MINI-REVIEW

The minor collagens in articular cartilage

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ABSTRACT

Articular cartilage is a connective tissue consisting of a specialized extracellular matrix (ECM) that dominates the bulk of its wet and dry weight. Type II collagen and aggrecan are the main ECM proteins in cartilage. However, little attention has been paid to less abundant molecular components, especially minor collagens, including type IV, VI, IX, XI, XII, XIII, and XIV, etc. Although accounting for only a small fraction of the mature matrix, these minor collagens not only play essential structural roles in the mechanical properties, organization, and shape of articular cartilage, but also fulfil specific biological functions. Genetic studies of these minor collagens have revealed that they are associated with multiple connective tissue diseases, especially degenerative joint disease. The progressive destruction of cartilage involves the degradation of matrix constituents including these minor collagens. The generation and release of fragmented molecules could generate novel biochemical markers with the capacity to monitor disease progression, facilitate drug development and add to the existing toolbox for in vitro studies, preclinical research and clinical trials.

KEYWORDS collagen, biomarker, arthritis

ARTICULAR CARTILAGE

Articular cartilage is the most widespread load-bearing cartilage in adults. It is a highly specialized and mechanically resilient connective tissue found on the surface of subchondral bone in diarthrodial joints. Cartilage contains specialized cells called chondrocytes. These cells occupy 1%-3% of the total tissue volume in fully developed tissue and their surrounding extracellular matrix (ECM) is a complex network made up of water, collagen, proteoglycans, and other noncollagenous proteins. Other four types of cartilage are fibroelastic cartilage, fibrocartilage, elastic cartilage, and epiphyseal cartilage.

COLLAGENS

Collagens are the most abundant family of ECM proteins, which account for two-thirds of the dry mass of adult articular cartilage (Eyre, 2004). Numerous collagen subtypes have been identified in articular cartilage, such as type II, IX, X, XI, VI, XII, and XIV collagen (Van der Rest, 1987). Articular cartilage collagen fibrils mostly consist of type II collagen accompanied with a lesser amount of minor collagens, which provide cartilage with tensile strength and contribute to the physical properties of the mature matrix (Heinegård and Saxne, 2011; Ichimura et al., 2000). However, little is known about the processing of these minor collagens and how their turnover is affected by the progression of osteoarthritis (OA). New knowledge about turnover of those minor collagens will lead to deeper understanding of the dynamics of cartilage turnover, thereby facilitating the development of novel biomarkers that reflect joint health and drug discovery in OA.

In this review, we present an outline of minor collagens in articular cartilage, focusing on the link between these extracellular matrix proteins to OA. Finally, we elaborate on how knowledge of these associations can be used to develop new biomarkers, which provide insight into the
translational medicine of OA. Such biomarkers also indicate the effect of a drug on cartilage metabolism and the mode of action. Even though a number of biomarkers already exist, there is a clear medical need for new biomarkers for personalized healthcare (PHC) in OA, biomarkers that more accurately reflect biological activity in different phenotypes of the disease as well as serve as tools in diagnosis and prognosis. This may assist in identification of patients that are in foremost need of treatment and may respond optimally, with the highest efficacy and lowest safety concerns, to a given treatment. Moreover, biomarkers aid pharmaceutical companies develop better targeted therapeutic strategies for selected subpopulations of OA patients. Biomarkers can also enable early decision-making and benchmarking. It is becoming increasingly clear, that one simple marker is insufficient for improved diagnosis, and thus multiple makers that reflect different aspects of the pathophysiology and clinical phenotypes may most likely be needed in combination (Kraus et al., 2015; Karsdal et al., 2014; Henrotin et al., 2016).

The various types of minor collagens found in articular cartilage are listed in Table 1 and schematically illustrated in Fig. 1.

DISTRIBUTION, STRUCTURE, AND FUNCTION OF MINOR COLLAGENS

Type VI collagen—a microfibrillar collagen

Although it only makes up 1% of total collagen in adult articular cartilage (Eyre et al., 2006), type VI collagen is mainly enriched in the pericellular matrix (PCM), involving the attachment and integrity of chondrocytes. Type VI collagen is able to bind to a wide variety of ECM proteins, including type II collagen (Bidanset et al., 1992), type XIV collagen (Brown et al., 1994), matrilin-1 (Wiberg et al., 2001), and decorin (Bidanset et al., 1992), thereby forming a network that anchors the chondrocyte to the PCM in articular cartilage. Due to the high affinity with numerous ECM components and cell membrane (Bidanset et al., 1992; Wiberg et al., 2001), type VI collagen has been hypothesized to play important roles in mediating cell–matrix interactions and intermolecular interactions (Pfaff et al., 1993).

The precise role of collagen VI has not yet been clearly defined. However, type VI collagen may serve as a filter or transducer for biochemical and/or biomechanical signals from the cartilage ECM. Type VI collagen with lower molecular weight was evident in the pathological osteoarthritic dogs sacrificed 3, 5, and 7 months after surgery in comparison to the controls (McDevitt et al., 1988). It indicated that degradation products of larger type VI chains might be significant in the role this molecule plays in osteoarthritis. The type VI collagen-deficient mice (Col6a1) exhibited accelerated development of hip osteoarthritis, a delayed secondary ossification process, and a loss of the stiffness of the articular cartilage PCM (Alexopoulos et al., 2009). Type VI collagen demonstrated an important role in regulating the physiology of the synovial joint. In another context, the deficiency of type VI collagen in mice resulted in decreased stiffness and increased chondrocyte swelling (Zelenski et al., 2015). These findings suggest that type VI collagen has essential roles in transmitting mechanical and osmotic stresses from the ECM to the chondrocytes (Zelenski et al., 2015). The soluble type VI collagen was reported to promote chondrocyte proliferation under both healthy and osteoarthritic conditions. However, proliferation was not observed upon treatment of immobilized type VI collagen in chondrocytes, indicating that soluble type VI collagen can be applied for autologous chondrocyte implantation to expand chondrocytes (Smeriglio et al., 2015). It was reported that a variant in the human Col6a4 gene is associated with knee OA in Japanese and Chinese populations, but not found in a Korean population (Lee et al., 2013) nor in European OA individuals (Wagener et al., 2009). The contradictory findings could be explained by either the ethnic differences in OA susceptibility genes or the differences of criteria in OA selection.

Type IX, XII, XIV, XVI, and XXII collagen—the FACIT collagens

These collagens are members of the fibril-associated collagen with interrupted triple helix (FACIT), which do not form fibrils by themselves, but are associated with the surface of various fibrils.

Type IX collagen

Type IX collagen simply makes up 1%–5% of total collagen in adult articular cartilage and 10% of that in fetal cartilage (Eyre et al., 2006). It is usually found in tissues containing type II collagen, like growth plate cartilage and adult articular cartilage (Eyre et al., 1987). It forms the unique heterofibril network in the matrix of cartilage via association with type II and type IX collagen (Wu et al., 1992). Type IX collagen is extensively cross-linked with type II collagen through the lysyl oxidase mechanism (Wu et al., 1992). Eyre et al. discovered that the covalent cross-linking formed at the N-telopeptide of α1(II) chain and the COL1 in all three chains of type IX collagen in both human and bovine cartilage (Eyre et al., 2004). Additionally, Eyre et al. also observed the binding inter type IX collagen molecules at the COL2 domain and the non-collagenous globular domain (NC1) domain (Wu et al., 1992).

