A Review Study: Effect of Growth Factors on Human Mesenchymal Stem Cells Differentiation into Cartilage Tissue

Babak Pourmollaabbassi[1], Batool Hashemibeni[2*], Ebrahim Esfandiari[2]

1. Department of Tissue Engineering, School of Basic Engineering, Islamic Azad University of Najafabad, Isfahan, Iran.
2. Department of Anatomical Sciences, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.

Babal Pourmollaabbasi Graduated from MSc tissue engineering, departement of tissue engineering at school of basic engineering in Islamic azad university of Najafabad, Isfahan, Iran. His interests are study and working on stem cells and scaffold for regeneration and tissue engineering of cartilage and bone defects.

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ABSTRACT

Hyaline cartilage is a vascular and neural tissue with scanty chondrocytes and limited regenerative ability. After some serious injuries of the cartilage, healing process will take place through the formation of fibrocartilage structures. Currently, tissue engineering and cell therapy are 2 interesting therapeutic fields dealing with regenerative medicine. In this regard, tissue regeneration has found mesenchymal stem cells (MSCs) with self-renewal and multipotential abilities as the best candidates for this process. Growth and differentiation of MSCs are induced by growth factors. The purpose of this review article is to evaluate the effect of growth factors and their signaling pathways involved in differentiation of mesenchymal stem cells into chondrocytes in vitro conditions.

1. Introduction

One of the most crippling diseases is arthralgia which leads to people's disabilities [1]. Arthralgia is caused by different factors such as osteoarthritis or trauma resulting from destruction of hyaline cartilage. About 36 million American people with arthralgia are suffering from osteoarthritis or joint injuries resulting from sports activities [2].

Physicians, surgeons, and researchers have tried to treat and improve degenerated cartilage. Current treatments have resulted in insufficient repair of cartilage and instead fibrocartilage formation. The main reason for the partial cure is the lack of blood vessels and low mitosis of chondrocytes in the joint cartilage. Thus, hyaline cartilage has a limited ability to repair its serious injuries [3, 4]. Successful efforts have been made over the past few years to cure joint cartilages by using mesenchymal stem cells (MSCs). The cells can be isolated from different sources such as bone marrow, adipose tissues, synovial

*** Corresponding Author:**
Batool Hashemibeni, PhD
Address: *Department of Anatomical Sciences, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.*
Tel: *+98 (31) 37929152*
E-mail: *hashemibeni@med.mui.ac.ir*

membrane, dental pulp, umbilical cord blood, placental, and so on [5-10]. MSCs are undifferentiated cells with self-renewal and multipotential abilities [11,12]. They express specific surface markers like MSCA-1, STRO-1, CD271, CD105, CD90, CD73, CD44, and CD29 [13,14,15]. These cells can differentiate into other cells by induction of appropriate growth factors. The growth factors like transforming growth factor-beta (TGP-β), fibroblast growth factor (FGF), and insulin-like growth factor (IGF) have been applied to differentiate MSCs into chondrocytes [16-18]. This review article tries to evaluate the effect of growth factors and pathways of signaling involved in the differentiation of MSCs into chondrocytes.

2. Transforming growth factor-beta superfamily

Some studies have been carried out to determine the types of growth factors and their effects on growth, differentiation, and apoptosis of chondrocytes, ultimately, leading to the discovery of the superfamily of the transforming growth factor-beta (TGF-β) [19]. This family includes more than 35 members, and it is involved in different biological processes such as cell proliferation, differentiation, development of embryo, immunity reaction, inflammation, and repair [20,21].

TGF-β family members affect in 2 separate signaling pathways, one is TGF/Nodal/ Activin branch, and the other is bone morphogenic protein (BMP) signaling branch [22]. Recent studies have shown that the TGF-β has 3 isotopes; β1, β2, and β3 produced as inactive form until the peptide, depending on cloning, is separated from them Latency Associated Peptide (LAP) [23]. The transforming growth factor-beta (TGF-β) members bind to the serine/threonine kinase receptors (type I, II) on the cell surface. After binding TGF-β members to their receptors, they get phosphorylated and activated [24]. Activated molecules trigger intracellular signaling via SMAD proteins (SMA=small body size, MAD=Mothers against decapentaplegic) [25]. The SMAD protein molecules that initiate the activity are Smad-2 and Smad-3 known as R-Smad.

Three groups of SMAD protein molecules family

The family of SMAD protein molecules is divided into 3 groups:

- Receptor-regulated SMADs (R-SMAD), which include SMAD1, SMAD2, SMAD3, SMAD5 and SMAD8/9 [26],
- Common-mediator SMAD (co-SMAD), which includes only Smad4, interacting with R-SMADs to participate in signaling [27].
- Antagonistic or inhibitory SMADs (I-SMAD), which includes SMAD6 and SMMAD7, blocking the activation of R-SMADs and co-SMADs [28].

Also, the expression of SMAD 1/4/5 in chondrocytes causes upregulation of interleukin-1 (IL1) [29]. R-SMADs activation is related to phosphorylation of SXs region located at C-terminal, which has a different behavior relative to Activin receptor-Like Kinases (ALK) [30].

