The role of growth factor in the repair of articular cartilage

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Abstract

Background: Natural degeneration or trauma of articular cartilage all can lead to its structural and functional damage. Because of its lack of blood supply and innervation, it has low metabolic activity and difficulty in self-repair after injury. Growth factors provide a new direction for the repair of articular cartilage damage and play an important role. This article will systematically summarize the research progress of traditional growth factors, mainly introduce the newly found growth factors and other synthetic compounds and inorganic particles that can induce stem cells to differentiate into cartilage.

Methods: English literatures published in PubMed and SCI databases from August 2000 to August 2019 were searched, Review the relevant literature, The two authors evaluated and screened the quality of the literatures respectively, and senior authors further evaluated them to resolve the disagreement on the inclusion of literatures.

Results: Growth factors can significantly promote stem cell proliferation and differentiation. A variety of growth factors can exert synergistically to promote the differentiation of stem cells into cartilage, so as to promote the regeneration of cartilage tissue and repair the damage of articular cartilage. Traditional growth factors that promote articular cartilage repair are bone morphogenetic proteins, cartilage derived morphogenetic protein, transcription growth factor β, fibroblast growth factors and insulin-like growth factors. Recent studies have found that kartogenin, platelet-rich plasma, platelet-rich fibrin, force growth factor, etc. can also effectively induce stem cells to differentiate into cartilage and maintain chondrocyte phenotype, synthetic compounds such as dexamethasone and some inorganic particles also promote chondrogenic differentiation.

Conclusions: The newly discovered growth factors promote the development of articular cartilage repair, but its mechanism of action is not clear. There are no in vivo experimental studies on dexamethasone and inorganic particles, and its repairing effect and safety are for further study. The synergistic or antagonistic effects between different growth factors, the optimal concentration ratio, and the differences in in vivo and in vitro roles need further study. At present, the research on growth factors mostly stays at the basic stage, and there are few clinical studies, which will be an important
direction for further research.

Background
Articular cartilage is an important part of smooth, painless and functional movement of joints. It is still one of the few self-healing tissues in the human body after thinning due to traumatic injury, disease or aging. However, articular cartilage is hyaline cartilage and widely hydrated. It has neither nerves nor blood vessels. Its low cell density only allows extremely limited self-renewal. Chondrocytes in matrix lacuna mainly obtain necessary nutrition and excrete metabolites through infiltration. Its low metabolic activity and poor blood supply of articular cartilage make its repair particularly difficult.

Articular cartilage defects It is often manifested as intractable pain and progressive joint dysfunction, which may eventually lead to degenerative osteoarthritis. For articular cartilage, whether acute injury or slow progress osteoarthritis will cause pain, leading to progressive destruction of the whole joint, resulting in partial or complete loss of joint function. According to the International Cartilage Repair Society (ICRs) classification method, articular cartilage injury can be classified as follows: (1) cartilage with a diameter of 1.0-2.0mm was damaged, and the repaired tissue was similar to normal hyaline cartilage; (2) Articular cartilage defects (ACD) is a kind of cartilage damage with a diameter of more than 3 mm. The repaired tissue is mainly fibrocartilage, but most of them can not be completely repaired; (3) ACD with a diameter of more than 6 mm can not repair itself, and it will further damage the surrounding bone wall and the surrounding articular cartilage, which will lead to the collapse of the surrounding subchondral bone and articular cartilage, and eventually inevitably lead to osteoarthritis. Knee joint injury→ACD→Osteoarthritis this disease pattern is very common in China and the world. According to the relevant statistics of who, 90% of women and 80% of men over the age of 65 suffer from OA. About 27 million people in the United States are affected by OA every year. The annual cost of health care system is about 89.1 billion US dollars.

If this disease process can be blocked by cartilage repair during ACD, the patients' pain and economic burden can be reduced. The traditional methods to treat articular cartilage injury include autogenous cartilage tissue transplantation, allogeneic cartilage microparticle transplantation, microfracture,
intra-articular injection of drugs, joint washing and cleaning, total knee replacement, etc.