Mice with a completely inactivated Col9a1 gene showed no detectable abnormalities at birth but thereafter had a severe degenerative joint disease resembling human OA at 4-months or older (Fässler et al., 1994). In a different context, the knockout of type IX collagen altered the time course of callus differentiation during bone fracture healing, and delayed the maturation of cartilage matrix (Opolka et al.,...
| Collagen | Distribution in cartilage | Binds to other ECM proteins | Disease-related model | Classifications | Susceptible to Proteinases |
|----------|---------------------------|-----------------------------|----------------------|-----------------|---------------------------|
| Type IV  | Pericellular matrix of articular cartilage | Integrins, nidogen, fibronectin, TGF-β (Eyre et al., 2006) | NA | Hexagonal network-forming collagen | MMP-2, 9, 12 |
| Type VI  | Pericellular matrix of articular cartilage | Type IV, biglycan, decorin, perlecain, NG2 proteoglycan, fibronectin, tenascin, integrin (Bidanset et al., 1992; Brown et al., 1994) | Col6a1 knockout mice showed accelerated development of osteoarthritis (Wiberg et al., 2001) | Beaded filament collagen (or microfibrillar collagen) | MMP-2, 9 |
| Type IX  | Growth-plate cartilage, adult articular cartilage | Matrilin-4, type XII collagen, thrombospondin-4, fibronectin, β1γ3, and epiphycan, type II collagen, COMP, fibronectin, fibromodulin, and osteoadherin (Pfaff et al., 1993; McDevitt et al., 1988; Alexopoulos et al., 2009; Zelenski et al., 2015; Smiraglio et al., 2015; Lee et al., 2013) | Femoral and tibial cartilage in ovalbumin-induced rheumatoid arthritis rabbit model showed significantly reduced type IX collagen content (Wagener et al., 2009) | FACIT | MMP-3, 13 |
| Type X   | Hypertrophic zone of the growth plate and basal calcified zone of articular cartilage | Anchorin CII | NA | Hexagonal network-forming collagen | MMP-1, 2, 3, 13 |
| Type XI  | Articular cartilage (Eyre et al., 2004; Fässler et al., 1994) | Heparin, heparan sulfate, and dermatan sulfate (Opolka et al., 2007) | Type XI collagen induced mild arthritis in DBA/1 mice (Hagg et al., 1997) Immunizing type XI collagen induced chronic arthritis, IgG deposits in cartilage, and joint destruction in the Lewis rat (Czarny-Ratajczak et al., 2001) | Fibril-forming collagen | MMP-2 |
| Type XII | Decorin, fibromodulin, tenascin-X, COMP (Lohiniva et al., 2000; Kuivaniemi et al., 1997) | NA | FACIT | NA |
A deficiency of α1(IX) in mice has been shown to lead to instability of hyaline cartilage (Hagg et al., 1997). Other studies suggested that mutations of α1(IX) (Czarny-Ratajczak et al., 2001), α2(IX), and α3(IX) (Lohiniva et al., 2000) can elicit multiple epiphyseal dysplasia, a heterogeneous skeletal disorder with early-onset OA as a manifestation. Mutations in the Col9a2 are also linked to multiple epiphyseal dysplasia characterized by symptoms ranging from pain and stiffness in joints to OA (Kuivaniemi et al., 1997). In another experiment, the mutated type IX collagen had a mild chondrodysplasia (Nakata et al., 1993). In a rabbit model of ovalbumin-induced rheumatoid arthritis, the NC4 domain of type IX collagen content was reduced in femoral and tibial cartilage, revealing early damage of type IX collagen in articular cartilage following induction of joint inflammation (Kojima et al., 2001). In a rabbit model of ovalbumin-induced rheumatoid arthritis, the NC4 domain of type IX collagen content was reduced in femoral and tibial cartilage, revealing early damage of type IX collagen in articular cartilage following induction of joint inflammation (Kojima et al., 2001). The immunohistochemical staining of type IX collagen in normal mature and spontaneously osteoarthritic canine tibial cartilage revealed that changes in type IX collagen distribution played crucial role in the chondron remodeling and chondrocyte cluster formation associated with osteoarthritic degeneration (Poole et al., 1997). All these findings highlight that type IX collagen may play important roles in the pathogenesis of arthritis diseases, the formation of a stable collagen network and in the maintenance of cartilage organization and integrity. In humans, Col9a1 has been identified as a susceptibility locus for female hip OA (Mustafa et al., 2000; Loughlin et al., 2002; Alizadeh et al., 2005), suggesting that Col9a1 is involved in hip OA. The decreased expression of type IX collagen in the cartilage may render the matrix more subject to mechanical forces, thereby resulting in the pathogenesis of human OA. Type IX collagen is also used to induce chronic arthritis in the DBA/1 mice (Boissier et al., 1990).

Taken together, type IX collagen is crucial for the maintenance of cartilage matrix and formation of collagen meshwork. Turnover of type IX collagen by proteases is an early event in degenerative joint disease. The reduced level of type IX collagen may contribute to the pathogenesis of OA.

**Type XII collagen**

Type XII collagen shares structural homologies with type IX and type XIV collagens (Yamagata et al., 1991). Additionally, in common with several other FACITs, the length of α1(XII) chains is affected by complex alternative splicing of type XII collagen primary transcripts. As a result, two distinct forms of type XII collagen—short(XIIb) and long(XIIa)—are generated. Although both forms of type XII collagen are present in cultured fibroblasts—the expression of long or short form being determined by whether cells grow in monolayer or 3D culture—the long transcript variant predominates. The long form is also the only type XII collagen variant expressed in human fetal chondrocytes (Keene et al., 1991).

### Table 1 continued

| Collagen | Distribution in cartilage | Binds to other ECM proteins | Disease-related model | Classifications | Susceptible to Proteinases |
|----------|---------------------------|-----------------------------|----------------------|----------------|---------------------------|
| Type XIV | Uniformly throughout the articular cartilage (Nakata et al., 1993) | Decorin and type I collagen (Kojima et al., 2001) | NA | FACIT | MMP-13 |
| Type XVI | Territorial matrix of chondrocytes (Poole et al., 1997) | Types II and XI collagen, fibrillin-1 and fibronectin (Poole et al., 1997; Mustafa et al., 2000) | NA | FACIT | NA |
| Type XXII | Articular surface of joint cartilage | Fibrillins, integrins (α2β1 and α11β1) (Loughlin et al., 2002; Alizadeh et al., 2005) | NA | FACIT | NA |
| Type XXVII | Proliferative zone chondrocytes (Boissier et al., 1990) | NA | Knockdown of COL27a1 in zebrafish embryos delayed and decreased vertebral mineralization, morphological abnormalities and scoliosis (Yamagata et al., 1991) | Fibril-forming collagen | NA |

FACIT = Fibril-associated collagens with interrupted triple helices. COMP = cartilage oligomeric matrix protein. NA = Not available.
In terms of biological function, type XII collagen has been implicated in fibril formation, cell adhesion, fibrosis and osteogenesis, and in areas of high mechanical stress may serve as a protector of tissue integrity (Chiquet et al., 2014; Arai et al., 2008). Immunohistochemistry staining and fibrillogenesis studies show that type XII collagen can be incorporated into type I collagen fibrils in dense connective tissues and bone. It potentially helps to mediate interactions between fibrils and other matrix macromolecules/cells, or acts as a ‘shock-absorber’ similar to proteoglycans in cartilage (Arai et al., 2008; Taylor et al., 2014). Type XII collagen associates with articular cartilage and growth plate region during rat forelimb development, and may be necessary for microenvironment that supports hyaline cartilage formation (Taylor et al., 2014; Gregory et al., 2001). Type XII collagen also has been shown to be present in the secretome of human passaged chondrocytes (Polacek et al., 2011), however, not in the secretome of cartilage explants (Taylor et al., 2014).

