初診時の血清COMPが2年間におけるOA進行を予知するマーカーとして有用と考えられた。

E．結論

OAにおいてもRAと同様に血清マーカーが病態の客観的評価法として有用であるが、単関節の評価として用いる際には他関節や脊椎椎間関節の影響も十分に考慮する必要がある。関節マーカーは現時点ではOA診断、評価の補助的手段とみなされているが、簡便性においては本法に優る手法はなく有病率の高いOAに対する有用性は高い。単一のマーカーの能力には限界があるが、反映する病態の異なる複数のマーカーを組み合わせることによってOA発症や進行の予知、病態判断もより正確に可能になると考えられる。以上のOA患者群についての縦断的な検討に加えて近日中に地域コホートの検体について測定を行い、研究を進める予定である。

F．健康危険情報

特になし

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H．知的財産権の出願・登録状況

（予定を含む。）

1. 特許取得

なし

2. 実用新案登録

なし

3. その他

なし

Ⅲ．研究成果の刊行に関する一覧表

別紙2

研究成果の刊行に関する一覧表

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6.

Anabolic Mediators of Cartilage Healing

Naoshi Fukui and Linda J. Sandell

6.1 Introduction

Although osteoarthritis (OA) is essentially a degenerative disease, anabolic activity of chondrocytes is significantly upregulated. Enhanced anabolism in OA chondrocytes was first reported more than 30 years ago [17,41, 47] and has since been confirmed by many studies. Often referred to as OA hyperanabolism, upregulation of synthetic activity is not limited to cartilage, but also affects other tissues inside and around the joint. For example, formation of osteophytes and sclerotic changes of the subchondral bone are pathologic events that symbolize vigorous anabolic activity.

Modern techniques have given us a more comprehensive idea about the metabolic changes in OA. Proteomic analysis has confirmed that synthesis of type II collagen is enhanced in OA cartilage [35], and microarray analysis has provided an overall picture of the metabolic changes that take place in the disease process [7]. To date, the significance of anabolism in the pathology of OA is not well understood.

Due to the dramatic changes in the metabolic activity of the chondrocytes in OA cartilage, the significance of anabolism in the pathology may be underestimated. Just like many other phenomena, anabolism in OA could have two faces. The enhanced synthesis of cartilage matrix components may prevent disease progression by counteracting catabolic events and initiating a repair process. On the other hand, the induction of pathologic proteins and possible disturbance in proper matrix synthesis observed in the disease may promote disease progression. This chapter provides an overview of the anabolism in OA, with emphasis on recent progress.

6.2 Anabolism in Osteoarthritis Cartilage

The primary components of articular cartilage are collagen and protoglycan. In cartilage, types II, IX, and XI collagens build up the fibrillar network that confers tensile strength to the matrix. Among the collagens, type II collagen is by far the most dominant, comprising more than 90% of total collagen [38]. The enhanced expression of type II collagen in OA is well known. The first evidence of an increase in type II collagen synthesis was the report of higher incorporation of [^{3}H]proline into OA cartilage [41]. Later, an antibody against the C-terminal propeptide of type II procollagen (CPII) was used to evaluate collagen synthesis [55]. The propeptide is cleaved and metabolized soon after collagen synthesis. Therefore, the presence of a CPII in OA cartilage indicates that the collagen is synthesized at a rate much higher than normal. We have recently compared the expression of type II collagen messenger RNA (mRNA) in OA and normal cartilage, analyzing regional differences with the aid of laser-captured

microdissection, a technique that permits small regions of cartilage to be isolated. The study revealed that the expression level of type II collagen mRNA differs considerably in different regions, and can be more than 20 times higher in OA than in normal cartilage [27,28] (Fig. 6.1).