Recent studies have shown that Protein Phosphatase PPM1A dephosphorylates Smad 2/3 controls the signaling pathway of TGF-β by phosphorylation and dephosphorylation of SMAD2 and 3 [31, 32]. Activated R-SMAD forms a complex with SMAD4 that is transferred into the nucleus and regulates the genes of chondrogenic differentiation [33]. Following the activation of the receptors, the mitogen- activated proteinkinase (MAPK) may get activated. In fact, 3 pathways, including extracellular signal-regulated kinases (ERK), C-Jun-NH2-terminal Kinase, and P38 are considered for MPAKs.

The other members of SMADs named SMAD6 and 7 confine the activities of SMAD2 and SMAD3 [34] and inhibit the chondrogenesis of MSCs [35]. RUNX2 is a transcription factor involved in osteochondrogenic differentiation pathway. Study has shown that blocking of RUNX2 expression causes inhibition of osteogenesis in mice [36]. When SMAD6 and SMAD7 interact with RUNX2 in SMAD pathways, the rate of proteases increases, and these enzymes by destroying Runx2, prevent differentiation process [37]. R-SMADs can also be inhibited by other pathways, including SARA (SMAD-anchored for receptor activation) membranous proteins [38]. The most important members of TGF-β superfamily that can be used for cartilage tissue engineering include TGF-β1, TGF-β2, BMP2, BMP4, BMP7, and GDF5 [39].

The transforming growth factor-beta 1

It has been revealed that the transforming growth factor-beta 1 (TGF-β1) stimulates the production of extracellular matrix in chondrocytes [40]. Moreover, this growth factor inhibits the catabolic activity of IL-I in cartilage tissue [41]. In vitro studies have shown that TGF-β1 affects the differentiation of MSCs into the chondrocytes. Additionally, TGF-β1 inhibits the production of type-I

collagen and increases the expression of type-II collagen and aggrecan genes in chondrogenic differentiation of MSCs [42].

The transforming growth factor-beta 3

Hashemibeni et al. have found that TGF-β promotes chondrogenesis of adipose-tissue-derived stem cells (ADSCs) in 3D scaffold-free pellet culture system [43]. Studies have shown that transforming growth factor-beta 3 (TGF-β3) enhances the synthesis of glycosaminoglycans (GAGs) in chondrogenesis of MSCs [44,45]. The findings showed that type II collagen, GAGs, and aggrecan are expressed in differentiated ADSCs in chondrogenic medium supplemented with TGF-β3. Meanwhile, they produce more AGC, GAG, and type I collagen in comparison to natural chondrocytes [46].

Esfandiari et al. have found that using both TGFβ3 and physical (EF) inducers has the best outcomes in chondrogenesis, expression of SOX9, and type II collagen genes [47].

Bone morphogenic proteins

Bone morphogenetic proteins (BMPs) are members of the transforming growth factor-beta superfamily that advance their signaling pathway through different pathways relative to TGF-β. They have 4 receptors at the cell surface, including BMPRIα (ALK2, ALK3), BMPRIB (ALK6), and BMPRII each of which activates different signaling pathways [48]. The BMP signaling pathway is initiated by binding ligand to its receptors and causing the activation of SMADs 1/5/8 by phosphorylation. Following the formation of complex by SMADs1/5/8 with SMAD4 and entering in nucleus, this complex stimulates the cascade of reacting and specific gene expression [49,50]. SMAD7 and suppressors of cytokine signaling (SOCS) have negative feedback effect on BMP signaling pathways [51].

Bone morphogenic protein-2

Bone morphogenetic protein-2 (BMP2) increases extracellular matrix production (ECM) and reduces type-I collagen expression. Sekiya et al. have found that using BMP2 on MSCs increases the production of aggrecan due to the application of other members of TGF-β [52].

Bone morphogenic protein-4

Bone morphogenic protein 4 (BMP4) is an important and effective protein in osteogenesis and chondrogenesis. The results of studies conducted on the effects of BMP4 on MSCs for differentiation into chondrocyte indicated that this growth factor leads to the production of chondroprogenitor lines and chondrogenic differentiation. In addition, BMP4 increases type-II collagen and aggrecan expression and at the same time, suppresses type-I and X collagens [53].

Bone morphogenic protein-7

This growth factor is synthesized by the chondrocytes inducing the anabolic activity to support the damaged cartilage [54]. Studies indicated that BMP7 reduces MSCs proliferation, but it stimulates the cartilage extracellular matrix production. Cheng et al. have found that the applications of BMP7 in combination with TGF-β1 and IGF-I would result in the best effects in chondrogenesis [55].

Growth differentiation factor

Researchers have found that among 15 members of subfamily of growth differentiation factors (GDFs), only GDF5 has chondrogenic potential and stimulates type-II collagen and aggrecan production in micromass or pellet culture systems [56, 57]. Also, GDF5 expresses in skeleton and joints development [58].

