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Epigenetics and Cartilage Regeneration

Samina Hyder Haq, Iqraa Haq, Atheer Ali Alsayah, Abir Alamro and Amani AlGhamdi

Abstract

Regenerative cartilage therapy has great potential for the treatment of debilitating diseases such as osteoarthritis and rheumatoid arthritis. Recent advances in the field of epigenetics have enabled us to understand more clearly the role of micro RNAs, DNA methylations and histone modification in disease progression, as well as its potential role in disease prevention. However, a thorough understanding of the external dietary and environmental factors that could affect the epigenetic events could be the key to unravelling novel therapeutic strategies for these diseases. There is, therefore, a need for identifying certain dietary or environmental factors that could change this downward epigenetics signalling cascade, stop or retard cartilage degradation and promote cartilage regeneration.

Keywords: cartilage regeneration, DNA methylations, epigenetics, therapeutic dietary supplements, DNMT inhibitors

1. Introduction

Articular cartilage is an aneural, avascular, alymphatic specialized fibrous connective tissue which covers the articulating surface of synovial joints. This is characterized by a small number of morphologically distinct populations of chondrocytes, which are primarily responsible for production, organization and maintaining the extensive network of an extracellular matrix. The balance between the hydration of matrix proteoglycans (PGs) and the resistance offered by the extensive network of the fibrous structure of the collagen provides the hydrodynamic load-bearing properties of articular cartilage, which is critical for joint movements and smooth transmission of mechanical compression across the joint. As articular cartilage is originally derived from the hyaline cartilage template, it is also classified as permanent hyaline cartilage. After the original phase of cartilage production, differentiation and resorption and closure of growth plate cartilage at puberty, it remains as a part of bone throughout the adult life. It is divided into four distinct horizontal layers: the superficial, transitional, deep and calcified cartilage layers (Figure 1).

The thin superficial zone protects the deeper layers from shear stress and injury and makes up 10–20% of articular cartilage thickness. This layer is characterized by small flattened disc-shaped chondrocytes, comparatively low proteoglycan content and densely packed layers of uniformly formed collagen fibres, which gives the characteristic hyaline opacity to cartilage. This layer is in direct contact to synovial fluids and is responsible for most of the tensile strength of the cartilage as well as
takes the direct brunt of inflammatory cytokines. It is well documented that the chronic inflammation in joints in osteoarthritis (OA) patients is due to synovial macrophages and high inflammatory cytokines that initiate the aggregenase, MMPs and other destructive enzymes. Immediately below the superficial zone is the middle or transitional layer which provides the functional bridge between the superficial and deep layers. The middle layer comprises of 40–60% of the total cartilage volume. In this layer, the chondrocytes attain a more rounded or spherical shape, the contents of proteoglycans increase, and thicker collagen fibres provide an oblique transitional network intermediate between the tangential superficial and radial deep layers. The deep layer is characterized by relatively mature rounded chondrocytes arranged in longitudinal columns, high proteoglycan contents, the largest diameter collagen fibrils in a radial disposition and the lowest water concentration. This zone represents approximately 30% of the total cartilage volume. The calcified layer is characterized by rounded hypertrophic chondrocytes surrounded by large clear lacunae. This is the area where the chondrocytes reach their terminal hypertrophic stage and the cartilage is ultimately being replaced by bone.

2. Molecular heterogeneity of articular cartilage

The extracellular phase of cartilage, and all connective tissues, consists of collagen fibres and a polysaccharide-rich ground substance. The polysaccharide constituents have been characterized as proteoglycans containing chains of chondroitin 4 sulphate, chondroitin 6 sulphate and keratin sulphate covalently linked to a central core protein [1].

2.1 Types of collagen present in cartilage

Articular cartilage consists of type II collagen as the major fibril-forming collagen, accompanied by lesser quantities of minor collagen which provide the tensile strength and help in maintaining the fine balance of the extracellular matrix. However, little is known about the processing of these minor collagens and their
role in the progression of cartilage degeneration and regeneration. Minor collagens found in articular cartilage along with type II collagen are type VI, IX, X, XI, XII and XIV.