Although types IX and XI collagen are critical for the collagen framework, it is not known whether their structure is altered in OA. Their synthesis is elevated [7,9], as is their gene expression [27,28]. Type VI collagen, a minor component in articular cartilage, occurs primarily in the pericellular matrix that surrounds the chondrocytes and may play a role in the maintenance of the pericellular microenvironment [34,61]. Type VI collagen is more highly expressed and constitutes a larger fraction in OA cartilage compared to normal cartilage from age-matched donors [34,64,67]. However, the distribution and organization of type VI collagen is significantly altered in OA. These changes in extracellular matrix may account for the altered chondrocyte metabolism in the disease.

Aggrecan is the predominant proteoglycan in articular cartilage. Aggrecan interacts with hyaluronic acid and link proteins to form large aggregates that endow the cartilage matrix with compressive stiffness. The expression of aggrecan is upregulated as OA progresses. Enhanced mRNA expression was shown by in situ hybridization [3,5], and the presence of new aggrecan molecules was demonstrated by the analysis of OA cartilage extracts [66]. The synthesis of link protein is also enhanced in OA [18], as is the expression of small proteoglycans, such as decorin, biglycan, fibromodulin and lumican, the large proteoglycan, perlecan [5,13,18,19,44,74], and some noncollagenous proteins, such as tenascin, cartilage oligomeric matrix protein (COMP), cartilage intermediate layer protein (CILP), and matrilin-3 [7,44,63].

Enhanced expression is also observed for genes that are expressed in normal cartilage at very low levels or not at all. Gene expression of types I and III collagens results from phenotypic change of chondrocytes to what could be considered a fetal phenotype [2,3]. Type II collagen is synthesized not only as the chondrocyte-characteristic type IIB splice form, but also the noncartilage splice form, type IIA [6]. Fibronectin accumulation in OA cartilage may be a repair response [37]. In OA cartilage, some chondrocytes undergo hypertrophic change as a result of the de-repression of genes for type X collagen, annexin VI, syndecan 3, osteocalcin, osteonectin, and osteopontin [62].

Osteoarthritic chondrocytes present diverse metabolic changes, stemming, at least partly, from considerable regional variations in different sites of OA cartilage [3,5]. Quantitative analysis of regional differences [27,28] has shown that expression of cartilage matrix genes is upregulated in the deeper cartilage zones, but their expression is considerably reduced at the surface of degenerated cartilage. This is especially true for aggrecan. Cells close to the

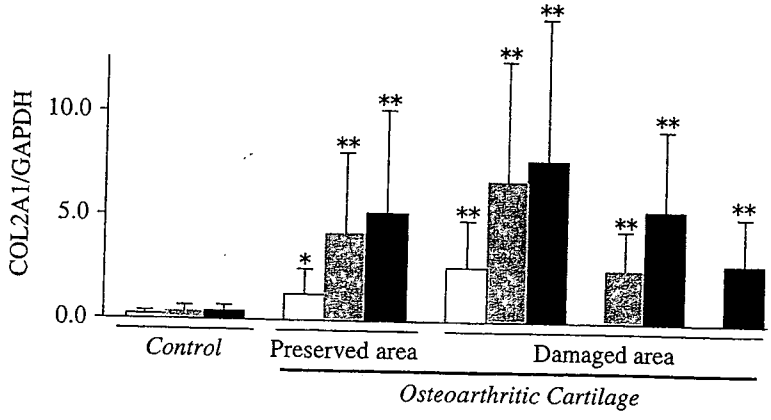

Figure 6.1. Expression of type II collagen mRNA in normal and OA cartilage. Cartilage obtained from normal and end-stage OA knee joints was divided into three cartilage zones by laser microdissection. Total RNA was extracted, cDNA was synthesized, and the expression of COL2A1 was evaluated in respective zones together with that of glyceraldehyde-3-phosphate dehydrogenase (GAPDH). In each OA joint, cartilage was harvested from several sites with and without macroscopic degeneration, and the samples from degenerated areas were assigned to three categories according to the number of cartilage zones remaining at the site. In the damaged cartilage category, patients are grouped according to which zones were present. The expression levels of superficial, middle, and deep cartilage zones are shown by open, shaded, and solid bars, respectively. *, $p < .05$, and **, $p < .01$ compared with the corresponding zone in normal cartilage.

degenerated surface, however, tend to express pathologic genes. Type X collagen is expressed mostly at the fibrillated area of OA cartilage, with induction of type III collagen more obvious in the degenerated regions. Evaluation of the metabolic changes in OA, therefore, must consider regional differences, particularly because chondrocytes in the degenerated regions seem more susceptible to phenotypic alteration.