[6] Regenerative techniques such as autologous chondrocyte transplantation (ACI) and stromal induced autologous chondrocyte transplantation (MACI) have been applied in cartilage repair,[7,8] but both have their limits. Autologous grafts rely on cartilage or osteochondral plugs in non-weight-bearing areas of cartilage to fill cartilage defects, resulting in limited donor site lesions and tissue sources. Allografts, on the other hand, use the same method as tissues from other donors, but are complicated by immune rejection, potential disease metastasis, and limited fusion with host tissue. Microfracture is mainly used for scar repair, including drilling into subchondral bone to release bone marrow to accelerate endogenous healing, but this method usually leads to the formation of fibrocartilage, which has poor biological and mechanical properties, and may be painful for patients.

[9] Intra-articular injection of drugs and joint washing and cleaning are only suitable for patients with early mild disease, but the long-term effect is not ideal; chondrocyte transplantation has poor effect on the repair of bone defects involving subchondral; total knee replacement is only suitable for patients with late severe disease, with high economic cost. Therefore, the above methods can not meet the current clinical needs. Figure 1.

Growth factor is a hot spot in the research of cartilage tissue engineering. It has a wide range of functions and provides a new treatment for cartilage damage repair. It can regulate the synthesis and metabolism of cartilage cell matrix, promote stem cells to differentiate into cartilage, promote chondrocyte proliferation, maintain chondrocyte phenotype, and then promote cartilage tissue regeneration, repair articular cartilage damage. In addition to the traditional growth factors, some new compounds that can regulate cell growth have been found, and some synthetic compounds and some non-polar particles also have certain differentiation inducing effect on stem cells. At present, for the latest development of growth factors, there are few studies on the classification of growth factors suitable for stem cells from different sources. It is of great significance for articular cartilage repair to fully understand the research status of growth factors. In this study, we reviewed the role and progress of growth factors in cartilage injury and repair, starting from the traditional research of
growth factors, newly found growth factors and other synthetic compounds that can promote stem cells to differentiate into cartilage.

Figure 1 Illustration of approaches to the restoration of cartilage. Abbreviations: matrix-induced autologous chondrocyte implantation (MACI); mesenchymal stem cells (MSCs); autologous chondrocyte implantation (ACI); chondrogenic stem/progenitor cells (CSPCs); embryonic stem cells (ESCs); induced pluripotent stem cells (iPSCs).

Methods
In this paper, the PubMed and SCI databases are searched with "artistic cartilage", "growth factor", "stem cells" and "repair" as subject words. The "and" algorithm is used between the subject words, and a total of 1072 references are retrieved. Inclusion criteria: ① basic research and clinical application of growth factors or cytokines in articular cartilage repair; ② published from August 2000 to August 2019; ③ select articles published in authoritative English journals in the same field, and select the core collection of papers by web of science. Exclusion criteria: ① content irrelevant or not closely related research; ② non-english literature, repeatability study; ③ arguments, evidence unreliable literature; ④ Some documents that cannot be extracted from the data. Finally, 81 related articles with high quality were included, all of which were in English.

(Finally, 81 articles were included in the literature, all of which were in English.)

Results
1 Traditional growth factors

Bone morphogenetic proteins (BMPs)
Bone morphogenetic proteins (BMPs), which are effective mediators for cell proliferation and mesenchymal stem cell differentiation, have been proved to be important molecules involved in cartilage repair.[10] BMP induces osteogenesis and cartilage formation in the cartilage/membrane,
and is important for maintaining bone integrity and fracture healing by inducing differentiation of mesenchymal stem cells into the osteoblast lineage. Currently, there are about 20 members of the BMPs family (BMP1-18, BMP-3b and BMP-8b). BMP-1, 2, 4, 5, 6, 7, 8, 14 can induce the formation of bone and cartilage, BMP-2, 7 can induce osteogenic / chondrogenic differentiation and bone and / or cartilage formation. BMP-2 can promote cartilage formation of chondrocytes and mesenchymal stem cells (MSCs), and is used to treat cartilage and cartilage interface injury. BMP-3, 4, 8 play a key role in the process of bone formation. BMP3 can induce the proliferation of MSCs and promote the formation of cartilage. BMP-3b can regulate cell growth and differentiation of embryo and adult tissues.

