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REVIEW ARTICLE

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Cartilage destruction by matrix degradation products

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Abstract The progressive destruction of articular cartilage is one of the hallmarks of osteoarthritis and rheumatoid arthritis. Cartilage degradation is attributed to different classes of catabolic factors, including proinflammatory cytokines, aggrecanases, matrix metalloproteinases, and nitric oxide. Recently, matrix degradation products generated by excessive proteolysis in arthritis have been found to mediate cartilage destruction. These proteolytic fragments activate chondrocytes and synovial fibroblasts via specific cell surface receptors that can stimulate catabolic intracellular signaling pathways, leading to the induction of such catalysts. This review describes the catabolic activities of matrix degradation products, especially fibronectin fragments, and discusses the pathologic implication in cartilage destruction in osteoarthritis and rheumatoid arthritis. Increased levels of these degradation products, found in diseased joints, may stimulate cartilage breakdown by mechanisms of the kind demonstrated in the review.

Key words Cartilage destruction · Fibronectin fragment (FN-f) · Integrin · Matrix metalloproteinase (MMP) · Mitogen-activated protein kinase

Introduction

The extracellular matrix of cartilage is primarily composed of the large proteoglycan aggrecan and fibrils containing type-II collagen.[1] Type-II collagen, composed of a triple helix of three identical α chains, forms fibrils stabilized by intermolecular crosslinks.[2] The fibrils provide tensile strength and serve to constrain the swelling of aggrecan that endows cartilage with its compressive stiffness.[1,3,4] Progressive destruction of cartilage, which results from an imbalance between the anabolic and catabolic processes, is a common feature of rheumatoid arthritis (RA) and osteoarthritis (OA). Proteoglycan loss that is observed in the development of early OA[5,6] results in a reduction in cartilage stiffness.[7,8] Degradation and loss of type-II collagen, which are observed in RA and OA,[9,10] result in an irreversible loss of tensile properties and structural integrity.[8] It is well known that proinflammatory cytokines including interleukin-1β (IL-1β) and tumor necrosis factor α (TNFα) have been shown to promote cartilage degradation by stimulating the production of matrix metalloproteinases (MMPs).[11]

The importance of understanding cell–matrix interactions at the level of regulation of matrix turnover is becoming very apparent. In addition to the proinflammatory cytokines, there is an increasing body of evidence that degradation products of cartilage matrix are another amplifier or catalyst in diseased joints, including RA and OA. This review focuses on the mechanism of cartilage destruction induced by matrix degradation products, especially by fibronectin fragments (FN-fs).

Structure of fibronectin

Fibronectin (FN) is an adhesive dimeric glycoprotein of 450 kDa found in the extracellular matrix of many tissues, including normal cartilage[12] and synovial membrane.[13] It is also present in such body fluids as synovial fluid and plasma. As shown in Fig. 1, FN consists predominantly of three types of homologous repeating segments (designated I, II, and III). Significant protein heterogeneity results from the alternative splicing of a single RNA.[14,15] The glycoprotein regulates functions of cellular adhesion and spreading, cell motility, cell growth, and differentiation and opsonization.[16] FN contains amino (NH_2)-terminal heparin-, gelatin-, cell- and carboxyl (COOH)-terminal heparin-binding domains. The central cell-binding region has an Arg-Gly-Asp (RGD) sequence in domain III10, recognized by several cell surface integrin family members.[17] Several sites in the heparin-binding domain that are COOH-terminal to the central

