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Review Article

Research Progress on the Role of Endoplasmic Reticulum Stress in Osteogenic Differentiation

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Abstract: The endoplasmic reticulum (ER) is the main site for regulating protein synthesis and processing. Endoplasmic reticulum stress plays a role in regulating the osteogenic differentiation of stem cells and general osteoblasts. Bone marrow stromal cells (BMSCs, also known as bone marrow mesenchymal stem cells) are a group of progenitor cells that contain a small number of bone stem cells (SSCs) that rebuild cartilage, bone, stroma, and fat cells that support hematopoiesis and bone marrow. Therefore, due to their self-renewal and differentiation capabilities, they have become an important resource for researching regenerative medicine and tissue engineering treatment strategies. Exposure of osteoblasts to physical and biochemical stimuli facilitates rapid activation of early tissue repair processes in organisms. Therefore, the rational regulation of the induction conditions of osteoblasts has become a hot research topic. This article reviews the recent advances in the role of endoplasmic reticulum stress in the process of osteoblast differentiation.

Keywords: Endoplasmic reticulum stress; BMSC; Osteoblast; Osteoblasts differentiation

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1 Introduction

ER (endoplasmic reticulum, ER) is an important plasma membrane structures in cells, regulate protein synthesis, protein folding, aggregation main places[1], the cells One of the main properties of calcium storage, but also cholesterol, steroids, and lipid synthesis place[2,3]. When ER environment changes, such as hypoxia, hunger, disorder of intracellular calcium, the expression of the mutant protein and alterations in the redox state of the protein, which would cause an unfolded or misfolded protein in the endoplasmic reticulum large aggregates, intralesional endoplasmic reticulum within the normal physiological function, start the endoplasmic reticulum stress (Endoplasmic reticulum stress, ERS)[4-6]. Initiator and unfolded protein response, and endoplasmic reticulum overload sterol regulatory cascade reaction. When cells slight stress, the steady-state can be self-healing. However, if the stimulus is too strong or too long duration, cell homeostasis does not recover in a timely manner, ERS program is initiated apoptotic cells[7-10].

1.1 The surface morphology of nanomaterials determines the process of osteogenic differentiation

Recently, many reports have shown that unfolded protein response (UPR) and osteogenic differentiation n are interrelated. Studied the relationship between the material morphology and the endoplasmic reticulum stress (ERS) and UPR pathway of cells during the process of osteogenic differentiation by preparing titanium materials with different surface morphologies. Titanium, a material with a different surface morphology, acts as a stressor, which initially causes a stress response marked by the accelerated discharge of the ER from unfolded or misfolded proteins. In addition, the activation of the PERK-eIF2α-ATF4 signaling pathway by titanium with a different morphology is consistent with its osteogenic induction capacity. More specifically, when the

PERK-eIF2α-ATF4 pathway is promoted or inhibited, respectively, osteogenic differentiation can be enhanced or weakened[11-12]. In addition, the use of different concentrations of thapsigargin to regulate the degree of ER stress indicates that mild endoplasmic reticulum stress (ERS) can promote osteogenic differentiation, and the excessive ER stress response generated by excessive stimulation can inhibit osteoblasts Differentiation even caused apoptosis. The results indicate that endoplasmic reticulum stress and unfolded protein response may play a key role in morphologically-induced osteogenic differentiation, which may help provide new insights into the study of morphological signal transduction[13-14].

1.2 Mechanical forces induce endoplasmic reticulum stress and promote osteoblast differentiation

Mimic the cyclic mechanical force of periodontal chewing stimulation to induce endoplasmic reticulum stress in hPDLCs cells and promote osteogenic differentiation[15]. Under the action of mechanical force, periodontal tissue is in a state of hypoxia. In this case, an inflammatory response occurs due to hypoxia and changes in blood vessels, and a circulation disorder occurs[16]. As a stress stimulus, hypoxia induces ERS in periodontal tissues and enhances the expression of several osteoblast marker genes (ATF4, OCN and BSP). In order to study the mechanism by which ERS promotes osteogenic differentiation, mechanical forces were applied to hPDLCs to induce ERS, then interfere with and overexpress the PERK gene, and then detect PERK signaling pathway-related factors[17]. The study found that overexpression of PERK increased the phosphorylation of eIF2α and the expression of ATF4, and further induced the expression of BSP and OCN, thus indicating that circulating mechanical forces can promote the effect of hPDLCs on bone regeneration. However, PERK-/- cells showed opposite results, and knockdown of PERK showed an effect of inhibiting bone differentiation. Therefore, ERS-mediated PERK-eIF2α-ATF4 signaling pathway has an impact on periodontal remodeling and osteogenic differentiation of hPDLCs during orthodontic tooth movement. In summary, the study demonstrated that the ERS-mediated PERK-eIF2α-ATF4 signaling pathway is involved in the osteogenic differentiation under the influence of circulating mechanical forces[18-19].