**Type XIV collagen**

Type XIV collagen is a large, non-fibrillar ECM protein, structurally similar to type XII collagen. In cartilage, a population of type XIV collagen exists a chondroitin sulfate proteoglycan, since it was sensitive to chondroitinases ABC and AC treatments (Watt et al., 1992). Type XIV collagen is prevalent within connective tissues that contain large amounts of fibrillar collagens, where it localizes near the surface of banded collagen fibrils (Nishiyama et al., 1994). Immunofluorescence localization showed that type XIV collagen was prominent at the ligament-bone junction, and in bovine cartilage. Type XIV collagen localizes relatively uniformly throughout the articular cartilage, but is absent from growth plate regions (Watt et al., 1992).

In addition to reported interactions with type I, II, V, and VI collagens, type XIV collagen also interacts with heparin, CD44, and cartilage oligomeric matrix protein (COMP) (Giry-Lozinguez et al., 1998). Type XIV collagen is predominantly expressed in differentiated tissues and late embryonic development. Ruehl et al. postulated that it is involved in tissue differentiation, and particularly, its first FN-III domain are potent inducers of reversible cellular quiescence and differentiation in human and mouse mesenchymal cells (Ruehl et al., 2005). Their study saw reduction of de novo DNA synthesis without alterations to cell numbers and viability and restoration of maximal proliferation upon serum supplementation. Similarly to type XII collagen, type XIV collagen is often found in areas of high mechanical stress.
Kvi  et  al.,  2008).  However,  controversially  it  was  reported  that  controversy  concerns  the  mechanical  stability  of  myotendinous  junctions  (Koch  et  al.,  2003).  In  cartilage,  type  XVI  collagen  is  a  component  of  small  heterotypic  D-banded  fibrils  (Kassner  et  al.,  2003)  and  is  strongly  expressed  in  differentiating  chondrocytes  (Lai  and  Chu,  1996).  Type  XVI  collagen  may  be  incorporated  into  structurally  and  functionally  discrete  matrix  aggregates  in  cartilage.  Its  main  function  is  to  organize  the  ECM  by  stabilize  collagen  fibrils,  anchoring  microfibrils,  mediating  intracellular  signaling  affecting  cell  adhesion,  proliferation,  invasiveness  as  well  as  the  formation  of  focal  adhesions.  It  has  been  shown  that  N-terminal  processing  of  type  XVI  collagen  results  in  182  kDa  and  78  kDa  fragments  (Kassner  et  al.,  2004),  whereas  C-terminal  and  subsequent  N-terminal  processing  results  in  150  kDa,  110  kDa,  50  kDa,  and  35  kDa  fragments,  respectively  (Grässel  et  al.,  1996).  Such  fragments  may  be  utilized  as  targets  of  biochemical  markers  for  cartilage  biology.

Type  XXII  collagen  is  expressed  at  the  junction  between  synovial  fluid  and  surface  of  articular  cartilage  (Koch  et  al.,  2004)  and  associated  with  the  extrabilir  matrix  in  cartilage.  Type  XXII  collagen  is  also  detectable  in  human  arthritic  joints,  but  the  immunofluorescence  staining  pattern  is  broadened  and  fuzzy.  Unlike  other  FACIT  collagens,  type  XXII  collagen  interacts  with  microfibrils,  such  as  fibrillins  or  type  VI  collagens  instead  of  collagen  fibrils  (Koch  et  al.,  2004).  Its  function  remains  unknown,  but  may  contribute  to  the  mechanical  stability  of  myotendinous  junctions  (Koch  et  al.,  2004;  Zwolanek  et  al.,  2014).  Type  XXII  collagen  could  serve  as  a  marker  to  explore  pathologic  processes  of  joint  diseases  and  to  study  tissue  junction  formation  during  development  and  regeneration  of  cartilage  due  to  its  expression  location.

**Type  IV  and  X  collagen—network-forming  collagen**

Type  IV  collagen  is  a  network  forming  collagen,  which  is  exclusively  found  in  the  pericellular  matrix  of  normal  articular  cartilage,  and  osteoarthritic  articular  cartilage  in  human  and  goat  (Foldager  et  al.,  2014;  Jeng  et  al.,  2013;  Kvist  et  al.,  2008).  However,  controversially  it  was  reported  to  be  absent  in  any  human  cartilage  subtypes  including  hyaline,  fibrous,  and  elastic  cartilage  (Wachsmuth  et  al.,  2006).  Overexpression  of  regulator  of  MMP-13  increased  the  expression  of  type  IV  collagen  in  chondrocytes  (Wang  et  al.,  2015).  Type  IV  collagen  may  be  involved  in  maintaining  chondrocyte  phenotype  and  viability  and  provide  clues  to  the  progression  of  degenerative  joint  disorders  (Kvist  et  al.,  2008).

Fragments  originating  from  type  IV  collagen  released  by  protein  remodeling  have  been  thoroughly  investigated  for  their  uses  as  biomarkers.  Several  formation  and  degradation  biomarkers,  e.g.  C4M,  C4M2  (Karsdal  et  al.,  2015),  C4M3a  (Sand  et  al.,  2016),  C4M12a1,  C4M12a3  (Sand  et  al.,  2013),  P4NP  7S  (Leeming  et  al.,  2013),  and  Tumstatin  (Hamano  et  al.,  2003)  have  been  developed,  indicating  the  role  of  type  IV  collagen  turnover  in  most  connective  tissue  diseases.

**Type  XVI  and  XXII  collagen**

Type  XVI  collagen  has  been  identified  in  the  territorial  matrix  of  the  chondrocytes,  associating  with  thin  weakly  banded  collagen  fibrils  containing  types  II  and  XI  collagen  (Kassner  et  al.,  2003).  In  cartilage,  type  XVI  collagen  is  a  component  of  small  heterotypic  D-banded  fibrils  (Kassner  et  al.,  2003)  and  is  strongly  expressed  in  differentiating  chondrocytes  (Lai  and  Chu,  1996).  Type  XVI  collagen  may  be  incorporated  into  structurally  and  functionally  discrete  matrix  aggregates  in  cartilage.  Its  main  function  is  to  organize  the  ECM  by  stabilizing  collagen  fibrils,  anchoring  microfibrils,  mediating  intracellular  signalling  affecting  cell  adhesion,  proliferation,  invasiveness  as  well  as  the  formation  of  focal  adhesions.
Type XI and XXVII collagen—the fibril-forming collagen

Type XI collagen is primarily cross-linked to each other in cartilage. The cross-linkages result in the formation of mature type XI collagen fibers with the help of type II and IX collagen. It is broadly distributed in articular cartilage, tendons, trabecular bone, and skeletal muscle (Mio et al., 2007). Like the other fibril-forming collagens, type XI collagen is synthesized as a procollagen which is subsequently degraded to the mature form depositing into the ECM (Sussman et al., 1984). The absence in the α chain of type XI collagen leads to abnormally thickened cartilage fibril (Hida et al., 2014) and OA (Rodríguez-Fontenla et al., 2014; Jakkula et al., 2005). It has been shown that a type XI collagen mutation results in increased degradation of type II collagen in articular cartilage (Lu et al., 2002).