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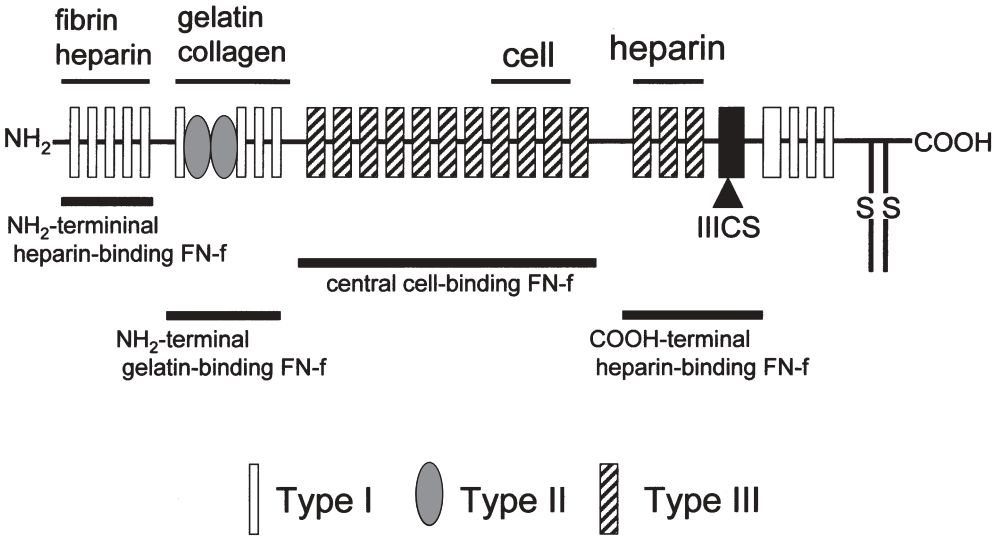

Fig. 1. Schematic representation of fibronectin and its fragments. The diagram shows one arm of the fibronectin dimer, which is linked by disulfide bonds. The fibronectin fragments (*FN-f*) described in this review are NH_2-terminal heparin-, NH_2-terminal gelatin-, central cell-, and COOH-terminal heparin-binding fragments of fibronectin

cell-binding domain also interact with the cell surface. Several peptides from domain III12–14 support cell attachment with varying affinities.[18–23] The IIICS, or the variable (V) region, contains the integrin-binding sites, CS-1 and CS-5.[24–28]

Fibronectin fragments in OA and RA

Elevated levels of FN are found in OA cartilage[29–31] and in OA synovial fluid.[31,32] While FN is ubiquitous within active rheumatoid synovium, enhanced accumulation of FN is found on the inflamed synovial and pannus surfaces in the knee joints of patients with RA.[33,34] Fibronectin is readily degraded into fragments by proteinases. Thus, activation of extracellular proteolysis in OA and RA may lead to the fragmentation of FN, indicating that FN-fs could be generated in vivo within cartilage and synovial fluid. Indeed, increased levels of FN-fs of 30–200 kDa are found in cartilage and synovial fluid from patients with OA and RA.[31,32] In OA synovial fluids, FN-fs of 100–200 kDa are found at approximately 1 μM.[32] The levels of FN-fs in OA cartilage are suggested to be similar to those in OA synovial fluids.[31] The FN-f concentrations that have been used in in vitro studies are less than 1 μM, similar to the levels in in vivo diseased joints. Since FN-fs can penetrate into cartilage tissue in vitro,[35] FN-fs in OA and RA cartilages may include the fragments from synovial fluid.

Cartilage destruction by fibronectin fragments

Native FN has various biologic functions including cell attachment, cell migration, wound healing, and oncogenic transformation.[14] However, native FN has no catabolic effect on cartilage.[36,37] Once FN is fragmented, those proteolytic fragments acquire catalytic activities. Of FN-fs, the central cell-, NH_2-terminal heparin-, and NH_2-terminal gelatin-binding fragments of FN have been shown to stimulate cartilage chondrolysis.[36] Recently, COOH-terminal heparin-binding FN-f has also been found to induce cartilage destruction.[37] Removal of FN and FN-fs from OA synovial fluid can diminish cartilage-damaging activity,[31] whereas injection of FN-fs into rabbit knee joints induces depletion of cartilage proteoglycan.[38] These findings support the pathophysiological significance of FN-fs.

Proteoglycan degradation by fibronectin fragments

Increased aggrecan degradation[1] is commonly observed in OA and RA. Homandberg et al. demonstrated for the first time that NH_2-terminal heparin-, NH_2-terminal gelatin-, and central cell-binding FN-fs enhance proteoglycan loss from bovine cartilage[36] and decrease proteoglycan synthesis.[39] In addition, COOH-terminal heparin-binding FN-f can promote loss of proteoglycan in bovine cartilage.[37]