BMP-4, 6, 7, 9, 12 and BMP 13 have been shown to induce MSCs differentiation. Bmp-7, 8 may be the bone inducer of epithelial osteogenesis, which plays a role in calcium regulation and bone homeostasis, and induces cartilage and bone formation. BMP 7 is used in cell carrier hydrogel to promote cartilage formation and extracellular matrix formation. When BMP 7 was cultured with articular cartilage or bone marrow mesenchymal stem cells (BMSCs), the synthesis of type II collagen and mucopolysaccharide could be promoted. Iwakura et al showed that BMP-7 or tgf-β 1 and BMP-7 could inhibit the differentiation of chondrocytes to mast cells in the early stage, and effectively promote the chondrogenesis of synovium. BMP has a strong regulatory effect on the formation and repair of bone and cartilage, cell proliferation and the stability of the internal environment of adult bone. They represent promising molecules in articular cartilage repair and play a role in accelerating and increasing bone integration.

**Cartilage derived morphogenetic protein (CDMP)**

The cartilage derived morphogenetic protein (CDMP) family has three members: CDMP-1, CDMP-2 and CDMP-3. They have highly similar structure or biological characteristics, participate in the whole process of cartilage tissue occurrence, growth and damage repair, and play an important role in the differentiation and regulation of chondrocytes. CDMP-1 and cdmp-2 have 82% homology. Different species of CDMPs have high homology and low immunity, so they generally do not cause
immune rejection. This low immunity attribute makes the cross species application of CDMPs have a broad prospect.\[20] In vitro experiments showed that CDMPs could promote the synthesis of proteoglycans from chondrogenic cell lines and fetal limb chondroblasts, indicating that CDMPs can stimulate the formation and differentiation of cartilage.\[23] Cho et al[21] showed that CDMPs can promote the production of glycosaminoglycan (GAG) by adult bovine and human articular chondrocytes, but the effect of CDMP-1 and cdmp-2 has no significant difference. Relevant studies have confirmed that CDMP-1 is mainly distributed in the cartilage rudiment formed by MSCs aggregation and the developing cartilage nucleus of long bone in human embryo, which are the sites of future joint formation, and CDMP-1 is also expressed in adult articular cartilage, This specific distribution suggests that it may be closely related to the formation of articular cartilage in the extremities, while the distribution of articular cartilage in adults may be related to the maintenance of chondrocyte phenotype. CDMP-1 has the ability to induce cartilage formation.\[22] Tkahara et al[23] found that some mesenchymal cells appeared apoptosis in the developing phalanx of short legged rat without CDMP-1, and the aggregation and differentiation of the cells in the finger (toe) were delayed when CDMP-1 was absent, so it was considered that CDMP-1 was indispensable in the development, maintenance and growth of the finger (toe).

CDMP-1 can regulate the growth and differentiation of tissue cells, maintain cell phenotype and promote apoptosis, and play a specific role in the differentiation of chondrocytes: ① Inducing differentiation of stromal stem cells into chondrocytes; ② promoting aggregation and concentration of MSCs, and inducing differentiation of MSCs into chondrocytes; ③ determine the correct segmental pattern of the finger (toe) bone; ④ maintain the stable phenotype of mature articular chondrocytes; CDMP-1 can regulate the differentiation of mesenchymal stem cells into chondrocytes, which is closely related to chondrogenesis and development.\[24] Spiro et al[25] have proved that CDMP-1 has induction activity through experiments. For example, implantation of matrix containing CDMP-1 into subcutaneous or muscle of mice can induce the formation of cartilage and bone tissue ectopic. CDMP-1 can also promote the formation of cartilage nodule by cultured parietal cells of peptide mice.
Katayama et al\textsuperscript{[26]} used cdmp-1 gene to transfect bone marrow mesenchymal stem cells to repair articular cartilage defects in rabbits, eight weeks after implantation of cdmp-1-transfected homologous BMSCs into articular cartilage defects of rabbits, the surface morphology of the repaired cartilage can be similar to that of the differentiated mature hyaline cartilage, and the subchondral tissue is completely repaired by the new thick layer of bone tissue close to the host subchondral bone. The results of Bobacz et al\textsuperscript{[27]} showed that CDMP-1 has the potential to induce fibroblasts to differentiate into cartilage. CDMP is also the inducer of osteogenesis in cartilage. CDMP-1 and cdmp-2 can promote the osteogenesis of BMSC in vitro. Compared with common medium, they can improve the activity of alkaline phosphatase, and this effect is dose-dependent.