Type XI collagen accounts for 3% to 10% of total collagen in adult articular cartilage and fetal cartilage, respectively (Eyre, 2002). It is preferentially retained at the chondrocyte surface and involved in the organization of the pericellular matrix via interaction with cartilage proteoglycans (Smith et al., 1989). In embryonic cartilage, type XI collagen has a uniform diameter of ~20 nm and diameter control is regulated by the proportion of collagen II and XI while collagen IX strongly increase the efficiency of fibril formation (Blauschke et al., 2000). The thin fibrils in embryonic cartilage are constructed from a 10 + 4 microfibrillar arrangement (central core of 2 microfibrils each of type II and type XI collagen) (Holmes and Kadler, 2006). This arrangement explains why the narrow fibrils are lacking in collagen XI knockout animals.

The mutation of type XI collagen in mice leads to Stickler’s syndrome, an autosomal dominant disorder with symptoms of mild spondyloepiphyseal dysplasia, OA, and sensorineural hearing loss (Kuivaniemi et al., 1997). In other experiments, the mice lacking type XI collagen exhibited age-dependent OA-like changes in knee and temporomandibular joints of heterozygous cho/+ mice (Xu et al., 2003, 2005). Mutations in Col11a1 and Col11a2 have also been shown to result in relatively mild chondrodysplasias associated with OA (Myllyharju and Kivirikko, 2001). In addition, two single-nucleotide polymorphisms (SNPs) in Col11a1 showed significant association with hip OA in a meta-analysis of nine genome-wide association studies (Rodríguez-Fontenla et al., 2014). Type XI collagen is often used to induce chronic arthritis in the DBA/1 mouse and rat (Cremer et al., 1994). Interestingly, type XI collagen was shown to be arthritogenic in Aderley Park rats but not in Sprague-Dawley rats, although type II collagen-induced arthritis in both strains (Morgan et al., 1983). 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 (Lu et al., 2002).

Although the role of type XI collagen in the formation of cartilage collagen fibrils remains unclear, type XI collagen may regulate cartilage formation in that it is the first cartilage collagen deposited by mesenchymal stem cells undergoing chondrogenic differentiation (Xu et al., 2008).

Type XXVII collagen is prominently located at sites of transition from cartilage to bone (Pace et al., 2003; Boot-Handford et al., 2003) and in the matrix surrounding proliferative chondrocytes in the epiphyseal growth plate (Plumb et al., 2011). The expression of type XXVII collagen is regulated by factors SOX9 and Lc-Maf in chondrocytes (Mayo et al., 2009; Jenkins et al., 2005).

In developing endochondral bone, type XXVII collagen plays a role in the transition of cartilage to bone during skeletogenesis (Hjorten et al., 2007). It is also believed to play a key structural role in the pericellular extracellular matrix of the growth plate and is required for the organization of the proliferative zone (Plumb et al., 2011).

MINOR COLLAGEN METABOLITES AS BIOCHEMICAL MARKERS OF JOINT DISEASE

Extracellular matrix remodeling (ECMR) is a delicate equilibrium and a prerequisite for maintenance of a healthy tissue, in which old proteins continuously are degraded and new proteins are formed (Karsdal et al., 2013). This delicate balance may be disturbed in connective tissues disease, resulting in an altered turnover of both formation and degradation, leading to a tissue imbalance. Irreversible degradation in the cartilage collagen network is believed to be a critical event involved in the pathophysiological progression of arthritis. During tissue remodeling, proteases release small protein fragments into the circulation that may be used as serological biomarkers of tissue degradation (Karsdal et al., 2013). A sub-set of pathological proteases are over-expressed in the affected tissue area, resulting in release of protease specific fragments of signature proteins of the arthritis ECM (Karsdal et al., 2010). These fragments may be utilized as early diagnostic or prognostic serological markers, as they originate from the structure of cartilage, which in part is the consequence of disease.

Although accounting for only a small fraction of the mature matrix, minor collagens not only play structural roles in the mechanical properties, organization, and shape of articular cartilage, but also have specific biological functions. Genetic studies of these minor collagens in articular cartilage
reveal they are associated with degenerative joint disease. The progressive destruction of cartilage involves the degradation of matrix constituents including these minor collagens. We speculate that the release of fragmented molecules from minor collagen could be potential complementary biomarkers of the existing one. It has been shown that pro-peptides of type VI collagen are released during collagen synthesis (Sun et al., 2015; Sand et al., 2015). However, whether pro-peptides of other minor collagens exist is still unknown. Many minor collagens of articular cartilage have been shown to be susceptible to degradation by MMPs (Eckhard et al., 2016), e.g. IV (Karsdal et al., 2013), VI, IX, and X collagen (He et al., 2014; Schmid et al., 1986). The degradation products of type IX collagen have been investigated in vitro, ex vivo, and in vivo cartilage models. An MMP-3 cleavage site within NC2 domain was revealed in vitro (Wu et al., 1991). D. Heinegård and colleagues observed two MMP-13 cleavage sites within NC4 and COL3 domain respectively, in a bovine nasal cartilage ex vivo induced by interleukin-1 (IL-1) (Danfelter et al., 2007). They claimed that these degradation events precede the major loss of type II collagen. This cleavage, which released NC-4 fragments into synovial fluid and serum of patients with OA or rheumatoid arthritis (RA), caused the collagen network swelling seen in articular cartilage in early experimental OA. Type X collagen is subject to interstitial collagenase and gelatinase cleavage at two distinct sites within triple helix domain (Golding et al., 2013). He et al. reported that C-Col 10, which is a C-terminal fragment of the NC1 domain in type X collagen, significantly elevated in OA patients compared to healthy subjects (He et al., 2014; Gudmann et al., 2016). Type XI collagen is resistant to collagenase but hydrolysed by gelatinases resulting in a number of degradation products. These events were believed to play a vital role in the turnover of articular cartilage in health and disease states. Type VI collagen was reported to be susceptible to degradation by MMP2 and MMP9 (Veidal et al., 2011).

The collagen of articular cartilage is a co-polymeric network of different types of collagen that interact specifically at the molecular level. Types II, IX, and XI collagen are cross-linked together, forming the extracellular framework of the tissue. Cross-linking plays an important role in the ECM meshwork, especially for the fibrillar collagens (types I–III) and minor collagens (types IV–XIV), and thereby in tissue integrity. Type XII and XIV collagen can be extracted without proteolysis, so they appear not to be covalently polymerized in the matrix (Watt et al., 1992), but are thought to bind physically to collagen fibril surfaces via their COL1/NC1 domains. It is vital for collagen to be able to cross-link with the neighboring collagen and/or other ECM components (Reiser et al., 1992). Understanding the details of ECM remodeling mechanisms in cartilage is critical for knowing the pathological process of joint diseases. ECMR is a continuous and dynamic process of cartilage development, maintenance, and pathogenesis. It results in uniquely modified proteins during the pathogenesis of disease. Specific proteolytic activities are required for a range of cellular functions and interactions with the ECM. However, in pathological condition, proteolysis of collagen framework is integral to the process of cartilage destruction and joint failure. So in theory, a range of type II, IX, and XI collagen metabolites could be exploited as molecular biochemical markers in arthritis.