1.3 Natural drug-induced ER stress promotes osteoblast differentiation

Costunolide is a sesquiterpene lactone, which is present in many herbs and has perfect anti-inflammatory and antioxidant functions, and promotes the expression of antioxidant genes[20]. Lignanolide increased expression of terminal homology box 5 (Dlx5), transcription factor 2 (Runx2), ALP, and osteocalcin (OC) in C3H10T 1/2 cells. In addition, lignans can increase ALP activity and matrix mineralization. Interestingly, ligol can increase ER stress through Bip-activated transcription factor 4 (ATF4) and C / EBP homologous protein (CHOP). However, it has no effect on the expression of activated transcription factor 6 (ATF6)[21]. Curcumin induces endoplasmic reticulum stress and promotes bone differentiation in mouse embryonic stem cells similar to bone morphogenetic protein 2 (BMP2)[22]. Curcumin is a natural phenolic product. Curcumin induces mild endoplasmic reticulum stress in mouse embryonic mesenchymal stem cells (C3H10T1/2), similar to the role of bone morphogenetic protein 2 (BMP2). Studies have also shown that curcumin increases the expression of endoplasmic reticulum stress-related genes (BiP, CHOP, ATF6, CREBH, and SMILE) in C3H10T1/2 cells in a time- and concentration-dependent manner. In addition, curcumin can also induce phosphorylation of Smad1/5/9 cells[22]. BMP2 regulates ATF6 expression and activation through ER stress-induced intramembrane proteolysis, and Runx2 regulates osteoblast differentiation. Curcumin can regulate C3H10T1/2 cells to achieve similar effects. The increase of ATF6 expression led to the up-regulation of osteoblast differentiation-related marker genes (ALP, OCN and Runx2). The results showed that curcumin increased the expression of osteoblast genes in C3H10T1/2 cells and promoted osteoblast differentiation[23].

1.4 Different concentrations of fluoride induce ER stress in osteoblast and promote osteogenic differentiation.

Determined the expression of classical osteogenic markers and unfolded protein response (UPR) signal factors by exposing MC3T3-E1 cells to different concentrations of fluoride[24]. Studies have shown that excessive intake of fluoride can cause some skeletal diseases, and endoplasmic reticulum stress

and UPR responses are involved in bone formation. When MC3T3-E1 cells were exposed to low doses of fluoride-containing medium, low concentrations of fluoride stimulated alkaline phosphatase (ALP), runt-related transcription factor 2 (Runx2), and osterix [25-26]. In addition, double-stranded RNA activates protein kinase (PKR) -like ER kinase, activates transcription factor 6, and increases expression of X-box binding protein 1. In addition, small interfering RNA (siRNA) technology was used to reduce the expression of bound immunoglobulin (BiP) mRNA. It was found that the knockdown of BiP led to inhibition of UPR pathway activation and osteoblast differentiation. In short, fluoride has a dual role in osteogenesis effect[27-29]. The upregulation of the three UPR marker factors is similar to the upregulation of osteogenic differentiation markers and transcription factors, which indicates that there is an inseparable relationship between osteoblast differentiation and the UPR pathway.

1.5 Bone formation inducing factors BMP-2 and Tmem119 promote the differentiation of myoblasts into osteoblasts.

Studies have found that BMP-2 and Tmem119 both promote the expression of osteoblast markers Runx2, Osterix, Col1a1, ALP and osteocalcin and the formation of mineralized structures[30]. Stimulation of BMP-2 activates the phosphorylation of ERK stress sensors PERK and eIF2α and leads to increased biosynthesis of osteoblast differentiation factor ATF4. When the selective inhibitor salubrinal blocked the dephosphorylation of eIF2α, the osteogenesis of BMP-2 and Tmem119 was further enhanced[31]. Although BMP-2 stimulation can increase the expression levels of P-eIF2α and ATF4, Tmem119 can only stimulate ATF4 expression and has no effect on P-eIF2α. Reduction of endogenous Tmem119 levels by siRNA reduces the basal and BMP-2 stimulation levels of ATF4 protein. In summary, BMP-2 stimulates myoblasts to differentiate into osteoblasts through the PERK-eIF2α-ATF4 pathway[32]. Reduction of endogenous Tmem119 levels by siRNA reduces the basal and BMP-2 stimulation levels of the ATF4 protein. But it also stimulated Tmem 119, which itself increased ATF4 expression.

2 Conclusions and Future Outlook

Regarding diseases of bone tissue damage caused by diseases or trauma, certain results have been achieved by regulating autogenous bone regeneration, but more tests are still needed to transform them into clinical practical applications. More and more studies provide solid evidence that the endoplasmic reticulum stress response plays an important role in the process of osteogenic differentiation. In the PERK signaling pathway activated by different stimuli, the up-regulated transcription factor ATF4 promotes osteogenic differentiation. By increasing our understanding of the endoplasmic reticulum and its response to stress, we believe that we can provide more reasonable and efficient means for treating bone injury diseases.

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