 3 (CREB3) transcription factor family comprises ER-localized proteins belonging to the bZIP family. They are transported from the ER to the Golgi apparatus, where they are cleaved by site-1 proteases (S1P) and site-2 proteases (S2P) in intramembrane proteases. This cleavage releases the N-terminal domain, which acts as a transcription factor [15]. Consequently, CREB3 family members regulate the expression of multiple genes and play roles in acute phase response, lipid metabolism, cell development, cell differentiation, and protein secretion. The ER stress response is initiated by CREB3 sensor proteins detecting organelle function deficiencies. These sensors activate one or more transcription factors, inducing the transcription of genes involved in organelle function regulation [16].

2. Functional study of CREB3L2 in sensing and regulating endoplasmic reticulum stress

The cAMP-responsive element-binding protein 3-like protein 2 (*CREB3L2*) gene was initially identified as part of the *FUS/CREB3L2* chimeric gene specific for low-grade fibromyxoid sarcoma (LGFMS). Spanning over 120 kbp, the gene comprises 12 exons and is expressed in most human tissues. As a member of the CREB3 family of transcription factors, the CREB3L2 protein consists of an N-terminal transactivation part, a basic DNA binding domain, a leucine zipper region, a transmembrane hydrophobic region, and a cavity domain [17]. Operating as a transmembrane protein within the ER, the CREB3L2 protein undergoes cleavage on the membrane under ER stress. In the luminal segment, intramembrane hydrolytic protein (RIP) cleaves CREB3L2, and the resulting cleaved fragment of the protein, which contains the N-terminal transactivation domain, basic DNA binding domain, and leucine zipper region, is transported into the nucleus. There, it binds to corresponding sites, activating the transcription of CREB3L2 target genes [18].

Throughout this process, unfolded proteins amass in the ER, prompting the transmission of signals from the ER to the cytoplasm and nucleus by the ER pressure sensors IRE1, PERK, and ATF6. Some scholars have identified astrocyte-specific inducing substance (OASIS) as an ER stress sensor of astrocytes. Interestingly, CREB3L2 exhibits structural homology to OASIS and undergoes cleavage during the ER stress response [19]. The cleaved fragments of CREB3L2 are then transported into the nucleus, binding to the cyclic AMP response element site and activating the transcription of target genes. Moreover, under normal conditions, CREB3L2 protein remains unexpressed; however, it is significantly induced at the translation level during ER stress. Other researchers have observed that in neuroblastoma cell lines, CREB3L2 overexpression inhibits cell death induced by ER stress, while small interfering RNA knockdown of CREB3L2 promotes ER stress-induced cell death. In summary, CREB3L2 emerges as an ER stress sensor, playing a pivotal role in preventing the accumulation of unfolded proteins [20].

3. Functional study of CREB3L2 in controlling protein transport and secretion

As a regulator of cellular secretion capacity, CREB3 members actively participate in ER and Golgi stress responses and contribute to cell differentiation processes. Research has uncovered their crucial role in the differentiation of endometrial stromal cells (EnSCs) into secretory cells during decidualization, a process vital for embryo implantation. Decidualization involves the release of numerous factors, necessitating the remodeling of extensive secretory pathways. Both CREB3L1 and CREB3L2 transcription factors are up-regulated during decidualization. Notably, simultaneous down-regulation of CREB3L1 and CREB3L2 damages the Golgi apparatus, resulting in reduced protein secretion. Thus, both CREB3L1 and CREB3L2 are indispensable for Golgi remodeling and efficient protein secretion [21].

Another study further supports the role of CREB3L2 in controlling protein transport and secretion. Liver fibrosis, stemming from an excessive wound-healing response to chronic injury, progresses to cirrhosis. During fibrosis, inflammatory cytokines induce the differentiation of hepatic stellate cells (HSCs) into myofibroblasts. This process entails an expansion of the ER and Golgi apparatus, indicating heightened protein synthesis and secretion in activated HSCs. The study observes isoform-specific upregulation of the transmembrane bZIP transcription factor CREB3L2, as well as components Sec23a and Sec24d of the endocoat protein complex II (COPII), during HSC activation. Knockout of these components hinders successful HSC activation, emphasizing the necessity of Sec23a/Sec24d-mediated transport from the endoplasmic reticulum to the Golgi apparatus for this process [22].