Insulin-like growth factor-1

Insulin-like growth factor-1 (IGF1) plays the most important role in cartilage tissue. It causes homeostasis of cartilages and proteoglycan synthesis, proliferation, and differentiation of chondrocytes in the growth plates in vitro and in vivo [59, 60]. This growth factor repairs cartilage by increasing the matrix and type II collagen synthesis [61, 62]. The studies indicated that IGFI could induce differentiation of MSCs into cartilage, but when used with other growth factors such as TGF-β1 and BMP7, it exhibits better results [63].

The activity of insulin growth factors in tissues and blood circulation is regulated by a group of IGF-related proteins (IGFBP) so that some of them stimulate and others suppress the effects of IGFI. Studies have shown that IGFBP1, IGFBP2, IGFBP4, and IGFBP6 act as inhibitors while IGFBP3 serves as a stimulator in IGFI signaling pathway [64, 65].

The IGFI activity starts by binding to tyrosine kinase receptor (IGF-IR) followed by the activation of SHC (SH2-containing inositol phosphatase) and members of insulin receptor-substrate (IRS) family, including IRS1 and IRS2. Following the phosphorylation of IRS, 3 cas-

cade pathways of PI3K (phosphoinositol 3-kinase), ERK (extracellular signal regulated kinase), and MAPK (mitogen–activated protein kinase) are activated.

Activated P13K stimulates AKt and P70-S6 kinase and affects the cell survival and synthesis of the proteins. On the other hand, binding of Grb2 (Growth factor receptor-bound protein-2) to IGF-R causes the activation of IRS-1, SHC, Ras and Raf/MEK/ERK/MAPK. Research indicated that IGF1 stimulates proteoglycan synthesis in serum and synovial liquid. Studies have shown that IGFI activates PI3K leading to chondrogenesis [66].

When chondrocytes are stimulated by insulin-like growth factor-1 (IGF1), PI3K causes proliferation of cells, gene expression, protein synthesis, type-II collagen and proteoglycans production, and prevention of apoptosis [67, 68]. Other studies indicated that IGF1 inhibits extracellular matrix production in the cartilage, thus IGF1 has opposite effects on cartilage tissues [69].

Fibroblast growth factor family

A total of 23 members of fibroblast growth factor (FGF) family from FGF1 to FGF23 are known so far [70]. Fibroblast growth factors are heparin–associated polypeptides involved in neovascularization in vivo and in the growth of new blood vessels during the wound healing and embryogenesis.

The fibroblast growth factors in vitro conditions cause proliferation, differentiation, and cell migration leading to the production of protease in endothelial cells involved with tyrosine kinase receptors (FGFRs) and glucosaminoglycan (GAG) binding to heparin (HLGC) [71]. After the connection of fibroblast growth factor (FGF) to its receptor on the cell surface, the FGF activates the signaling pathways comprising of phosphoinositol kinase (PI3K) [72], phospholipase, mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinases (ErK/p42/44), and P38 [73, 74]. Evidently, 2 members of the family of fibroblast growth factors; FGF-2 and FGF-18 (FGF), play the most important role in chondrogenic induction [75].

Fibroblast growth factor-2

Fibroblast growth factor (FGF) is known as an important factor for the regulation of cartilage homeostasis, and its mitogenic role [76]. Using fibroblast growth factor-2 (FGF2) in monolayer culture prepares the required conditions for extracellular matrix synthesis and expression of specific phenotype in chondrocytes [77]. Studies have shown that FGF2 increases proliferation and production of proteoglycan in MSCs and also it induces human adipose-derived stem cells chondrogenesis in Transwell culture, which may be beneficial to cartilage tissue engineering [78].

In addition, FGF2 preserves the multipotency of the MSCs in vitro [79]. FGF2 in the joint cartilage and meniscus decreases the ratio of type-I collagen to type-II collagen and thus fibrocartilage replaces with hyaline cartilage for the repair of damaged tissue [80].

Fibroblast growth factor-18

Fibroblast growth factor-18 (FGF18) induces the cell growth, tissue repair, tumor growth, homeostasis protection, and extracellular matrix (ECM) of cartilage formation [81]. In vitro studies demonstrated that when FGF18 binds to FGFR3, receptors suppress cell proliferation and improve the differentiation and production of ECM [82].Tonia et al. showed that FGF18 has a positive effect on the chondrogenesis and can repair the damaged cartilage in animal model study [83].

3. Discussion

Today, joint damages and pains are the most important problems that have affected human health in spite of life modernization. Current treatments such as subchondral drilling, arthroplasty, and autologous chondrocyte implantation do not have satisfactory results, as cartilage repair is incomplete. Thus, researchers have focused on the application of MSCs to repair damaged cartilage.

Using MSCs for desired cartilage tissue engineering requires appropriate growth factors like FGF, IGF, and TGF families. Over the past several years, in vitro and in vivo studies have been conducted to introduce MSCs into joint cartilage. Now, it is time to study the signaling pathways of each growth factor and determine what factors stimulate or inhibit the signaling pathway of chondrogenesis. With regard to the studies and research conducted so far, some positive effects and achievements have been attained, but occasionally some irreversible damages and negative effects have also been observed [84].

In summary, more research should be carried out on chondrogenic induction of MSCs and clinical application of engineered cartilage tissue.

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