Type VI collagen constitutes only 1–2% of the total collagen in adult articular cartilage and it is mainly rich in the pericellular matrix and involved in the integration and attachment of chondrocytes [2]. In articular cartilage, chondrocytes in the middle and deep layers are embedded in pericellular matrix enriched with a high content of proteoglycans and hyaluronic acid. Increased levels of type VI collagen are found in the experimental model of osteoarthritis (OA) and human OA [3]. Higher levels of type VI collagen found in OA emphasizes its role as a bridge between the extracellular matrix and the chondrocyte surface, thus influencing the signalling pathways from the extracellular matrix into the cells [4].

Type IX collagen makes up 1–5% of the total collagen in adult articular cartilage and 10% in foetal cartilage [5]. It is usually present in close association with type II collagen found in growth plate cartilage and adult articular cartilage [6]. Type IX collagen is extensively crosslinked to type II collagen through oxidation of lysyl residue bonds forming a unique heterofibrillar structure [7]. Type IX collagen is crucial for the maintenance of cartilage matrix and formation of a collagen fibril meshwork. Decreased expression of type IX collagen in the cartilage was thought to render the matrix more prone to mechanical forces and degradation, resulting in the pathogenesis of OA [8].

Type X constitutes about 1% of the total collagen found in articular cartilage [9]. It was revealed that 45% of the total collagen produced by the hypertrophic chondrocytes is type X collagen [10]. Type X collagen, as produced exclusively by hypertrophic chondrocytes, indicated its unique role in mineralization. The hypertrophic chondrocytes synthesized a variety of proteins and enzymes which help in the transition of extracellular matrix from cartilage to bone. Apart from type X collagen, hypertrophic chondrocytes also synthesize a variety of matrix metalloproteinases as well as alkaline phosphatase enzymes, which are not usually secreted by the normal proliferating chondrocytes. As type X collagen has a direct role in mineralization, it has been found to be expressed in human OA especially in the vicinity of lesions, but not in the healthy human articular cartilage [11].

Type XI collagen constitutes 3–10% of the total adult articular and foetal cartilage, respectively [2]. Type XI collagen is normally crosslinked to each other in cartilage, this crosslinking results in the formation of mature type XI collagen with the help of type II and type IX collagen. It has been shown that a mutation in type XI collagen caused an increase in degradation of type II collagen in articular cartilage [12]. Lu et al. observed that immunization of rats with homologous type XI collagen led to chronic and relapsing arthritis with different genetics and joint pathology than arthritis induced with homologous type II collagen [12]. The role of type XI collagen in cartilage collagen fibril formation and assembly is not clear; type XI collagen may regulate cartilage formation and it was the first collagen deposited by mesenchymal stem cells undergoing chondrogenic differentiation [13]. Type XII shares structural homologies with type IX and type XIV collagen [14]. Type XII collagen is implicated in fibril formation, cell adhesion, fibrosis and osteogenesis, and in areas of high mechanical stress, it may serve as a protector of tissue integrity [15]. Type XII collagen is associated with articular cartilage and growth plate cartilage during rat forelimb development and may be important for microenvironment that supports the hyaline cartilage formation [16].

Type XIV collagen is a large nonfibrillar extracellular matrix protein structurally similar to type XII collagen. In cartilage, a population of type XIV exists as chondroitin sulphate proteoglycans (PGs) as it is sensitive to chondroitinase ABC and AC treatments [17]. Its association with other cartilage collagens such as type I, II,
V and VI are reported, but it also interacts with heparin CD44 and cartilage oligomeric matrix protein [18]. It is found in areas of high mechanical stress similar to type XII collagen, suggesting its role in fibrillogenesis and maintaining the integrity and mechanical property of the tissue.