Degradation of aggrecan that occurs early in cartilage damage is caused by aggrecanases[40,41] and MMPs.[42] Neoepitope antibodies specific for aggrecanase- or MMP-degraded aggrecan fragments distinguish between these activities in vivo.[42] Anti-ITEGE^{373} and anti-A^{374}RGSV antibodies identify aggrecanase cleavage site in the aggrecan interglobular domain, whereas anti-DIPEN^{341} and anti-F^{342}FGVG antibodies detect MMP cleavage site in the same region. Both sites of aggrecanase cleavage are found in OA and RA cartilage.[43] Treatment with NH_2-terminal gelatin-binding FN-f results in the generation of aggrecanase-derived ITEGE^{373} neoepitope in porcine cartilage.[44] Amino acid sequencing of aggrecan from cartilage with treatment with NH_2-terminal heparin-binding FN-f also confirms cleavage at the aggrecanase site in bovine cartilage.[45] However, there is no direct evidence on aggrecanase induction by FN-f in chondrocytes. In contrast to aggrecanase-derived neoepitope, levels of MMP-derived DIPEN^{341} neoepitope are unchanged in the FN-f-treated cartilage.[44]

Type-II collagen degradation by fibronectin fragments

Matrix metalloproteinases are a family of zinc-dependent enzymes that mediate the turnover of extracellular matrix proteins. Upregulation of MMPs has been implicated in numerous pathologic processes, including OA and RA. The MMP family is classified into gelatinases, which degrade type-IV collagen and other basement membrane proteins; collagenases, which degrade the stromal fibrillar collagens (types I, II, and III); and others, which degrade additional matrix components.[46] Of MMPs, collagenases are particularly important because of their ability to cleave fibrillar collagen, the most abundant component of the extracellular matrix.[47] MMP-1 (collagenase-1) is expressed ubiquitously and is found in various cells, including fibroblasts, chondrocytes, and multiple tumor cells.[47] MMP-8 (collagenase-2) is expressed mainly in neutrophils.[47] MMP-13 (collagenase-3) exhibits the broadest substrate specificity of the collagenases, with the highest activity against type-II collagen, the main collagen in cartilage.[48,49] Furthermore, MMP-13 degrades types I, III, IV, X, and XIV collagen, fibronectin, and aggrecan core protein.[50–52] While MMP-13 expression is restricted to bone development and bone maintenance under normal physiologic conditions,[53,54] it is upregulated under pathologic conditions like in OA chondrocytes, rheumatoid synovium, and tumor cells.[55–57] MMP-2 and MMP-9 are widely expressed and are best known as gelatinases.

Werb et al. demonstrated for the first time that treatment of cultured rabbit synovial fibroblasts with the central cell-binding FN-f stimulates expression of MMP-1 and MMP-3.[58] The FN-f can induce MMP-13 in human chondrocytes.[59] NH_2-terminal gelatin-binding FN-f stimulates production of MMP-13 and MMP-3 in porcine chondrocytes.[44] NH_2-terminal heparin-binding FN-f enhances MMP-3 and gelatinase expressions.[36,60] While treatment with COOH-terminal heparin-binding FN-f results in increased production of MMP-3 and MMP-13 in bovine cartilage,[37] the FN-f stimulates production of MMP-1, MMP-2, MMP-9, and MMP-13 in human cartilage.[61] The COOH-terminal heparin-binding FN-f also induces MMP-1, MMP-3, and MMP-13 in RA synovial fibroblasts.[62] In association with MMP production, the immunoassay for detection of type-II collagen cleavage by collagenase[55] has demonstrated that COOH-terminal heparin-binding FN-f enhances collagenase-mediated cleavage of type-II collagen in human[61] and bovine[37] cartilages. Matrix metalloproteinase-13 is a candidate collagenase responsible for the cleavage of type-II collagen because MMP-13 inhibitor can suppress the FN-f-induced collagen cleavage.[37]

Nitric oxide production by fibronectin fragments

Nitric oxide (NO) is a short-lived free radical that is synthesized enzymatically from L-arginine by a family of NO synthase (NOS) isoenzymes.[63,64] Nitric oxide is produced by a variety of cells, including chondrocytes.[65] Inducible NOS (iNOS) is expressed in response to bacterial endotoxin and proinflammatory cytokines such as IL-1. Once synthesized, iNOS generates large amounts of NO. Inducible NOS is strongly expressed in synovium and cartilage of patients with inflammatory joint diseases.[66] NO acts principally as a proinflammatory and destructive mediator. The pathogenetic role of NO in arthritis is certainly supported by the observation that inhibitors of NOS can suppress the development of disease in animal models, such as adjuvant arthritis and streptococcal cell wall arthritis.[67,68] Of FN-fs, NH_2-terminal heparin-binding FN-f has been shown to stimulate NO production in association with iNOS induction in human normal chondrocyte monolayer cultures.[69] Another FN-f, COOH-terminal heparin-binding FN-f, also causes increased NO production in RA cartilage.[70]