**Transcription growth factor \( \beta \) (TGF-\( \beta \))**

Transcription growth factor \( \beta \) (TGF-\( \beta \)) is a kind of polypeptide growth factor with many functions, which widely exists in platelets and bone. It has many biological effects such as regulating cell growth, differentiation, apoptosis and extracellular matrix synthesis, and is also the strongest cell growth factor at present. TGF-\( \beta \) can also reduce chondrocyte hypertrophy and osteogenic differentiation, help promote the single process of chondrocyte differentiation during repair of articular cartilage damage, and improve cartilage repair in vivo\textsuperscript{[28]}. Five types of TGF-\( \beta \) have been discovered in humans, namely TGF-\( \beta \)1, TGF-\( \beta \)2, TGF-\( \beta \)3, TGF-\( \beta \)4 and TGF-\( \beta \)5. They can effectively induce stem cells to differentiate into chondrocytes, and the role of TGF-\( \beta \)1 in cartilage damage repair is more important\textsuperscript{[29]}. It promotes cartilage damage repair in two ways: \( \textcircled{1} \) promote the synthesis of cartilage cells II type collagen and proteoglycan, maintain chondrocyte phenotype; \( \textcircled{2} \) play an induction role, promote stem cells to cartilage differentiation, in the process of mouse development, TGF- \( \beta \)1 mRNA has been located in cartilage, cartilage intima, indicating TGF- \( \beta \)1 has the role of promoting the growth and differentiation of cartilage tissue\textsuperscript{[30]}. TGF \( \beta \)1 can significantly increase cartilage related gene expression, promote cell adhesion molecule expression and cell aggregation, while TGF \( \beta \)3 can promote cell proliferation and regulate stem cell differentiation to cartilage, TGF \( \beta \)1 and TGF \( \beta \)3 affect the different stages of chondrogenic differentiation of stem cells. Therefore,
combined use of TGF β 1 and TGF β 3 may be better to induce stem cells to differentiate into chondrocytes. [31-35] Li et al [36] found that TGF- beta not only induced chondrogenic differentiation, but also inhibited the absorption of cartilage tissue engineering new cartilage. In addition, TGF - β can also regulate the expression and action of other cytokines in cartilage, TGF-β can stimulate the synthesis of prostaglandins and type II collagen, and can down regulate cartilage degrading enzyme. It is an important synthetic metabolic factor in osteoarthritis. TGF-β can protect cartilage from injury by counteracting the inhibition of IL-1 on prostaglandins. [37]  

**Fibroblast growth factors (FGF)**  
Fibroblast growth factors (FGF) can promote the division and proliferation of fibroblasts, induce the morphogenesis and differentiation of cells, and play an important role in the repair of bone and cartilage injury. [38] In different tissues of the adult, FGFs play an important role in the regulation of growth and tissue regeneration. At present, FGF-2 and FGF-18 play an important role in maintaining the homeostasis of articular cartilage, regulating chondrocyte differentiation and promoting the development of osteoarthritis (OA). FGF2 is derived from heparan sulfate proteoglycan in the extracellular matrix of articular cartilage, and its specific role in cartilage metabolism remains controversial. [39] According to the related experimental studies, PI3K-AKT and ERK1 / 2 pathway activated by FGF2 can promote the proliferation of BMSCs, also can up regulate the Sox9 gene expression, start the differentiation of BMSCs into cartilage, and promote the synthesis of extracellular matrix such as type II collagen. [40-42] Argün et al [43] successfully repaired the full-thickness defect of rabbit articular cartilage by periosteal transplantation and injection of recombinant FGF-2. Shi et al [44] stimulated the proliferation of adult bovine articular chondrocytes by FGF-2, which up-regulated SOX9 and increased ECM production. In the rabbit model of articular cartilage injury, exogenous FGF2 can significantly promote the repair of articular cartilage. FGF-18 is a famous synthetic metabolic factor, which can promote the proliferation of chondrocytes and participate in the formation of cartilage and repair of damaged cartilage. Zhang et al [45] after co culture of chondrocytes from OA patients with MSC and intervention of FGF-18, it was found that the co cultured
cells could produce more type II collagen than OA chondrocytes alone. It was believed that FGF-18 could promote the reconstruction and repair of damaged articular cartilage. Mori et al.[46] found that recombinant FGF-18 may be mediated by tissue inhibitor of metalloproteinase-1 (TIMP-1), which protects articular cartilage by gene expression profiling. Howard et al.[47] injected recombinant human FGF-18 into the articular cavity of sheep with medial femoral condyle defect, and the articular cartilage was well repaired. Through in vitro studies, Barr et al.[48] found that recombinant FGF18 could significantly increase the synthesis of proteoglycan, repair the number of cells, and prevent apoptosis, which played an important role in promoting the repair of mechanically damaged articular cartilage.