**PERSPECTIVES**

Our understanding of the biology of joint disease has been hampered by the lack of well-characterised biomarkers that perform well in clinical studies. Imaging markers, e.g. radiographs, which are the traditional method of defining clinical arthritis, can only detect advanced, relatively gross changes in joint anatomy and joint space narrowing only after significant deterioration has already taken place. According to the FDA critical path, there is an unmet need for the development of novel diagnostic and prognostic OA biomarkers for use in clinical trials (Karsdal et al., 2009). A strong prognostic or burden of disease biomarker for osteoarthritis would be of great value to healthcare all over the world, as the prevalence of OA is continuously increasing.

Therefore biochemical markers are receiving increased attention for their capability to detect earlier stages of the disease process, monitor the progress of destruction and prognose the development of arthritis, accurately and relatively quickly assess the efficacy of therapy. Recently the US National Institutes of Health (NIH)-industry partnership funded by the OA Biochemical Markers Network (Bauer et al., 2006; van Spil et al., 2010) proposed the BIPED (Burden of disease, Investigative, Prognostic, Efficacy of intervention, and Diagnostic) classification system. It seems unlikely that any single marker can offer sufficient sensitivity and specificity to predict the progression of arthritis and detect response to medical treatment. This classification system will help to improve the capability to develop and analyze arthritis biomarkers (Henrotin et al., 2016; Bay-Jensen et al., 2016; Kraus et al., 2015).

The release of protease degradation products provides exciting opportunities for monitoring disease progression in arthritis patients, and to investigate whether these fragments are involved in facilitating the existing pathology, for example, by inducing inflammation. As the fragmented molecules of type II collagen have shown promise as molecular markers of joint disease, it is likely that identification of cleavage fragments and other post-translational modifications (PTMs), including cross-linking and isomerization from various minor collagens in cartilage may produce unique joint disease-specific biomarkers.

Development of simple and reliable non-invasive biomarkers of OA is an important goal in clinical rheumatology and will facilitate the design and evaluation of clinical trials on disease modifying osteoarthritis drugs (DMOADs). Biomarkers that measure the stages and phenotypes of OA and, ideally, predict risk of joint-related outcomes would significantly improve decision-making in terms of dosing, treatment time, etc.
risk/benefit ratio, and transfer knowledge to label. By implementing biochemical markers in all stages of drug development, novel drug candidates may be identified at early decision points and potential safety issues may be addressed in a timely way, thereby increasing efficiency, reducing costs and prompting efficient allocation of limited resources. Thus, there is a need for different types of biochemical markers for different stages of drug development in OA.

In conclusion, development of biomarkers assessing the turnover of minor collagens may provide novel and translational diagnostic tools for investigating the effect of known drug targets on cartilage in preclinical or clinical settings, thereby providing proof of principle for test of those drugs in OA clinical trials.

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ABBREVIATIONS

BIPED, burden, investigatory, prognostic, efficacy and diagnostic; CTX-II, C-terminal telopeptide of type II collagen; CIIM, MMP-generated neo-epitope of type II collagen; COMP, cartilage oligomeric protein; DMOADs, disease modifying osteoarthritis drugs; ECM, extracellular matrix; ECMR, extracellular matrix remodeling; FACIT, fibril-associated collagen with an interrupted triple helix; MMP, metalloproteinase; MRI, Magnetic resonance imaging; OA, osteoarthritis; PHC, Personal Health Care; PIIANP, type IIA procollagen N-terminal peptide; PIIBNP, type IIB procollagen N-terminal peptide; PTMs, post-translational modifications.

COMPLIANCE WITH ETHICS GUIDELINES

The authors declare no potential conflicts of interest with respect to research, authorship, and/or publication of this article.

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REFERENCES

Alexopoulos LG, Youn I, Bonaldo P, Guilak F (2009) Developmental and osteoarthritic changes in Col6a1-knockout mice: biomechanics of type VI collagen in the cartilage pericellular matrix. Arthritis Rheum 60(3):771–779
Alizadeh BZ, Njajou OT, Bijkerk C, Meulenbelt I, De Wildt SC, Hofman A, Pols HAP, Slagboom PE, Van Duijn CM (2005) Evidence for a role of the genomic region of the gene encoding for the α1 chain of type IX collagen (COL9A1) in hip osteoarthritis: a population-based study. Arthritis Rheum 52(5):1437–1442
Alvarez J, Balbin M, Santos F, Fernandez M, Ferrando S, Lopez JM (2000) Different bone growth rates are associated with changes in the expression pattern of types II and X collagens and collagenase 3 in proximal growth plates of the rat tibia. J Bone Miner Res 15(1):82–94
Appleton CTG, Pitelka V, Henry J, Beier F (2007) Global analyses of gene expression in early experimental osteoarthritis. Arthritis Rheum 56(6):1854–1868
Arai K, Nagashima Y, Takemoto T, Nishiyama T (2008) Mechanical strain increases expression of type XII collagen in murine osteoblastic MC3T3-E1 cells. Cell Struct Funct 33(2):203–210
Bauer DC, Hunter DJ, Abramson SB, Attur M, Felson D, Heinegård D, Jordan JM, Kepler TB, Lane NE, Saxne T, Tyree B, Kraus VB, For the Osteoarthritis Biomarkers Network (2006) Classification of osteoarthritis biomarkers: a proposed approach. Osteoarthritis Cartil 14(8):723–727
Bay-Jensen A-C, Henrotin Y, Karsdal M, Mobasher A (2016) The need for predictive, prognostic, objective and complementary blood-based biomarkers in osteoarthritis (OA). EBioMedicine 7:4–6
Bidanset DJ, Guidry C, Rosenberg LC, Choi HJ, Timp R, Hook M (1992) Binding of the proteoglycan decorin to collagen type VI. J Biol Chem 267(8):5250–5256
Blaschke UK, Elkenberry EF, Hulmes DJS, Galla HJ, Bruckner P (2000) Collagen XI nucleates self-assembly and limits lateral growth of cartilage fibrils. J Biol Chem 275(14):10370–10378
Boissier MC, Chiocchia G, Ronziere MC, Herbage D, Fournier C (1990) Arthritogenicity of minor cartilage collagens (types IX and XI) in mice. Arthritis Rheum 33:1–8
Boot-Handford RP, Tuckwell DS, Plumb DA, Farrington Rock C, Poulsom R (2003) A novel and highly conserved collagen (proα1 (XXVII)) with a unique expression pattern and unusual molecular characteristics establishes a new clade within the vertebrate fibrillar collagen family. J Biol Chem 278(33):31067–31077
Brew CJ, Clegg PD, Boot-Handford RP, Andrew JG, Hardingham T (2010) Gene expression in human chondrocytes in late
osteoarthritis is changed in both fibrillated and intact cartilage without evidence of generalised chondrocyte hypertrophy. Ann Rheum Dis 69(1):234–240

Brown JC, Golbik R, Mann K, Timpl R (1994) Structure and stability of the triple-helical domains of human collagen XIV. Matrix Biol 14(4):287–295

Chen S, Mienaltowski MJ, Birk DE (2015) Regulation of corneal stroma extracellular matrix assembly. Exp Eye Res 133:69–80