Cytokine production by fibronectin fragments

The early phase of cartilage degradation is associated with enhanced release of proinflammatory cytokines.[71,72] In human cartilage NH_2-terminal heparin-binding FN-f stimulates a pulsed release of TNFα and IL-1β, followed by a decrease in a few days. Enhanced release of IL-6 occurs earlier and continues for three weeks. IL-1α release shows a lag period.

Although cell responses to FN-fs and proinflammatory cytokines including IL-1 are qualitatively similar,[71,73] the involvement of cytokines in FN-f effects is controversial. The cytokine release by FN-f could partly account for the catabolic effects of NH_2-terminal heparin-binding FN-f on MMP-3 production and proteoglycan synthesis in human cartilage because antibodies to these cytokines partially block the FN-f activities.[72] Inhibition of FN-f effects with IL-1 receptor antagonist indicates that IL-1 could mediate type-II collagen cleavage by collagenase stimulated with COOH-terminal heparin-binding FN-f in bovine cartilage[37] and MMP-3 synthesis enhanced by RGD-containing peptide of central cell-binding FN-f in rabbit chondrocytes.[74] In contrast, MMP induction by NH_2-terminal gelatin-binding FN-f in porcine chondrocytes[44] and by COOH-terminal heparin-binding FN-f in RA synovial fibroblasts[62] is not via an IL-1 autocrine loop. Nitric oxide production by NH_2-terminal heparin-binding FN-f in human chondrocytes is also IL-1-independent.[69]

Receptors for fibronectin fragments

Cell–matrix interactions control cell function and behavior by signal transduction through a variety of cell surface receptors. FN can bind several integrins and other cell surface protein ligands.[75]

Integrin

Integrins are heterodimeric transmembrane proteins consisting of α and β subunits. Integrins bind extracellular matrix molecules and mediate cell adhesion, migration, and

invasion during development, tissue repair, tumor invasion, and metastasis. In concert with growth factor or cytokine receptors, integrins regulate cell proliferation, differentiation, and survival.[76,77] Integrins also serve as cell surface receptors that transduce intracellular signals.[78–80] Although the cytoplasmic domains of the integrin α and β subunits have no intrinsic enzymatic activity, integrin signaling is achieved by coupling signaling molecules to the cytoplasmic and transmembrane domains of the integrin subunits.[81] Integrins activate signaling pathways that are either common to all integrins or heterodimer-specific.[82] The cytoplasmic domains of α subunits may trigger signaling events that are specific for each individual integrin heterodimers.[83,84]

There is evidence that integrin regulates FN-f action. FN can bind α5β1 integrin through the cell-binding domain in III10 via RGD sequence (Fig. 1).[85,86] Matrix matalloproteinase production by the central cell-binding FN-f is probably mediated by α5β1 integrin because anti-α5β1 integrin antibody and RGD-containing peptide induce MMP-1 and gelatinase in rabbit synovial fibroblasts.[58] The cell-binding FN-f and anti-α5β1 integrin antibody can increase MMP-13 production in human chondrocytes.[59] Recent studies using antisense oligonucleotides to α5 integrin subunit have also shown the involvement of α5 integrin in cartilage proteoglycan degradation induced by NH_2-terminal heparin-binding and NH_2-terminal gelatin-binding FN-fs without cell-binding RGD sequence in addition to the central cell-binding FN-f.[87] These two NH_2-terminal FN-fs can be chemically cross-linked to α5 integrin subunit in chondrocytes.[88] However, employment of α5β1 integrin by NH_2-terminal heparin-binding FN-f remains to be investigated because blocking antibodies to α5 or β1 integrin subunit fail to inhibit the FN-f-stimulated NO production.[69] Integrin α5β1 is the primary receptor involved in the assembly of dimeric fibronectin into the extracellular matrix.[89] The I1–5 repeats of NH_2-terminal heparin-binding FN-f block the assembly of FN into fibrils, and FN dimers lacking these domains fail to be incorporated into fibrils.[90–93] NH_2-terminal heparin-binding FN-f may interfere with FN assembly and indirectly alter α5β1 signaling.