2.2 Types of PGs in different layers

Proteoglycans have the highest concentrations in the intermediate zone and lowest in the superficial and deep zones. Small PGs comprise of less than 10% of the total PG content in the cartilage matrix. Most are aggrecans (large PGs) with approximately 150 GAG chains (chondroitin sulphate and keratin sulphate and both O-linked and N-linked oligosaccharides attached). The GAGs are heterogeneously distributed along the protein core, with CS-rich and KS-rich regions, respectively. The protein core itself is heterogeneous with three globular regions. Aggrecan varies significantly in length, molecular weight and composition with the amount of KS-rich molecules and ratios of chondroitin 6-sulphate and chondroitin 4-sulphate increasing throughout development and ageing. Most aggrecans in cartilage are attached to a hyaluronic (HA) molecule via a globular (HABR) region; this binding was stabilized by a link protein. Several hundred aggrecans are attached to a single HA core molecule, the latter being a non-sulphated disaccharide chain up to 4 μm in length. PGs are closely associated with collagen fibrils and are thought to be involved in their structural organization and maintaining their compressive stiffness.

There is now conclusive evidence of the fact that OA is not simply due to wear and tear and a result of ageing; but in numerous studies, it has been reported that early onset of OA is due to activation of inflammatory response. These inflammatory responses could be due to increased oxidative stress to the tissues, resulting in initiation of catabolic enzymes and factor that actively breakdown the major extracellular matrix components of cartilage, namely type II collagen, and the proteoglycans and aggrecan.

3. Control of chondrogenesis

The commitment of mesenchymal cells to the chondrogenic lineage is the key event in bone formation. Work over the past few decades, using both in vivo and in vitro systems, has identified a number of signalling and transcription factors as well as cell shape that regulates the progressive change in chondrocyte phenotype, from their initial induction to their terminal fate. The disruption of these finely tuned pathways for chondrocyte maturation can result in skeletal pathology. A thorough knowledge of these signalling pathways would help us to identify the factors that maintain chondrocyte proliferation and differentiation. Some of the major signalling pathways are described below.

3.1 Bone morphogenic protein signalling

Bone morphogenic proteins (BMPs) are identified as positive regulators of chondrogenesis and endochondral ossification. BMPs are a member of the transforming growth factor beta (TGFβ) superfamily that has wide-ranging biological activity, ranging from cellular regulation of proliferation, apoptosis, differentiation and migration [19, 20]. BMP signalling is mediated by their receptors BMPR1a, BMPR1b and BMPR2, leading to the SMAD signalling pathway [19]. In cartilage, it initiates cartilage synthesis and decreases the activity of catabolic cytokines such as IL-1, IL-6, IL-8, MM1 and MM13 [21, 22]. Though there are several members of
Bone morphogenic protein (BMP) growth factors, most promising among them in the treatment of OA is BMP-7, which promotes the cartilage-specific extracellular matrix proteins such as collagen II and VI, decorin, fibronectin and hyaluronate (HA) by upregulation of hyaluronan synthase [23, 24]. In experiments when it was applied to other types of cells in knee, BMP-7 has shown to increase Extracellular matrix (ECM) in synovial and bone marrow-derived Mesenchymal Stem cell (MSC), both alone and in combination with TGFβ [25]. This profound anabolic effect of BMP-7 is due to its regulatory properties of modulating other growth factors such as insulin-like growth factor 1 (IGF1 and fibroblast growth factor (FGF)) [26]. Despite having anabolic activity, BMP-7 has not shown to induce chondrocyte hypertrophy or other changes in the chondrocyte phenotype, nor did BMP-7-treated animal knee display any proliferation of fibroblast or osteocyte [25]. These properties make it a promising therapy for OA.

3.2 Transforming growth factor (TGF) signalling pathway

TGFβ is a cytokine secreted by many cells; it plays an important role in cell proliferation, differentiation, development, apoptosis, tissue homeostasis and the immune system. Signalling occurs through SMAD pathways. TGFβ1 is shown to be involved in chondrocyte proliferation and remarkable reduction of catabolic activity of IL1 and TNF [27]. Studies have shown a significant enhancement of cartilage repair with the application of TGF-β1 in scaffold applied to defect, and in human MSC transfected with TGF-β1 gene via an adenovirus [28, 29]. Numerous human trials are underway for the treatment of different stages of OA with the injections of TGF-β1 in the knee, which showed TGF-β1 as a promising therapy.