**Insulin-like growth factors (IGFs)**

Insulin-like growth factors (IGFs) are single-chain polypeptides whose structure is homologous to insulin and regulated by growth hormone. IGFs are one of the first growth factors to have chondrogenesis. IGFs have two family members, i.e. IGF-1 mainly regulates the growth and development of adults. IGF-2 plays an important role in the growth and development of fetus. In normal articular cartilage, IGF plays a role in maintaining chondrocyte metabolic homeostasis, maintaining the balance of proteoglycan synthesis and decomposition in vitro. IGF-1 can promote chondrocyte proliferation, induce mesenchymal stem cells to differentiate into cartilage tissue, maintain cartilage phenotype stability, and promote articular cartilage repair. Orth et al.[49] Study showed that transplantation of alginate hydrogel coated with articular chondrocytes into rabbits could promote the high expression of IGF 1. At 14 weeks, IGF 1 could improve articular cartilage regeneration and promote the formation of subchondral bone, and enhance the repair of full-thickness cartilage damage and osteochondral surface damage. Madry et al.[50] have shown that overexpression of IGF 1 can significantly promote the repair of damaged cartilage and reduce the degeneration of cartilage around the damaged area of osteoarthritis. Lu et al.[51] have shown through experiments that increasing the content of IGF 1 in hydrogel complex can also promote cartilage formation. Loffredo et al.[52] implanted the collagen membrane loaded with IGF-1 into cartilage
defects. The results showed that low dose IGF-1 could promote the repair and reconstruction of subchondral bone, and high dose IGF-1 could help cell survival, promote the formation of new cartilage and cartilage integrity. IGFs can promote the proliferation of chondrocytes, induce stem cells to differentiate into cartilage, stimulate cells to secrete extracellular matrix and inhibit extracellular matrix degrading enzymes, and then promote the repair of articular cartilage.\[53\]

2 Newly discovered cell growth factor

2.1 Kartogenin

Johnson et al\[54\] first found kartogenin (KGN), a small molecule that can enhance the differentiation of human mesenchymal stem cells (hMSCs) into chondrocytes. Their research shows that KGN not only maintains the chondrocyte phenotype, but also protects the cartilage matrix from degradation. Under the condition of simulated pathophysiology in vitro, KGN can significantly reduce nitric oxide produced by chondrocytes and levels of glycosaminoglycans (GAGs) secreted by cartilage explants, suggesting that KGN has cartilage protective effect on chondrocytes under pathological conditions. Yohei et al\[55\] found that KGN inhibited the collapse of ECM and aggrecan mediated by IL-1β and aggrecanase, stabilized the homeostasis of hyaluronic acid and CD44, and protected cartilage from injury. Xu et al\[56\] established a model of rabbit articular cartilage injury and injected KGN into the cartilage defect, which proved that KGN can significantly enhance the regeneration of articular cartilage. Studies by Decker et al\[57\] have shown that KGN not only promotes the formation of cartilage, but also enhances the development of limbs and joints in mice. Kwon et al\[58\] showed that KGN can maintain the cartilage phenotype and prevent the destruction of extracellular matrix by matrix metalloproteinase (MMP), which indicates that KGN not only has the function of repairing articular cartilage, but also had the protective effect on the original articular cartilage. Liu et al\[59\] showed that KGN can promote the repair of cartilage damage by stem cells, and has strong chondrogenic differentiation ability to both SMSCs and BMSCs. Liu et al\[60\] found that KGN, TGF-β1 and BMP 7 could synergistically promote the secretion of Lubricin in chondrocytes.
**2.2 Platelet-rich fibrin (PRF) and platelet-rich plasma (PRP)**