Rheumatoid arthritis synovial fibroblasts at the cartilage–pannus junction express integrin subunits α4, α5, and β1.[94] Integrin α4β1 recognizes CS-1 in alternatively spliced IIICS domain of FN.[95,96] Inhibition of MMP production with anti-α4 integrin antibody indicates that COOH-terminal heparin-binding FN-f, which contains CS-1 (Fig. 1), stimulates MMP-1, MMP-3, and MMP-13 in RA synovial fibroblasts via α4β1 integrin.[62] Indeed, CS-1 peptide induces these MMPs in the cells.[62] Since α4β1 integrin is newly expressed on articular chondrocytes in OA cartilage,[97,98] the COOH-terminal heparin-binding FN-f may work via the integrin in OA chondrocytes.

Excessive amounts of RGD peptide are required to induce proteoglycan release in cartilage explant culture while the central cell-binding FN-f at the same level causes stronger release of proteoglycan.[36] Compared with CS-1 peptide, the COOH-terminal heparin-binding FN-f can induce greater levels of MMPs.[62] Thus, FN-f could activate integrins more effectively than synthetic peptides.

CD44

Another cell surface receptor that could mediate FN-f action is CD44, a principal hyaluronan receptor.[99] The CD44 gene has 20 exons, 12 of which may be alternatively spliced to produce a number of different isoforms.[100] Restricted expression of CD44 isoforms and post-translational glycosylation of the parent protein provide diverse functions of CD44. Of CD44 isoforms, CD44H is commonly expressed in human articular chondrocytes.[101] Although CD44H is predominant, mRNA containing V3 exon of CD44 is also found in chondrocytes.[101] The diversity of CD44 is further amplified by the differential use of glycosaminoglycan attachment sites on its extracellular domain. While chondroitin sulfate proteoglycan is attached to the membrane proximal portion of external domain of CD44H,[102] heparan sulfate proteoglycan can bind CD44 at V3 in the membrane proximal extracellular domain of CD44v.[103] Chondroitin sulfate and heparan sulfate proteoglycans employ identical or overlapping binding sites in the repeats III13 and III14 of COOH-terminal heparin-binding FN-f (Fig. 1).[104,105] The COOH-terminal heparin-binding domain of FN is known to bind CD44.[104] While MMP production is up-regulated by COOH-terminal heparin-binding FN-f in human articular cartilage, anti-CD44 antibody can block the enhanced MMP production.[61] Suppression of the FN-f-stimulated MMP production by peptide V[61] suggests that the peptide V domain, a binding site of COOH-terminal heparin-binding FN-f for cell surface heparan sulfate proteoglycan,[106] is required for the FN-f-activated MMP induction. Thus, COOH-terminal heparin-binding FN-f may directly bind glycosaminoglycans on CD44 through the peptide V sequence, resulting in MMP induction.

CD44 is upregulated in articular cartilage from patients with OA[107] and RA.[108] Compared with normal cartilage, RA cartilage produces higher NO in response to the COOH-terminal heparin-binding FN-f.[70] Anti-CD44 treatment using the monoclonal anti-CD44 antibody and the peptide V reveals that NO production enhanced by COOH-terminal heparin-binding FN-f is mediated by CD44 in RA cartilage.[70] The inhibitory effects of anti-CD44 treatment are stronger in RA cartilage than in normal one, probably because CD44 is upregulated in RA cartilage and the proportion of CD44-positive chondrocytes is significantly higher than that in normal cartilage.[70] These findings indicate that increased NO production by COOH-terminal heparin-binding FN-f in RA cartilage is associated with elevated levels of CD44 on chondrocytes under such pathologic conditions. Of interest, FN-fs themselves may upregulate CD44 on chondrocytes because NH_2-terminal heparin-binding FN-f enhances CD44 expression in chondrocytes cultured in alginate beads,[109] which allows abundant cartilage matrix deposition around chondrocytes like in vivo cartilage.[110]

Intracellular signaling pathways activated by fibronectin fragments

Some FN-fs have been shown to activate the intracellular signaling pathways, mitogen-activated protein kinase (MAPK) and nuclear factor (NF)-κB pathways, leading to cartilage destruction.