Chiquet M, Birk DE, Bönnemann CG, Koch M (2014) Collagen XII: protecting bone and muscle integrity by organizing collagen fibrils. Int J Biochem Cell Biol 53:51–54

Cremer MA, Ye XJ, Terato K, Owens SW, Seyer JM, Kang AH (1994) Type XI collagen-induced arthritis in the Lewis rat. Characterization of cellular and humoral immune responses to native types XI, V, and II collagen and constituent alpha-chains. J. Immunol. 153:824–832

Czarny-Ratajczak M, Lohiniva J, Rogala P, Kozlowski K, Perälä M, Carter L, Spector TD, Kolodziej L, Seppänen U, Glazar R, Króllewski J, Latos-Bielenska A, Ala-Kokko L (2001) A mutation in COL9A1 causes multiple epiphyseal dysplasia: further evidence for locus heterogeneity. Am J Hum Genet 69:969–980

D’Angelo M, Yan Z, Nooreyazdan M, Pacifici M, Sarment DS, Billings PC, Leboy PS (2000) MMP-13 is induced during chondrocyte hypertrophy. J Cell Biochem 77(4):678–693

Danfelter M, Önnerfjord P, Heinegård D, Saxne T (2011) The role of the cartilage matrix in protecting bone and muscle integrity by organizing collagen fibrils. Int J Biochem Cell Biol 53:51–54

Goldring SR, Purdue PE, Crotti TN, Shen Z, Flannery MR, Binder NB, Ross FP, McHugh KP (2013) Bone remodelling in inflammatory arthritis. Ann Rheum Dis 72(Suppl 2):ii52–ii55

Grässel S, Timpl R, Tan EM, Chu ML (1996) Biosynthesis and processing of type XVI collagen in human fibroblasts and smooth muscle cells. Eur J Biochem 242:576–584

Gregory KE, Keene DR, Tufa SF, Lunstrum GP, Morris NP (2001) Developmental distribution of collagen type XII in cartilage: association with articular cartilage and the growth plate. J Bone Miner Res 16(11):2005–2016

Gudmann NS, Munk HL, Christensen AF, Ejsstrup L, Sørensen GL, Loft AG, Karsdal MA, Bay-Jensen A-C, He Y, Siebhuhr AS, Junker P (2016) Chondrocyte activity is increased in psoriatic arthritis and axial spondyloarthritis. Arthritis Res Ther 18(1):141

Hagg R, Hedborn E, Möllers U, Aszódi A, Fässler R, Mo U, Aszo A, Fa R (1997) Absence of the α1(IX) chain leads to a functional knock-out of the entire collagen IX protein in mice. J Biol Chem 272(1):832–839

Hamano Y, Zeisberg M, Sugimoto H, Lively JC, Maeshima Y, Yang C, Hynes RO, Werb Z, Sudhakar A, Kalluri R (2003) Physiological levels of tumstatin, a fragment of collagen IV α3 chain, are generated by MMP-9 proteolysis and suppress angiogenesis via αVβ3 integrin. Cancer Cell 3(6):589–601

He Y, Siebhuhr AS, Brandt-hansen NJ, Wang J, Su D, Zheng Q, Simonsen O, Petersen KK, Arendt-nielsen L, Eskehave T, Hoecn HC, Karsdal MA, Bay-jensen AC (2014) Type X collagen levels are elevated in serum from human osteoarthritis patients and associated with biomarkers of cartilage degradation and inflammation. BMC Musculoskelet Disord 15:309

Heinégård D, Saxne T (2011) The role of the cartilage matrix in osteoarthritis. Nat Rev Rheumatol 7(1):50–56

Hemmavanh C, Koch M, Birk DE, España EM (2013) Abnormal corneal endothelial maturation in collagen XII and XIV null mice. Invest Ophthalmol Vis Sci 54(5):3297–3308
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Henrotin Y, Sanchez C, Bay-Jensen AC, Mobasher A (2016) Osteoarthritis biomarkers derived from cartilage extracellular matrix: current status and future perspectives. Ann Phys Rehabil Med 59(3):145–148

Hida M, Hamaotaka R, Okamoto O, Yamashita K, Sasaki T, Yoshioka H, Matsuo N (2014) Nuclear factor (NF-Y) regulates the proximal promoter activity of the mouse collagen a1(XI) gene (Col11a1) in chondrocytes. In Vitro Cell Dev Biol Anim 50(4):358–366

Hjorten R, Hansen U, Underwood RA, Telfer HE, Fernandes RJ, Krakow D, Sebalde H, Wachsmann-Hogiu S, Bruckner P, Jacquet R, Landis WJ, Byers PH, Pace JM (2007) Type XXVII collagen at the transition of cartilage to bone during skeletogenesis. Bone 41(4):535–542

Holmes DF, Kadler KE (2006) The 10+4 microfibril structure of thin cartilage fibrils. Proc Natl Acad Sci USA 103(46):17249–17254

Huber JR, Johnson KA, Kraus VB, Terkeltaub RA (2009) Transglutaminase 2 is a marker of chondrocyte hypertrophy and osteoarthritis severity in the Hartley guinea pig model of knee OA. Osteoarthritis Cartil 17(8):1056–1064

Ichimura S, Wu JJ, Eyre DR (2000) Two-dimensional peptide mapping of cross-linked type IX collagen in human cartilage. Arch Biochem Biophys 378(1):33–39

Jakkula E, Melkonien M, Kiviranta I, Lohiniva J, Räinä SS, Perälä M, Warman ML, Ahonen K, Kröger H, Göring HHH, Ala-Kokko L (2005) The role of sequence variations within the genes encoding collagen II, IX and XI in non-syndromic, early-onset osteoarthritis. Osteoarthritis Cartil 13(6):497–507

Jeng L, Hsu H-P, Spector M (2013) Tissue-engineered cartilaginous constructs for the treatment of caprine cartilage defects, including distribution of laminin and type IV collagen. Tissue Eng Part A 19(19–20):2267–2274

Jenkins E, Moss JB, Pace JM, Bridgewater LC (2005) The new collagen gene COL27A1 contains SOX9-responsive enhancer elements. Matrix Biol 24(3):177–184

Karsdal MA, Henriksson K, Leeming DJ, Mitchell P, Duffin K, Barascuk N, Klickstein L, Aggarwal P, Nemirovskiy O, Byrjalsen J, Kvist AJ, Nyström A, Hultenby K, Sasaki T, Talts JF, Aspberg A (2013a) Extracellular matrix remodeling: the common denominator in connective tissue diseases. Possibilities for evaluation and current understanding of the matrix as more than a passive architecture, but a key player in tissue failure. Assay Drug Dev Technol 11(2):70–92

Karsdal MA, Bay-Jensen AC, Leeming DJ, Henrikson K, Christiansen C (2013b) Quantification of ‘end products’ of tissue destruction in inflammation may reflect convergence of cytokine and signaling pathways—implications for modern clinical chemistry. Biomarkers 18(5):375–378

Karsdal MA, Christiansen C, Ladel C, Henrikson K, Kraus VB, Bay-Jensen AC (2014) Osteoarthritis—a case for personalized health care? Osteoarthritis Cartil 22(1):7–16

Karsdal MA, Genovese F, Madsen EA, Manon-Jensen T, Schuppan D (2015) Collagen and tissue turnover as a function of age: implications for fibrosis. J Hepatol 64:103–109