Platelet-rich fibrin (PRF) and platelet-rich plasma (PRP) are platelet concentrates prepared from whole blood by different centrifugation methods. They are rich in growth factors, including platelet-derived growth factor (PDGF), IGF, bFGF, TGF-β and vascular endothelial growth factor (VEGF) can promote fracture healing, chondrocyte proliferation and cartilage extracellular matrix synthesis.\(^{[61]}\) PRP can promote the synthesis of cartilage tissue in the defect site by promoting the proliferation of chondrocytes and the synthesis of cartilage-related matrices. Miyakoshi et al.\(^{[62]}\) showed that the IGF-1 complex hyaluronic acid substance in PRP was implanted in the defect of rabbit animal model, and the results showed that the complex could promote cartilage anabolism and repair cartilage defects. Akeda et al.\(^{[63]}\) found that sheep chondrocytes were cultured in 10% PRP for 72 h, and the number of chondrocytes was significantly higher than that in normal culture medium. Lee et al.\(^{[64]}\) showed that PRP was added to the culture medium of rabbit chondrocytes with hydrogel as scaffold, and it was found that PRP can promote the proliferation of chondrocytes, repair bone defects and promote cartilage formation. A prospective study by Siclari et al.\(^{[65]}\) showed that 52 patients with knee joint cartilage injury were treated with the combination therapy of subchondral drilling and PRP, and the follow-up showed that the prognosis of these patients was good. The release of cytokines from PRP preparations is mainly in the early stage after use, and the release is less in the later stage, and the release is not persistent and uneven, and the release site is mainly near the time point when the exogenous additive is added. However, the pattern of PRF releasing cytokines is different from that of PRP. Because PRF has no exogenous additives, the cytokines in its products can be released relatively long-lasting and more in line with clinical needs.

**2.3 Mechano-growth factor (MGF)**

Mechano growth factor (MGF) is one of the selectivity splicing products of IGF-1. It only contains 24 peptides, which form when IGF-1 splice variants of exon 4 spliced to exon 5 (or exon 6) are named MGF (or IGF-IEc) in humans and IGF-IEb in rodents, MGF and IGF gist 1 are regulated and expressed by the same gene and are isomers of IGF gist 1 family, but their physiological functions differ greatly.
Tong et al\cite{67} showed that MGF can regulate the migration of MSCs through PI3K/AKT signaling pathway and Erk1/2 pathway, and promote the proliferation and osteogenic differentiation of MSCs. Luo et al\cite{68} demonstrated that MGF is a catalyst for promoting TGF-β3 induced cartilage regeneration. In animal experiments, fibroin scaffolds carrying TGF beta 3 and MGF have the function of recruiting BMSCs to migrate during the repair of articular cartilage defects in rabbits, and inhibit the occurrence of fibrosis on the cartilage surface, which can promote the regeneration and repair of articular cartilage in a long time. Deng et al\cite{69} injected 28.5mg/kg and 57 μg / kg MGF into the bone deformation area of rabbits to promote osteogenesis, and proved that high dose MGF was more effective than low dose MGF. In vitro, MGF can significantly promote the migration of BMSCs, promote the differentiation of BMSCs into cartilage by TGF-β3, and reduce the synthesis of typeⅠ collagen during cartilage differentiation. The surface of the new cartilage is smooth and flat, and the proteoglycan matrix is rich in content. Although there is no type I collagen expression, it can express normal type II collagen. The repair effect of MGF is very similar to that of normal cartilage. Song et al\cite{70} have shown that MGF can stimulate anabolism in the process of OA, and MGF can up-regulate cartilage ECM synthesis genes ColII, ACAN, SOX9 and HAS. With the increase of MGF dose, the expression of cola, scan and Sox9 increased linearly, indicating that MGF has a stable effect on ECM regeneration and cartilage formation.