3.3 Fibroblast growth factor signalling pathway

Fibroblast growth factor (FGF) family plays an important role in human embryonic development, cell growth, morphogenesis, tissue repair, tumour growth and invasion. FGFs are heparin-binding proteins and interact with heparan sulphate proteoglycans on the cell surface for signal transduction. Vincent et al. proposed that in articular cartilage, the chondrocytes are surrounded by a pool of FGF-2. This mediated the chondrocyte activation on cartilage loading and release of FGF-2 in response to injury. They proposed that FGF-2 antagonizes the PG degradation by IL-1 or other catabolic stimuli, thus it has an anti-catabolic chondroprotective role [30]. However, the role of FGF-2 in the production of ECM is controversial and its role as pro-catabolic or anti-catabolic is debatable. Furthermore, FGF-2 has been shown to suppress type II collagen and PG synthesis and promote the expression of aggregenase and TNF-α receptors [31, 32]. FGF-18 signalling through FGFR3 promotes chondrocyte proliferation at embryonic stages. When development is complete, the same receptor signalling suppresses chondrocyte proliferation and prevents chondrocyte differentiation hypertrophy [33, 34]. FGF-18 has also shown to exhibit the ability to stimulate type II collagen and PG synthesis, which makes it a promising therapy for OA.

3.4 Connective tissue growth factor

Connective tissue growth factor (CTGF) is an ECM-associated heparin-binding protein, which plays an important role in cellular proliferation, migration, adhesion, survival and synthesis of ECM proteins. CTGF has shown to play an important role in skeletal tissue and initial chondrocyte proliferation and differentiation in growth plate cartilage [35]. Nishida and colleagues demonstrated that local
administration of recombinant CTGF gelatin hydrogel stimulated cartilage repair in rat model [36]. Other studies showed that the bone marrow-derived mesenchymal stem cells when transfected with CTGF provided hyaline-like cartilage regeneration similar to normal cartilage in a rabbit model of focal articular cartilage defects [37]. However, further studies are needed to elucidate the critical role of CTGF for the protection and regeneration of cartilage.

3.5 Insulin-like growth factor (IGF)

IGF-I and IGF-II both were reported to control the cartilage destruction [38]. IGF-I is a known anabolic factor for chondrocytes and thought to regulate the skeletal development in the embryo [39]. Although IGF-I has been reported as being involved in chondrocyte proliferation and maturation, its exact role in OA has not been clearly known as it was found that the expression of IGF-I was upregulated rather than downregulated in synovial fluids and in articular cartilage [40]. However, the role of IGF-II in combating inflammatory response in OA was found to be more promising and ideal for cartilage regeneration. It has been reported that in the presence of IL-1β, IGF-II significantly inhibited MMP expression and promoted cartilage production in normal human chondrocytes. IGF-II has also shown to have a similar effect on OA chondrocyte, which expresses high levels of IL-1β mRNA [41]. The role of IGF-II was reported to be more chondroprotective and maintaining the extracellular matrix and preventing its destruction in adverse conditions.

4. Cell signalling in chondrogenesis

Gene expression changes during different stages of endochondral ossification. The immature chondrocytes in the resting zone express the transcription factors Sox 5, Sox6, Sox9 and the structural protein type II collagen and aggrecan. The pre-hypertrophic zone is characterized by the presence of parathyroid receptor 1(PTH-1R) and Indian hedgehog expression (Ihh). The next stage goes into the early hypertrophic zone, which is characterized by type X collagen and alkaline phosphatase enzyme expression, and, subsequently, the reduced amount of type II collagen and reduced expression of Sox5, Sox6 and Sox9 transcription factors. Finally, the chondrocytes proceed to their final phase of a late hypertrophic stage, which is characterized by the expression of vascular endothelial growth factor A (VEGFA), matrix metalloproteinase 13(MMP13) and osteopontin. These changes in gene expression herald the cartilage ECM being replaced by bone.

Wnt signalling is important for many developmental processes. It has been shown that activation of Wnt signalling promotes osteoblast differentiation but inhibits chondrocyte differentiation of MSC [42, 43]. Wnt signalling acts through β-catenin to promote chondrocyte hypertrophy and reports suggested that genetic inactivation of β-catenin increased Sox9 expression both in the intramembranous bone formation and endochondral ossification [44, 45]. It was also reported that osteoblast precursor lacking β-catenin expression can develop into chondrocytes [42]. Wnt signalling is also important for proper orientation of chondrocyte column in growth plate cartilage.

