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Mechanism of osteogenic differentiation of umbilical cord mesenchymal stem cells

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Abstract: Mesenchymal stem cells (MSCS) exist in a variety of tissues and have multi-lineage differentiation potential. Mesenchymal stem cells have great application prospects in the treatment of bone injury diseases. The rapid initiation and efficient induction of osteogenic signaling pathways are the key to mesenchymal stem cell-based bone tissue engineering technology. Multiple signaling pathways have been confirmed to play a regulatory role in the process of osteogenic differentiation of mesenchymal stem cells. This article reviews the research progress of the mechanism of osteogenic differentiation of mesenchymal stem cells.

Keywords: Mesenchymal Stem Cells; Osteogenic Differentiation; Signaling Pathways

1. Overview of mesenchymal stem cells

Mesenchymal stem cells (MSCs) are adult stem cells derived from the mesoderm, which have multi-lineage differentiation potential and repetitive self-renewal ability. They can be isolated from various tissues such as bone marrow, umbilical cord blood, umbilical cord, placenta, and adipose tissue. MSCs have the characteristics of high expression of CD73, CD105, CD90, and low expression of CD45, CD34, CD14, HLA-DR, which is also commonly used to detect whether cells are MSCs. So far there have been several studies have shown that MSCs in immune and hematopoietic regulation, anti-inflammatory, promote angiogenesis and tissue repair are play an important role in the process, and because the MSCs has safe, easy separation, amplification, characteristics of frozen and large-scale preparation, MSCs have become clinically used in stem cell therapy, tissue engineering and regenerative medicine ideal candidate, MSCs therapy also has broad prospects for development. MSCs have the ability to differentiate into osteoblasts, adipocytes, and chondrocytes. More and more studies have revealed a wider range of differentiation potential of MSCs, such as differentiation into muscle cells and neurons.

2. Osteogenic differentiation of mesenchymal stem cells

Mesenchymal stem cells (MSCS) have the ability of multi-lineage differentiation and can differentiate into osteoblasts under certain inducing conditions. MSCS derived from bone marrow, umbilical cord blood, adipose tissue and other tissues all show similar osteogenic differentiation ability. Rapid initiation and efficient induction of osteogenic signaling pathways of mesenchymal stem cells is the key to their application in bone tissue engineering technology.

3. Mechanism of osteogenic differentiation of MSCS

A large number of in vitro studies have found that the pathways regulating osteogenic differentiation of MSC mainly include Wnt/β-Catenin signaling pathway, TGFβ signaling pathway, P38MAPK signaling pathway, ERK signaling pathway, PI3K/AKT signaling pathway, Notch signaling pathway, STAT3 signaling pathway, and NF-κB signaling pathway.

3.1. the Wnt/beta - Catenin signaling pathway

The Wnt/ β-catenin signaling pathway comprises a series of proteins that play key roles in embryonic development and adult tissue homeostasis. On the basis of earlier studies, the Wnt pathway has been divided into classical and non-classical signaling pathways. The classical Wnt pathway, also known as the Wnt/β-Catenin pathway, is associated with nuclear translocation of β-Catenin, which activates target genes via T cell cytokines/lymphopotentiators. The canonical Wnt pathway is mainly related to cell proliferation, while the non-canonical Wnt pathway regulates cell polarity and migration. These two major pathways form a network that can regulate each other.

3.2. TGFβ signaling pathway

The TGFβ superfamily is composed of more than 40 members, which are divided into TGFβs, bone morphogenetic proteins, growth differentiation factors and other subfamilies. There are five isoforms of TGFβ, namely TGF-β1, -β2, -β3, -β4 and -β5. There are only three isoforms of TGFβ in mammals: TGF-β1, -β2 and -β3. TGFβ signaling pathway plays an important role in different environments and tissues, regulating basic processes including embryonic development, proliferation, differentiation, morphogenesis, stem cell maintenance and regeneration. Smad is a crucial transcription factor in TGFβ signaling transduction. The Smad proteins are classified into two types: Co-Smads: Smad4, Smad10; Receptor activated Smads (R-Smads) : Smad1, Smad2, Smad3, Smad5, Smad8; And inhibitory Smads (I-Smads) : Smad6, Smad7. TGFβ pathway is a classical receptor-mediated signaling pathway that activates transcription factors from membrane to nucleus. TGFβ receptors are divided into three types: type I, type II and type III. Type III receptors are not directly involved in signal transduction, while type I and type II receptors are involved in signal transduction and both belong to transmembrane serine/threonine kinase receptor proteins. The activated R-Smads combine with Co-Smads to form complexes and enter the nucleus to directly bind to DNA. The transcription of specific target genes such as Runx2 and Osterix plays a regulatory role. Although the pathway is simple in nature, the TGFβ family has a variety of functional and diverse responses due to the interactions between heteromeric receptors and Smad complexes, the interactions between receptors, the combinatorial interactions between proteins, the interactions between proteins and Smad, and the cooperation with sequence specific transcription factors.[1]

3.3. P38MAPK signaling pathway

Mitogen-activated protein kinases belong to serine/threonine protein kinases. The MAPK signaling pathway plays a regulatory role in a variety of cells, and plays a key role in the process of transmitting signals from extracellular to intracellular to trigger various cellular responses. Mitogen-activated protein kinase kinase kinase phosphorylates the serine site of mitogen-activated protein kinase kinase, followed by phosphorylation of the threonine/tyrosine site of MAPK. P38MAPK is a kind of protein kinase whose tyrosine site can be phosphorylated in 1993. It belongs to the subclass of MAPKs, including six subtypes: α1, α2, β1, β2, γ and δ. The activation of P38MAPK pathway was as follows: MEKKs/TAK→MKK3/MKK4/MKK6→P38MAPK pathway. Different MEK activate different P38MAPK isoforms, and different P38MAPK isoforms can activate different substrates. After activation, P38MAPK can enter the nucleus to regulate a variety of target genes.