6.3 Significance of Osteoarthritis Hyperanabolism in Disease Progression

As a result of the higher metabolic rate of OA chondrocytes, newly synthesized matrix may constitute a significant proportion of cartilage matrix. This is evidenced by elevated quantities of CPII, with the amount of CPII directly related to the content of total type II collagen [55]. A recent study based on an evaluation of racemization has provided direct evidence for the replacement of type II collagen in OA cartilage. In articular cartilage, the turnover of matrix molecules is exceptionally low, and for type II collagen, the half-life in cartilage is estimated to be over 100 years [48]. During its long sojourn in the matrix, the collagen molecule undergoes changes and modifications, with racemization; conversion of the L-amino acid to the D-enantiomer is one such change. Because racemization is fastest in the case of aspartic acid, residence time is often estimated by the accumulation of D-aspartic acid. In articular cartilage, the ratio of L- to D-aspartic acid in type II collagen molecule increases with age [80], but this process is slowed or stopped altogether in OA-affected cartilage [59]. Consequently, a substantial fraction of type II collagen molecules in OA cartilage would have to be synthesized after the onset of the disease.

Osteoarthritic cartilage also contains newly synthesized proteoglycan molecules as evidenced by the uptake of [^{35}S]sulfate into cartilage matrix [75]. Subsequent studies have revealed the details of aggrecan turnover. In normal cartilage, the molecular size of aggrecan decreases with age due to the accumulation of truncated molecules [11]. In OA, the size of aggrecan molecules increases as the disease progresses [66]. The change is accompanied by an increase in 846 epitope, characteristic of fetal tissue aggrecan, and considered to be a marker for newly synthesized aggrecan molecules [19,32,60,66]. In fact, the epitope was found on the largest aggrecan molecule in the tissue [66]. Osteoarthritis cartilage must therefore contain a large quantity of new aggrecan molecules, an amount that will increase further as the disease progresses. Small proteoglycans are also synthesized and incorporated into OA cartilage matrix. Other molecules that occur in OA cartilage in increased amounts include decorin, biglycan, fibromodulin, and lumican [18,19].

It seems certain that OA cartilage contains many matrix molecules that have been synthesized in the course of disease progression. The question then arises as to whether the newly synthesized cartilage has functional properties equal to those of normal cartilage. If not, the new molecules may facilitate rather than hinder the disease process. Several studies have suggested that the matrix synthesized in OA cartilage is indeed different from that of normal tissue [2, 62] and that the presence of these proteins may change the quality of matrix because its assembly has been altered. One report called attention to the possibility that the induced type III collagen may copolymerize with type II collagen and thereby impair fibril assembly [4].

The composition of the collagen framework, comprised of type II collagen, together with types IX and XI collagen, may be altered in OA cartilage. To evaluate the repair capacity of OA chondrocytes, we have compared the expression of six genes that encode the three types of collagen in OA and normal cartilage with the aid of laser-captured microdissection [27,28]. The expression of all six genes was found to be enhanced in OA cartilage, whereas the expression of types IX and XI collagen was reduced in OA cartilage, when compared to age-matched normal cartilage.