Ihh signalling is a key regulator of pre-hypertrophic and early hypertrophic chondrocytes. Ihh signalling directly affects chondrocyte proliferation, premature chondrocyte hypertrophy and failure of osteoblast development and endochondral bone.

Runx2 and Runx3 are members of the Runx transcriptional factors family important for chondrocyte hypertrophy. Several studies demonstrated that ectopic
expression of Runx2 in immature chondrocytes leads to the expression of hypertrophic markers such as COLX α1, MM13 and VEGF [46–48].

As cartilage is an avascular tissue and its nutritional needs are met by surrounding synovial fluids, chondrocytes are adapted to survive in low oxygen levels and they secrete hypoxia-inducible factor 1 (HIF-1) which insures its survival and maintenance in low oxygen tension. Synthesis of type II collagen and aggrecan is upregulated in low oxygen levels, and also, it is associated with the rounded chondrocytic morphology. In the presence of high oxygen tension, chondrocytes become more spindle shaped. HF-1 also showed inhibition of type I collagen synthesis by inhibiting its promoter activity [49].

5. Epigenetic control of chondrogenesis

In the growth of long bone formation, the chondrocyte passes through discrete stages of proliferation, maturation, hypertrophy, calcification and apoptosis, so it offers a very good model of cellular differentiation and ageing. The detailed underlying molecular mechanisms that drive these changes are still not fully known, but epigenetic modifications are thought to play a pivotal role in the differentiation of chondrocytes. Epigenetic changes include DNA methylation, histone modification and microRNAs (miRNAs).

5.1 DNA methylation

DNA methylation involves the addition of a methyl group to a DNA at CpG dinucleotide, to convert cytosine to 5-methylcytosine. CpG islands are usually clustered near the promoter in about 30% of the gene. Methylation of these sequences results in silencing of these genes, and vice versa, hypo-methylation results in expression of the respective genes. DNA methylation factors are established and modified according to the environmental factors by three DNA methyltransferases (DNMT1, DNMT3a and DNMT3b). Earlier studies using chick embryos indicate the possible role of methylation in gene expression of type I and type II collagen in chondrocyte differentiation and dedifferentiation [50]. In our studies on chick chondrocytes in culture, we noticed a strong correlation of chondrocyte morphology to DNA methylation status as shown in Figure 2. The chondrocytes when treated with DNMT inhibitor 5-aza-2’deoxycytidine exhibit fibroblastic morphology and express type I and type X collagen with an upregulation of alkaline phosphatase enzyme [51]. Two CpG sites within the type X collagen promoter appear to be demethylated during MSC differentiation into chondrocyte morphology [52]. Recently, it was demonstrated that Wnt signalling caused both repressive chromatin mark (H3K27me3) and DNA methylation over the SOX9 promoter and that Wnt-induced irreversible silencing of Sox9 gene requires DNA methylation of this locus that is specifically countered by FGFR signalling [53]. FGF blocks the recruitment of DNMT3a to the SOX-9 promoter by inducing the interaction and phosphorylation of DNMT3a by extracellular kinases ERK 1and ERK 2. Similarly, a number of studies indicated the control of Runx2 promoter activation by methylation. The number of MMP promoters show decreased methylation at single CpG island in OA cartilage as compared to normal.

5.2 Histone modifications

Gene regulation is also controlled through the close packaging of eukaryotic DNA into nucleosomes. Nucleosomes are thought to be repressive for
transcription; but through the post-translational modification of histones such as acetylation, phosphorylation, methylation and ubiquitination, this inhibition can be regulated.

Acetylation is mediated through acetyltransferase (HAT) and occurs on specific lysine residues on the N-terminal tails of histones, loosening the histones: DNA interactions, thus employing the access of transcriptional factors to the DNA. Deacetylation is of two types, one that requires Zn-catalysed deacetylation (HDAC) and the sirtuin deacetylase that requires NAD⁺, and removes these acetyl groups resulting in hypo-acetylation. Numerous transcriptional activators or repressors recruit HDAC and HAT activity.