3.4. ERK signaling pathway

ERK was first discovered and most studied in the MAPK family, mainly located in the cytoplasm. ERK Ser/Thr protein kinases, including two co-workers isomer ERK1 and ERK2, ERK signaling pathway is the most clear MAPK signaling pathways in the study of a classic pathway, can regulate cell proliferation, differentiation and transformation. The main pathway of ERK signal transduction is Ras/Raf/MEK/ERK. Ras is a monomeric protein with endogenous gtpase activity, which catalyzes the decomposition of GTP to GDP. Raf belongs to Ser/Thr protein kinase, which is a MAPKKK. MEK belongs to the MAPKK family, which has the bispecific function of phosphorylating tyrosine and threonine residues and activating its downstream substrates, including MEK1 and MEK2. ERK signal transduction process: receptor tyrosine kinase is activated by various signals to signal transduction, which activates Ras, and then activates Raf after binding MEK to form a dimer to activate it. After MEK is activated, ERK can be activated by phosphorylation. The activated ERK is transferred to the nucleus and plays a role in the corresponding substrates, most of which are activated by phosphorylation.

3.5. PI3K/AKT signaling pathway

Phosphatidylinositol 3-kinase/protein kinase B pathway is an important intracellular signaling pathway that can regulate the proliferation, differentiation and apoptosis of various types of cells. PI3K can be divided into three types: I, II and III. The substrate of type III PI3K is PI, the substrate of type II is PI and phosphatidylinositol phosphate, and the substrate of type I is PI, PIP and PIP2. PI3K can act on growth factor receptors with phosphorylated tyrosine residues or junction proteins to change their dimer conformation, and can also be ac-

tivated by directly binding to Ras and P110. Neurotrophins or extracellular growth factors bind to transmembrane tyrosine kinase receptors and self-phosphorylate them to recruit and activate PI3K. Activated PI3K catalyzes PIP2 to PIP3 on the cell membrane, and PIP3 can act as a second messenger to bind to intracellular signaling factors AKT and phosphatidylinositol-dependent protein kinase. PDK1 activates AKT phosphorylation and regulates downstream target genes.

3.6. Notch signaling pathway

Notch signaling pathway can regulate almost all cell proliferation and differentiation, and is essential for multiple physiological or pathological processes such as cell proliferation, differentiation, and apoptosis. The Notch pathway includes 4 receptors Notch1/2/3/4, a class of DNA binding protein CSL protein, 5 ligands Delta1/3/4 and Jagged1/2, Hes genes and regulatory molecules. The activation of Notch signaling pathway is mainly through two pathways: One is dependent on the cellular transcription factor CSL, which starts with cell-cell contact. After the Notch ligand on the cell surface binds to the receptor on the neighboring cell membrane, the receptor is cleaved twice by the proteasome, releasing the Notch intracellular domain to the nucleus, binding to CSL protein, and recruitment of co-activator to form a trimer to change the action of CSL protein. It turns from a transcriptional inhibitor to a transcriptional activator, and then regulates the downstream target genes of the Notch signaling pathway. Another way of activation does not depend on the CSL, NICD of Notch signaling pathway in the cytoplasm interaction with the other signaling pathways, such as PI3K/AKT/mTOR, beta catenin pathway, regulate the expression of the corresponding protein.

3.7. Others

In addition to the above signaling pathways, other signaling pathways also regulate osteogenic differentiation of MSCs. Studies have found that nicotinamide mononucleotide (NMN) and vitamin D3 play a role in promoting osteogenic differentiation of MSCs in vivo and in vitro by upregulating SIRT1 signaling pathway. Crosstalk between multiple signaling pathways can also occur to jointly regulate the process of osteogenic differentiation. Cao et al. found that Notch signaling significantly enhanced the activity of BMP9-induced BMP/Smad signaling in vitro and in vivo, and increased the gene expression of essential osteogenic factors in BMP9-induced MSCs. Although the above pathways have been found to be related to the osteogenic differentiation of MSCs, the currently known signaling pathways need to be further studied to explore more effective targets. At the same time, more research is needed to explore more unknown signaling pathways related to the osteogenic differentiation of MSCs.[2]

4. Summary and prospect

With the development of tissue engineering, mesenchymal stem cells have a key application value and broad development prospects in the repair of bone defects and the treatment of bone regeneration, which also makes mesenchymal stem cell therapy a hot topic in bone tissue reconstruction, but mesenchymal stem cell therapy is still a relatively novel treatment. We between the osteogenetic differentiation of mesenchymal stem cells gene regulatory network is more obvious, still need more further research to improve the osteogenetic differentiation of mesenchymal stem cells between the specific mechanism of action, mining more targets, safe and reliable for between mesenchymal stem cells in the treatment of bone defect and bone regeneration provides more possibilities, We also look forward to more breakthroughs in mesenchymal stem cell therapy in the future, and more patients with bone defects and fractures can benefit from mesenchymal stem cell therapy.

References

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