3 Synthetic compound that promotes differentiation of stem cells into cartilage

3.1 Inorganic particles

Various types of hydrogels derived from different natural or synthetic polymers and their hybrids, it has been used to reconstruct the defective osteochondral interface or articular cartilage tissue.\cite{71} Hydrogel complex containing inorganic particles is a new functional material used for the treatment of osteochondral surface and full-layer cartilage damage. Inorganic particles can enhance the mechanical properties of hydrogel, and have prominent bone conductivity and osteogenic induction ability.\cite{72,73} Khanarian et al\cite{74} added hydroxyapatite nanoparticles into agarose hydrogels, which can increase the total amount of proteoglycan, collagen and calcification, and promote the
regeneration of bone cartilage interface and calcified cartilage. Han et al\textsuperscript{[72]} added calcium silicate microparticles to alginate hydrogels to stimulate osteogenic differentiation of MSCs and significantly increase the deposition of extracellular bone-like minerals. Filardo et al\textsuperscript{[75]} treated 27 patients with exfoliated osteochondritis with a three-dimensional scaffold composed of type I collagen and hydroxyapatite with permeability, before operation, open operation was used to expose cartilage defect and remove sclerotic subchondral bone, after 2 years of follow-up, magnetic resonance imaging (MRI) showed that cartilage defects were repaired, most patients have morphological changes in the subchondral bone and have uneven regeneration tissue.

MSCs is the most widely used stem cell in regenerative medicine. Because of its rich sources, low immunogenicity, no ethical problems, it can be encapsulated in various hydrogels, therefore, the MSCs carrier hydrogel has become the most promising biomaterial for cartilage tissue engineering, and can be used for osteochondral interface regeneration and cartilage repair. Different hydrogels showed different abilities to support cartilage formation and osteogenesis. Histological and immunohistochemical staining confirmed that MSCs formed cartilage and bone ECM after being cultured in alginate, chitosan and silk protein hydrogels for 8 weeks\textsuperscript{[76]}, however, the differentiation of MSCs is multidirectional. It is necessary to add specific cell growth factors in order to correctly induce MSCs to differentiate into chondrocytes. Stem cells from different sources and different types of hydrogels show different abilities to support cartilage formation and bone formation. Different growth factors are needed to induce stem cells to differentiate into chondrocytes. (Table 1)\textsuperscript{[12,13,31-36,40,42,46,54,56,58,65,73,74]}
Table 1: Some common cell growth factors for cartilage repair

| Types                      | Family members | Commonly used types | Applicable stem cells | Animal          |
|----------------------------|----------------|---------------------|-----------------------|-----------------|
| Traditional growth factors |                |                     |                       |                 |
| Bone morphogenetic proteins | BMP-1-18; BMP-3b; BMP-8b | BMP-2; BMP-7        | BMSCs; ESCs; ADSCs; SMSCs | Rabbit; condyl |
| Cartilage derived morphogenetic protein | CDMP-1; CDMP-2; CDMP-3 | CDMP-1             | BMSCs; ADSCs         |                 |
| Transcription growth factor - β(TGF-β) | TGF-β1; TGF-β2; TGF-β3; TGF-β1β2; TGF-β4; TGF-β5 | TGF-β1; TGF-β3 | BMSCs; PSCs; ESCs; ADSC | Rabbit; patella osteochondral model |
| Fibroblast growth factors | aFGF; bFGF | bFGF;FGFG-2,FGF-18 | BMSCs                |                 |
| Insulin-like growth factors | IGF-1;IGF-2 | IGF-1             | BMSCs; ADSCs         | Rabbit; model   |
| Kartogenin (KGN) | KGN | KGN             | BMSCs; SMSCs         | Rabbit; model   |
| Mechano-growth factor | MGF | MGF             | BMSCs                |                 |
| Inorganic particles | Phosphate compounds; Silicate compound et al Dexamethasone | phosphate compounds; Silicate compound et al Dexamethasone | BMSCs; SMSCs |                 |
| Synthetic compound | Dexamethasone | Dexamethasone | BMSCs; ESCs; ADSCs; SMSCs |                 |

Table 1: annotations

ESCsEmbryonic stem cellsPSCsPluripotent stem cellsReference[12,13,31-34,40,42,46,54,56,58,65,73,74].