Histone methylation is important for the formation of active and inactive genomic regions and is associated with transcription activation and silencing. Methylation of histone tails of lysine and arginine residues is catalysed by histone methyltransferase (HMT) and protein arginine methyltransferase (PRMT) which can add one or more methyl groups to regulate transcription [54]. Although histone methylation is more dynamic than DNA methylation, some specific histone methylation is tightly regulated and maintained through DNA replication. HDAC can block cytokine-induced PG release and cartilage resorption in cartilage explant model indicating that HDAC activity is important for the catabolic activity of chondrocytes [55, 56].

5.3 Micro RNA

MiRNA is a small 20–23 base pair-long cytoplasmic RNA that regulates post-transcriptional gene expression through binding to target mRNA. This
interaction of miRNA with the target mRNA results in degradation of mRNA, thus suppression of translation. The first studied miRNA in cartilage was miR-140, which was first identified as cartilage restricted in developing zebrafish [57]. In humans, the expression of miR-140 increases during chondrogenesis and is more abundant in articular cartilage, but its expression is reduced in OA [58]. It has also been reported that the expression of miR-140 is regulated by the cartilage-specific master transcriptional factor Sox-9 in zebrafish and mammalian cells [59].

6. Epigenetics as a future therapy for cartilage regeneration

Articular cartilage has a relatively high incidence of damage due to several factors such as injury, trauma and inflammation. The inflammatory markers could induce a number of MMPs, which could degrade the ECM, as the cartilage has a limited ability to repair and regenerate, resulting in a total loss of cartilage tissue. The destruction and loss of articular cartilage is also central to the development of OA. The research work over the past few decades confirms that epigenetics plays a pivotal role in the phenotypic modulation that articular chondrocytes undergo during OA. Epigenetics changes the normal chondrocytes to ‘altered’ chondrocytes that overexpress the cartilage-degrading proteins or enzymes such as collagenases and aggregenase and inflammatory mediators. This disruption in homeostatic balance between the matrix production and ECM destruction results in the progression of OA. There is a direct pathological loop that involves inflammation and epigenetic modifications, which accelerates disease progression. Until now, no detailed global methylation analysis has been performed in the pathogenesis of OA. Low penetrance polymorphism in the population partly due to epigenetic modification is the reason for limited data generation to aid in the identification of genes responsible for the genetic susceptibility to OA. A number of inflammatory genes have been identified which are controlled through epigenetics and are directly involved in the pathogenesis of OA (Table 1).

6.1 Future prospects in cartilage regeneration

MCS is becoming a more popular source of cells for cartilage regeneration due to in vitro expansion without running the risk of losing their phenotype. However, MSC tends to develop hypertrophic phenotype and further differentiation into the endochondral bone formation. It is becoming more crucial to carefully examine the detailed molecular and epigenetic events that lead the transformation of a chondrocyte to its terminally differentiated pathway. There is a growing need to develop strategies to control chondrocyte hypertrophy and be able to arrest the chondrocyte at one desirable phenotypic stage that helps to maintain the cartilage-specific ECM as described in Figure 3. With the current epigenetic knowledge, it is possible to identify a number of epigenetic factors as listed in Table 1 that can make cartilage regeneration possible.

Other option in cartilage regeneration is the application of hydrogel through injection or through arthroscopy. These hydrogels are capable of controlled release of chondroinductive and chondroprotective drugs [60–62]. These cell-laden hydrogels can be combined with other types of solid scaffolds such as collagen sponge, decellularized cartilage as well as synthetic scaffolds of polyglycolic acid for cartilage repair and clinical applications.
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Table 1. Major Epigenetic events remodelling the regeneration of Cartilage.
7. Conclusion

In summary, although there has been progress made in identifying factors outlining OA disease progression, a more detailed analysis of the factors surrounding the epigenetics should be conducted in order to reveal any potential therapies. The control of chondrogenesis via bone morphogenic protein signalling, transforming growth signalling, fibroblast growth factor signalling, connective tissue growth factor and insulin-like growth factor all play important roles in chondrocyte formation and destruction. This in addition to the fact that cellular mechanisms controlled by gene expression and epigenetic changes including DNA methylation, histone modification, and microRNAs can all help us gain an understanding of regenerative cartilage therapies.

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Conflict of interest

There is no conflict of interest to declare.
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