CREB3L2's role in controlling protein transport and secretion extends to cartilage development. Following cleavage, the N-terminal of CREB3L2 promotes the secretion of extracellular matrix proteins by inducing the expression of Sec23a, functioning as a transcription factor. The C-terminal part of the protein regulates the parathyroid hormone-related protein signaling pathway, promoting chondrocyte proliferation and inhibiting hypertrophic differentiation. CREB3L2 also acts on the transcriptional activation axis during chondrocyte differentiation to accelerate the secretion of cartilage matrix proteins. Additionally, its expression increases during the transformation of human B-cells into antibody-secreting cells, suggesting a crucial role in the secretory pathway during this process [23-25].

4. Research on the function of CREB3L2 in tumor progression

The pivotal role of CREB3L2 in cancer primarily stems from the chromosome-specific translocation t(7;16)(q33;p11), giving rise to the chimeric gene *FUS/CREB3L2*. In instances like LGFMS, a rare, slow-growing cancer typically found in the deep soft tissues of the legs or trunk, this chimeric gene is implicated in the regulation of CD24 expression [26]. Additionally, in malignant glioma, the RAS/MAPK signaling pathway cascade, activated by the FRS2/PAK1 oncogene, induces the upregulation of CREB3L2. CREB3L2 then directly binds to the ATF5 promoter, resulting in ATF5 transcription – a transcription factor pivotal for cell survival. The activation of HSCs in liver cancer is also closely associated with CREB3L2. In essence, CREB3L2 assumes a critical role in tumor development [27-29].

5. Functional studies of CREB3L2 during development

CREB3L2 assumes a crucial role in development, particularly in neural and skeletal development.

Nerve growth factor (NGF) stimulates various cellular physiological processes, such as growth, differentiation, and survival, maintaining the phenotypes of multiple neuron types. The CREB3 transcription factor acts as a signaling hub, regulating numerous genes associated with the secretory pathway and Golgi

homeostasis. It integrates signals from various sources to oversee protein secretion, post-translational modification, and transport. Scholars utilized NGF-induced differentiation of PC12 cells, a commonly used neural cell line, to scrutinize the expression and signaling mechanisms of CREB3 transcription factor family members. The outcomes revealed that NGF treatment induced an enlargement of the Golgi apparatus, coupled with an increase in the expression of proteins and mRNAs essential for membrane transport. In addition, a significant elevation in CREB3L2 protein and mRNA levels was observed in response to NGF. This response necessitated mitogen-activated protein kinase (MAPK) and cAMP signaling pathways, and CREB3L2 overexpression impeded NGF-induced synaptic growth. In summary, this study underscores CREB3L2 as a crucial downstream effector in the NGF activation pathway, promoting neuronal differentiation [30,31].

In the context of cartilage formation, CREB3L2 plays a vital role. Many tissues possess specific signaling systems for ER dysfunction. As an ER-localized basic leucine zipper transcription factor, CREB3L2 activates in response to ER stress and is expressed in cartilage, with high expression in proliferating chondrocytes. These chondrocytes, under ER stress, exhibit abnormal expansion of ER and can secrete aggregated type II collagen (Col2) and cartilage oligomeric matrix protein (COMP). Sec23a, responsible for transporting proteins from the ER to the Golgi apparatus, is a target of CREB3L2. CREB3L2 directly binds to the promoter region of Sec23a, activating its transcription. Introduction of Sec23a into CREB3L2 chondrocytes fully restored damaged cartilage matrix protein transport and secretion. This highlights the pivotal role of the CREB3L2-Sec23a pathway in cartilage development and formation through the activation of protein secretion [32,33].

6. Research on the functions of CREB3L2 in other life processes

Beyond its contribution to nerve and cartilage development, CREB3L2 plays a pivotal role in various organs and life processes.