Kassner A, Hansen U, Mösge N, Reinhardt DP, Aigner T, Bruckner-Tuderman L, Bruckner P, Grässel S (2003) Discrete integration of collagen XVI into tissue-specific collagen fibrils or beaded microfibrils. Matrix Biol 22(2):131–143

Kassner A, Tiedemann K, Notbohm H, Ludwig T, Mörgelin M, Reinhardt DP, Chu ML, Bruckner P, Grässel S (2004) Molecular structure and interaction of recombinant human type XVI collagen. J Mol Biol 339(4):835–853

Keene DR, Lunstrum GP, Morris NP, Stoddard DW, Burgeson RE (1991) Two type XII-like collagens localize to the surface of banded collagen fibrils. J Cell Biol 113(4):971–978

Koch M, Schulze J, Hansen U, Ashwodt T, Keene DR, Brunken WJ, Burgeson RE, Bruckner P, Bruckner-L (2004) A novel marker of tissue junctions, collagen XXII. J Biol Chem 279(21):22514–22521

Kojima T, Mwale F, Yasuda T, Girard C, Poole AR, Laverty S (2001) Early degradation of type IX and type II collagen with the onset of experimental inflammatory arthritis. Arthritis Rheum 44(1):120–127

Kraus VB, Blanco FJ, Englund M, Karsdal MA, Lohmander LS (2015a) Call for standardized definitions of osteoarthritis and risk stratification for clinical trials and clinical use. Osteoarthritis Cartil 23(8):1233–1241

Kraus VB, Blanco FJ, Englund M, Henrotin Y, Lohmander LS, Losina E, Önnerfjord P, Persiani S (2015b) OARSI clinical trials recommendations: soluble biomarker assessments in clinical trials in osteoarthritis. Osteoarthritis Cartilage 23(5):686–697

Kuivaniemi H, Tromp G, Prockop DJ (1997) Mutations in fibrillar collagens (types I, II, III, and XI), fibril-associated collagen (type IX), and network-forming collagen (type X) cause a spectrum of disease of bone, cartilage, and blood vessels. Hum Mutat 9(4):300–315

Kvist AJ, Nyström A, Hultenby K, Sasaki T, Talts JF, Aspberg A (2008) The major basement membrane components localize to the chondrocyte pericellular matrix—a cartilage basement membrane equivalent? Matrix Biol 27(1):22–33

Kwan APL, Cummings CE, Chapman JA, Grant ME (1991) Macromolecular organization of chicken type X collagen in vitro. J Cell Biol 114(3):597–604

Lai CH, Chu ML (1996) Tissue distribution and developmental expression of type XVI collagen in the mouse. Tissue Cell 28(2):155–164

Lee SJ, Kim MJ, Kee SJ, Song SK, Kweon SS, Shin MH, Park DJ, Park YW, Lee SS, Kim TJ (2013) Association study of the candidate gene for knee osteoarthritis in Koreans. Rheumatol Int 33(3):783–786

Leeming DJ, Karsdal MA, Rasmussen LM, Scholze A, Tepel M (2013) Association of systemic collagen type IV formation with
survival among patients undergoing hemodialysis. PLoS ONE 8 (8):e71050
Lohiniva J, Paassilta P, Seppänen U, Vierimaa O, Kivirikko S, Ala-Kokko L (2000) Splicing mutations in the COL3 domain of collagen IX cause multiple epiphyseal dysplasia. Am J Med Genet 90:216–222
Loughlin J, Mustafa Z, Dowling B, Southam L, Marcelline L, Räinä SS, Ala-Kokko L, Chapman K (2002) Finer linkage mapping of a primary hip osteoarthritis susceptibility locus on chromosome 6. Eur J Hum Genet 10(9):562–568
Lu S, Carlsen S, Hansson AS, Holmdahl R (2002) Immunization of rats with homologous type XI collagen leads to chronic and relapsing arthritis with different genetics and joint pathology than arthritis induced with homologous type II collagen. J Autoimmun 18:199–211
Luckman SP, Rees E, Kwan APL (2003) Partial characterization of cell-type X collagen interactions. Biochem J 372(Pt 2):485–493
Matsumoto T, Cooper GM, Gharaiheb B, Meszaros LB, Li G, Usas A, Fu FH, Huard J (2009) Cartilage repair in a rat model of osteoarthritis through intrarticular transplantation of muscle-derived stem cells expressing bone morphogenetic protein 4 and soluble Flt-1. Arthritis Rheum 60(5):1390–1405
Mayo JL, Holden DN, Barrow JR, Bridgewater LC (2009) The transcription factor Lc-Maf participates in Col27a1 regulation during chondrocyte maturation. Exp Cell Res 315(13):2293–2300
McDevitt CA, Pahl JA, Ayad S, Miller RR, Uratsuji M, Andrish JT (2005) Experimental osteoarthritis is associated with susceptibility to lumbar disc herniation. Am J Hum Genet 81(6):1271–1277
Morgan K, Evans HB, Firth SA, Smith MN, Ayad S, Weiss JB, Lennox PJ (1983) Holt, 1 Alpha 2 alpha 3 alpha collagen is arthritogenic. Ann Rheum Dis 42(6):680–683
Mustafa Z, Chapman K, Irven C, Carr AJ, Clipsham K, Chitnavis J, Sinsheimer JS, Bloomfield VA, McCarter NY, Cox O, Sykes B, Loughlin J (2000) Linkage analysis of candidate genes as susceptibility loci for osteoarthritis-suggestive linkage of COL9A1 to female hip osteoarthritis. Rheumatology (Oxford) 39(3):299–306
Myllyharju J, Kivirikko KI (2001) Collagens and collagen-related diseases. Am Med 33(1):7–21
Nakata K, Ono K, Miyazaki J, Olsen BR, Muragaki Y, Adachi E, Yamamura K, Kimura T (1993) Osteoarthritis associated with mild chondrodysplasia in transgenic mice expressing alpha-1(IX) collagen chains with a central deletion. Proc Natl Acad Sci USA 90(7):2870–2874
Nishiyama T, McDonough AM, Bruns RR, Burgeson RE (1994) Type XII and XIV collagens mediate interactions between banded collagen fibers in vitro and may modulate extracellular matrix deformability. J Biol Chem 269(45):28193–28199
Opolka A, Ratzinger S, Schubert T, Spiegel HU, Grifka J, Bruckner P, Probst A, Grässel S (2007) Collagen IX is indispensable for timely maturation of cartilage during fracture repair in mice. Matrix Biol 26(2):85–95
Pace JM, Corrado M, Missero C, Byers PH (2003) Identification, characterization and expression analysis of a new fibrillar collagen gene, COL27A1. Matrix Biol 22(1):3–14
Pfaff M, Auramiley M, Specks U, Knolle J, Zerwes HG, Timpl R (1993) Integrin and Arg-Gly-Asp dependence of cell adhesion to the native and unfolded triple helix of collagen type VI. Exp Cell Res 206(1):167–176
Plumb DA, Ferrara L, Torbica T, Knowles L, Mironov A, Kadler KE, Briggs MD, Boot-Handford RP (2011) Collagen XXVII organises the pericellular matrix in the growth plate. PLoS ONE 6(12):e29422
Polacek M, Bruun J-A, Elvenes J, Figenchau Y, Martinez I (2011) The secretory profiles of cultured human articular chondrocytes and meniscal stem cells: implications for autologous cell transplantation strategies. Cell Transplant 20(9):1381–1393
Poole CA, Gilbert RT, Herbage D, Hartmann DJ (1997) Immunologic localization of type IX collagen in normal and spontaneously osteoarthritic canine tibial cartilage and isolated chondrons. Osteoarthrits Cartil 5:191–204
Reiser K, McCormick RJ, Rucker RB (1992) Enzymatic and nonenzymatic cross-linking of collagen and elastin. FASEB J 6(7):2439–2449
Rodriguez-Fontenla C, Calazas M, Evangelou E, Valdes AM, Arden N, Blanco FJ, Carr A, Chapman K, Deloukas P, Doherty M, Esko T, García-Aletá CM, Gomez-Reino Carnota JJ, Helgdadott H, Hofman A, Jonsdottir I, Kerkhof HMJ, Kloppenburg M, McCaskie A, Ntzani EE, Ollier WER, Oreiro N, Panoutsopoulos K, Ralston SH, Rmans YF, Rianco JA, Rivadeneira F, Slagboom PE, Styrkarsdottir U, Thorsteinsdottir U, Thorleifsson G, Tsezou A, Utterlind AG, Wallis GA, Wilkinson JM, Zhai G, Zhu Y, Felson DT, Ioannidis JPA, Loughlin J, Metspalu A, Meulenbelt I, Stefansson K, Van Meurs JB, Zeggini E, Spector TD, Gonzalez A (2014) Assessment of osteoarthritis candidate genes in a meta-analysis of nine genome-wide association studies. Arthritis Rheumatol. 66(4):940–949
Ruehl M, Erben U, Schuppan D, Wagner C, Zeller A, Freise C, Al-Hasani H, Loesekann M, Notter M, Wittig BM, Zeitz M, Dieterich W, Somasundaram R (2005) The elongated first fibronectin type III domain of collagen XIV is an inducer of quiescence and differentiation in fibroblasts and preadipocytes. J Biol Chem 280 (46):38537–38543
Sand JM, Larsen L, Hogaboam C, Martinez F, Han M, Larsen MR, Nawrocki A, Zheng Q, Karsdal MA, Leeming DJ (2013) MMP mediated degradation of type IV collagen alpha 1 and alpha 3 chains reflects basement membrane remodeling in experimental and clinical fibrosis—validation of two novel biomarker assays. PLoS ONE 8(12):1–12
Sand JMB, Knox AJ, Lange P, Sun S, Kristensen JH, Leeming DJ, Karsdal MA, Bolton CE, Johnson SR (2015) Accelerated extracellular matrix turnover during exacerbations of COPD. Respir Res 16(1):69
Sand JM, Martinez G, Midjord AK, Karsdal MA, Leeming DJ, Lange P (2016) Characterization of serological neo-epitope biomarkers reflecting collagen remodeling in clinically stable chronic obstructive pulmonary disease. Clin Biochem 49(15):1144–1151
Schmid TM, Linsenmayer TF (1985) Immunohistochemical localization of short chain cartilage collagen (type X) in avian tissues. J Cell Biol 100(2):598–605