Mitogen-activated protein kinase pathway

Activator protein-1 (AP-1), which includes members of the Jun and Fos families, is a pivotal transcriptional factor that regulates the production of cytokines and MMPs. The upstream regulatory regions of MMP genes contain the AP-1 recognition site.[111,112] Activator protein-1 can be activated by protein kinases that phosphorylate specific amino acid residues, especially by MAPK families.[113] Three major MAPK families have been identified: extracellular signal-regulated kinase (ERK), p38 MAPK, and c-Jun NH_2-terminal kinase (JNK).[114,115] All the three MAPK pathways are involved in the transcriptional regulation of Fos and Jun family genes.

The central cell-binding FN-f activates ERK, p38, and JNK, and increases the production of MMP-13 and gelatinases by human articular chondrocytes.[59] Another fibronectin fragment, NH_2-terminal heparin-binding FN-f, stimulates NO production in association with the activation of ERK, p38, and JNK in human chondrocytes.[69] Furthermore, collagenase induction leading to type-II collagen breakdown by COOH-terminal heparin-binding FN-f involves all the three MAPK pathways in human articular cartilage.[116] The COOH-terminal heparin-binding FN-f also causes phosphorylation of ERK1/2, JNK, and p38 for MMP production in RA synovial fibroblasts[62] and in human natural killer cells.[117]

Individual MAPK pathways may play different roles in the production of individual MMPs in response to FN-f. In RA synovial fibroblasts ERK seems to be involved in MMP-1, MMP-3, and MMP-13 production with COOH-terminal heparin-binding FN-f stimulation, whereas p38 MAPK may contribute to MMP-3 induction by the FN-f. JNK seems to promote the production of MMP-1 and MMP-13 in the FN-f-stimulated RA synovial fibroblasts.[62]

Different fragments of fibronectin may activate different isoforms of JNK. In human normal chondrocytes, NH_2-terminal heparin-, central cell-, and COOH-terminal heparin-binding FN-fs have been shown to individually activate ERK1/2 and p38.[59,69] The NH_2-terminal heparin-binding FN-f activates JNK1[69] whereas the central cell-binding fragment induces the activation of JNK1/2.[59] In contrast, the COOH-terminal heparin-binding FN-f activates JNK2.[116]

Coupling of integrin receptors to MAPK pathways has been reported.[118] Anti-α5β1 integrin antibody can activate ERK, p38, and JNK1/2 in human chondrocytes.[59] In addition, CS-1 peptide, which binds α5β1 integrin, causes the phosphorylation of these three MAPKs in RA synovial fibroblasts.[62] Thus, some integrin-binding FN-fs may employ integrin as a signaling receptor for MAPK activation. Upstream events in activation of MAPK cascades in association with FN-f stimulation remain to be clarified.