Liver fibrosis, a common feature in chronic liver diseases leading to cirrhosis and hepatocellular carcinoma (HCC), has been linked to the *microRNA 92b* (*miR-92b*) gene in HCC progression. Research indicated that miR-92b-3p is highly expressed in fibrotic liver tissues, as well as in human hepatic cell line LX-2 under transforming growth factor beta 1 (TGF-β1) stimulation. In addition, researchers also found that miR-92b-3p mimics can promote the activation, proliferation, and migration of LX-2 and HSC-T6 cells. TargetScan database analysis identified CREB3L2 as a potential target of miR-92b-3p, and luciferase assays confirmed that miR-92b-3p inhibits CREB3L2 expression. Mechanistically, miR-92b-3p activates the Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway through CREB3L2, thereby promoting liver fibrosis progression, and providing novel insights into liver fibrosis diagnosis and treatment [34].

During progesterone stimulation, EnSCs undergo decidualization, releasing factors crucial for embryo implantation. This process requires significant remodeling of the secretory pathway, particularly the Golgi complex. Transcriptomic analysis of decidualized EnSCs *in vitro* revealed a set of co-regulated genes related to vesicle trafficking and early secretion, sharing CREB3L1 and CREB3L2 binding elements in their promoter region. Simultaneous down-regulation of CREB3L1 and CREB3L2 during decidualization adversely affects Golgi remodeling, resulting in drastic changes, including Golgi apparatus fragmentation and expanded endothelial cells. This leads to collagen accumulation in reticulum cisterns and an overall reduction in protein secretion. Hence, both CREB3L1 and CREB3L2 are crucial for Golgi remodeling, efficient protein secretion, and successful decidualization [35].

In prostate cancer (PCa), where the androgen receptor (AR) drives progression, CREB3L2 collaborates with AR to mediate transport from the ER to the Golgi apparatus. Single-cell transcriptome analysis reconstructing the transcriptional network of AR in Pca revealed direct regulation of genes in the ER-to-Golgi

protein vesicle-mediated transport pathway by AR. The expression of these genes relies on androgen transport from the ER to the Golgi apparatus, highlighting the key role of CREB3L2 in the cooperation with AR-mediated expression and dysfunction of ER-to-Golgi transport in PCa progression [36].

Lastly, in Alzheimer's disease (AD), β-amyloid acts as a trigger, promoting the formation of pathological CREB3L2-ATF4 transcription factor heterodimers in neurons. Examination of AD datasets and a chemical genetics approach to genomic binding profiles of heterodimeric transcription factors (ChIPmera) revealed that CREB3L2-ATF4 activates a transcriptional pathway interacting with about half of the genes differentially expressed in AD, including subsets associated with beta-amyloid and tau neuropathology. CREB3L2-ATF4 activation drives hyperphosphorylation and secretion of tau protein in neurons and misregulates reverse transcriptase, a complex implicated in AD pathogenesis. This suggests that differential transcription factor CREB3L2-ATF4 dimerization is a crucial mechanism in the development of pathogenic cell states in AD [37].

7. Summary

In previous studies, researchers have obtained a preliminary understanding of the functions and roles of the CREB3 family. As transcription factors located in the ER, they play crucial roles in acute phase response, lipid metabolism, cell development, cell differentiation, organelle autoregulation, and protein secretion. Consequently, they are closely linked to specific human diseases and life processes. As a member of the CREB3 family, CREB3L2 has been unequivocally associated with the onset of liver cirrhosis, nervous system development, and chondrocyte formation. Presently, scholars have delved into *in vitro* and animal model experiments related to CREB3L2, particularly its connection with cancer metastasis, sparking heightened research interest.

While exploring novel functions of CREB3L2 in various contexts is intriguing, a more critical endeavor involves accurately analyzing the underlying mechanisms through which CREB3L2 finely regulates diverse biological events and pathways in distinct cell types. A comprehensive understanding of CREB3L2 and its regulatory modes will contribute to unraveling how the ER stress-sensing mechanism orchestrates multiple cellular components to maintain tissue homeostasis and impact disease progression. This knowledge will further elucidate CREB3L2's role in cancer development, providing novel targets and insights for cancer treatment.

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