3.2 Dexamethasone

Dexamethasone is a kind of adrenocortical hormone, which is often used to treat osteoarthritis caused by articular cartilage injury, it has been proved to promote chondrogenesis and osteogenic differentiation of stem cells.[77] Adding dexamethasone into culture medium or covalently bound to hydrogel can induce MSCs to differentiate into osteoblasts, thereby improving osteogenesis.[78]

Florine et al.[79] have shown that in the presence of TGF- beta, dexamethasone can enhance chondrogenic differentiation of MSCs and ESCs and the formation of chondro-related proteins. Dexamethasone is usually used as a supplement of TGF or BMP to further promote cell proliferation and maximize chondrogenesis or osteogenic induction, so as to achieve optimal chondrogenesis or osteogenic effect.[80]

Discussion

The repair of articular cartilage injury is an extremely complex process. Chondrocytes are in a specific "cartilage microenvironment" with complex and diverse internal components, not only a single growth factor, in "cartilage microenvironment", multiple growth factors cooperate to enhance cartilage matrix
synthesis and promote cartilage repair. Recent studies have shown that the effect of combined application of multiple growth factors is significantly better than that of single factor. Previous studies have focused on traditional growth factors, and many studies have studied the role of single growth factors, and there are few studies on the combined application of different growth factors. The synergistic or antagonistic effects of different growth factors, the differences between in vivo and in vitro, and the optimal concentration ratio need further study. At present, most of the researches on growth factors are basic researches, but clinical trials and clinical researches are few, so clinical research is the next key research direction. There is no experimental study on dexamethasone and inorganic particles in vivo at present, and the repair effect and safety of dexamethasone and inorganic particles in vivo need further study.

Conclusions
Despite the continuous progress of surgical technology, the treatment of cartilage injury is still a huge clinical challenge. Although the newly found growth factor has greatly promoted the development of articular cartilage repair, some of the results have been applied in clinical practice, but its specific mechanism is not clear. At present, researchers have focused more on the effects of growth factors on the proliferation of chondrocytes and their effects on chondrocyte morphogenesis, but the signaling pathways that affect growth factors are less concerned. Through in-depth research on its mechanism of action, the potential of growth factors in cartilage repair will be further explored. With the in-depth study of the influence of the interaction between various growth factors on the repair process of cartilage and the influence of external factors on the "cartilage microenvironment", it is possible to develop and use growth factors to treat cartilage tissue damage.

Abbreviations
Matrix-induced autologous chondrocyte implantation (MACI); mesenchymal stem cells (MSCs); autologous chondrocyte implantation (ACI); chondrogenic stem/progenitor cells (CSPCs); embryonic stem cells (ESCs); induced pluripotent stem cells (iPSCs); pluripotent stem cells (PSCs); bone morphogenetic proteins (BMPs); cartilage derived morphogenetic protein (CDMP); Transcription growth factor β (TGF-β); fibroblast growth factors (FGF); insulin-like growth factors (IGFs); kartogenin
(KGN); human mesenchymal stem cells (hMSCs); platelet-rich fibrin (PRF); vascular endothelial growth factor (VEGF); platelet-rich fibrin (PRF); platelet-rich plasma (PRP); Mechano growth factor (MGF).

Declarations

1. **Ethics approval and consent to participate**

Not applicable

2. **Consent for publication**

Not applicable

3. **Availability of data and material**

All data generated or analysed during this study are included in this published article.

4. **Competing interests**

The authors declare that they have no competing interests.

5. **Funding**

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6. **Authors' contributions**

Yu Zhang designed this paper to analyze and interpret data about growth factors in articular cartilage repair. Zishu Chai did the data collection, and Chengcheng Yu, Youcai Wu and Yufu Ou were responsible for the literature analysis. Yu Zhang was responsible for the writing and was the main contributor to the manuscript. Jianxun Wei was responsible for the proofreading and Yu Zhang was responsible for the article. All the authors read and approved the final manuscript.

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8. **Authors' information (optional)**

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Figures
Illustration of approaches to the restoration of cartilage. Abbreviations: matrix-induced autologous chondrocyte implantation (MACI); mesenchymal stem cells (MSCs); autologous chondrocyte implantation (ACI); chondrogenic stem/progenitor cells (CSPCs); embryonic stem cells (ESCs); induced pluripotent stem cells (iPSCs).
Figure 2

Document retrieval flowchart

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