In the degenerated regions of OA cartilage, the ratio of Col9a1 to Col2a1 was less than one-third that in control cartilage (Fig. 6.2). Analysis of human hereditary diseases and gene-mutated mice has shown what is the proper level of type IX and type XI collagen expression necessary to maintain the integrity of articular cartilage [56]. Our observation indicates that the

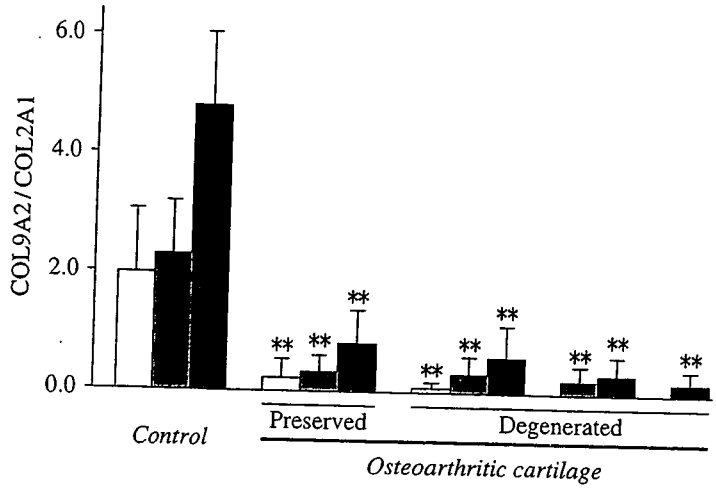

Figure 6.2. Expression ratio of type IX and type XI collagen relative to type II collagen in normal and OA cartilage. Cartilage was obtained by cartilage layers from normal and OA knee joints as described for Figure 6.1, and the expression of COL9A2 and COL11A1 was evaluated by real-time polymerase chain reaction (PCR) together with that of COL2A1. The expression ratio was obtained between type IX or type XI collagen and type II collagen, and compared between normal and OA cartilage in respective cartilage zones. The expression levels of superficial, middle, and deep cartilage zones are shown by open, shaded, and solid bars, respectively. **, $p < .01$ compared with the corresponding zone in normal cartilage.

collagen composition synthesized in OA cartilage may not have normal functional properties due to the paucity of minor collagens.

Collagen synthesized in OA cartilage may be altered by still another mechanism. Previous work on human cartilage revealed that the ratio of the pepsin-soluble fraction of collagen is significantly increased in OA cartilage, compared with normal tissue [67]. To test the hypothesis that this could be due to a reduction in crosslinking, we examined the expression of lysyl oxidase, a primary enzyme for crosslink formation. Our preliminary data have shown that the expression level of this enzyme is reduced in OA cartilage, notwithstanding the obvious upregulation of other collagen genes (N. Fukui, unpublished observation). Reduced crosslinking, therefore, may be another cause of the fragility of the collagen framework.

Changes in proteoglycan structure have been observed in OA. The aggrecan molecule synthesized in OA tends to have more chondroitin-4-sulfate [19,47,66], although the chain lengths of the chondroitin sulfate are unchanged [66]. Changes are also found in other proteoglycan molecules. The core proteins of small proteoglycans are often found without glycosaminoglycan [19], a change, however, that may not be the result of altered synthesis, but rather of proteolytic degradation. Even though there is a general increase in expression in OA cartilage, the degree of upregulation of the various proteoglycans differs considerably [7,18]. The imbalance of small proteoglycan expression may have some influence on the quality of the cartilage matrix. It therefore seems clear that matrix synthesis in OA cartilage differs considerably from that in normal tissue. Why OA progresses in spite of vigorous anabolism in the affected cartilage is not known; it could be due to matrix failure.

6.4 Disease Progression, Anabolism, and the Difference in Anabolic Response Between Joints

Notwithstanding the various animal models of OA, the disease is still best studied in human samples, to which there is, unfortunately, limited accessibility. Samples of end-stage OA are relatively easily obtained in the course of total joint replacement, but it is rare that one can obtain samples of early or progressing stages. Yet, in the early phase of the disease, metabolic activity of the chondrocytes may be considerably different from that in the late stage. Microarray analysis has revealed that type II and type VI collagens are not upregulated until the late stage of the