Schmid TM, Mayne R, Jeffrey JJ, Linsenmayer TF (1986) Type X collagen contains two cleavage sites for a vertebrate collagenase. J Biol Chem 261(9):4184–4189

Shen G (2005) The role of type X collagen in facilitating and regulating endochondral ossification of articular cartilage. Orthod Craniofac Res 8(1):11–17

Smereglio P, Dhulipala L, Lai JH, Goodman SB, Dragoo JL, Smith RL, Maloney WJ, Yang F, Bhutani N (2015) Collagen VI enhances cartilage tissue generation by stimulating chondrocyte proliferation. Tissue Eng Part A 21(3–4):840–849

Smith GN, Hasty KA, Brandt KD (1989) Type XI collagen is associated with the chondrocyte surface in suspension culture. Matrix 9(3):186–192

Steiner AF, Proffen B, Kunz M, Hendrich C, Ghivizzani SC, Nöth U, Rethwilm A, Eulert J, Evans CH (2009) Hypertrophy is induced during the in vitro chondrogenic differentiation of human mesenchymal stem cells by bone morphogenetic protein-2 and bone morphogenetic protein-4 gene transfer. Arthritis Res Ther 11(5):R148

Sun S, Henriksen K, Karsdal MA, Byrjalsen I, Rittweger J, Armbrecht RL, Mörgelin M, Heinegård D (2001) Biglycan and decorin bind close to the N-terminal region of the collagen VI triple helix. J Biol Chem 276(22):18947–18952

Wu JJ, Lark MW, Chun LE, Eyre DR (1991) Sites of stromelysin cleavage in collagen types II, IX, X, and XI of cartilage. J Biol Chem 266(9):5625–5628

Wu JJ, Woods PE, Eyre DR (1992) Identification of cross-linking sites in bovine cartilage type-IX collagen reveals an antiparallel type-II-type-IX molecular relationship and type-IX to type-IX bonding. J Biol Chem 267(22):18947–18952

Xu L, Flahiff CM, Waldman BA, Wu D, Olsen BR, Setton LA, Li Y (2003) Osteoarthritiss-like changes and decreased mechanical function of articular cartilage in the joints of mice with the chondrodysplasia gene (cho). Arthritis Rheum 48(9):2509–2518

Xu L, Peng H, Wu D, Hu K, Goldberg MB, Olsen BE, Li Y (2005) Activation of the discoidin domain receptor 2 induces expression of matrix metalloproteinase 13 associated with osteoarthritis in mice. J Biol Chem 280(1):548–555

Xu J, Wang W, Ludeman M, Cheng K, Hayami T, Lotz JC, Kapila S (2008) Chondrogenic differentiation of human mesenchymal stem cells in three-dimensional alginate gels. Tissue Eng Part A 14(5):667–680

Yamagata M, Yamada KM, Yamada SS, Shinomura T, Tanaka H, Nishida Y, Obara M, Kimata K (1991) The complete primary structure of type XII collagen shows a chimeric molecule with reiterated fibronectin type III motifs, von Willebrand factor A motifs, a domain homologous to a noncollagenous region of type IX collagen, and short collagenous domains with an Arg-Gly-Asp structure of type XII collagen. J Biol Chem 266(9):5625–5628

Wagener R, Gara SK, Kobbe B, Paulsson M, Zaucke F (2009) The knee osteoarthritis susceptibility locus DVWA on chromosome 3p24.3 is the 5’ part of the split COL6A4 gene. Matrix Biol 28(6):307–310

Walker GD, Fischer M, Gannon J, Thompson RC, Oegema TR (1995) Expression of type-X collagen in osteoarthritis. J Orthop Res 13(1):4–12

Wang G, Zhang Y, Zhao X, Meng C, Ma L, Kong Y (2015) MicroRNA-411 inhibited matrix metalloproteinase 13 expression in human chondrocytes. Am J Transl Res 7(10):2000–2006

Watt SL, Lunstrums GP, Mcdonough AM, Keene DR, Burgesons RE, Morrissil NP (1992) Characterization of collagen types XII and XIV from fetal bovine cartilage. Biochemistry 267(28):20093–20099

Wiberg C, Hedborn E, Khairullina A, Lamandé SR, Oldberg Å, Timpl R, Mörgelin M, Heinegård D (2001) Biglycan and decorin bind close to the N-terminal region of the collagen VI triple helix. J Biol Chem 276(22):18947–18952