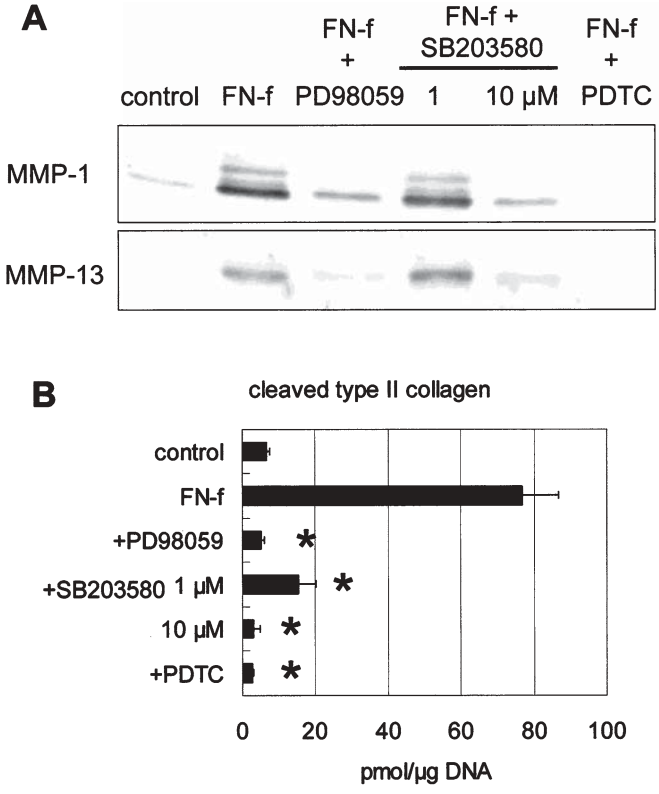

Fig. 2. Effects of mitogen-activated protein kinase (MAPK) and nuclear factor (NF)-κB inhibitors on matrix metalloproteinase (*MMP*) production (**A**) and type-II collagen cleavage by collagenase (**B**) by human articular cartilage with treatment with COOH-terminal heparin-binding fibronectin fragment (*FN-f*). Articular cartilage explants were preincubated with one of PD98059 at 50 μM that inhibits MEK, SD203580 at 1 μM that inhibits p38 or at 10 μM that inhibits p38 and JNK, and pyrrolidine dithiocarbamate (*PDTC*) at 30 μM (NF-κB inhibitor), and thereafter stimulated with the FN-f. Control cultures were without any additives. **A** Levels of proMMP-1 and proMMP-13 in conditioned media were analyzed by immunoblotting. **B** The collagenase-generated cleavage epitope in type II collagen was measured by enzyme-linked immunosorbent assay in conditioned media and cartilage (the latter following proteolysis of collagen to release epitope). Values are the mean ± SD of four determinations. $*P < 0.05$ versus FN-f-treated cultures

Nuclear factor-κB pathway

Nuclear factor-κB is another key regulator for MMPs.[119,120] Activation of NF-κB is dependent on the phosphorylation and degradation of IκB, an endogenous inhibitor that binds to NF-κB in the cytoplasm.[121] The released NF-κB then translocates to the nucleus, where it binds to specific NF-κB DNA binding sites and initiates gene expression including MMPs.

In contrast to MAPKs, NF-κB activation by FN-fs has rarely been studied. Phosphorylation of IκB by anti-α5β1 antibody suggests that the integrin-binding FN-fs could

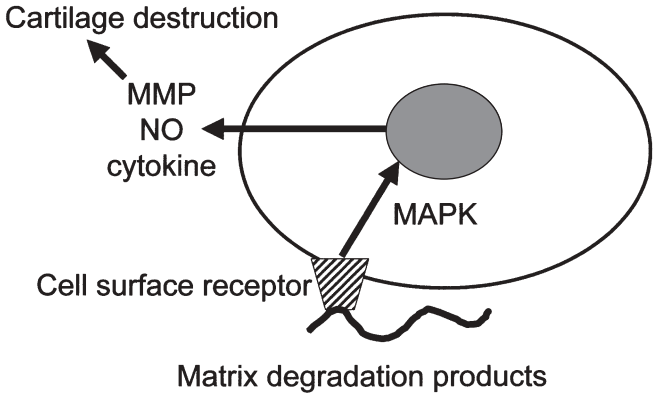

Fig. 3. Schematic diagram of cartilage destruction by matrix degradation products. Increased proteolytic matrix fragments activate chondrocytes and synovial fibroblasts, leading to the induction of matrix metalloproteinase (*MMP*), nitric oxide (*NO*), and cytokines via cell surface receptors such as integrins that can stimulate catabolic intracellular signals, including mitogen-activated protein kinase (*MAPK*)

activate the NF-κB pathway.[59] Our preliminary study using NF-κB inhibitor showed that NF-κB could be involved in collagenase production and type-II collagen cleavage by collagenase in human cartilage with treatment with COOH-terminal heparin-binding FN-f (Fig. 2). Further investigations will be required to clarify the involvement of NF-κB in catabolic actions of FN-fs.

Other degradation products of cartilage

Other fragments of matrix component can affect chondrocyte metabolism. For instance, fibrillar collagens and their degradation products influence cell-mediated proteolysis. Native and denatured forms of type-II collagen stimulate interstitial collagenase production by skin fibroblast.[122] Human monocytes produce elevated levels of IL-1 when exposed to native type-II collagen.[123,124] Synovial fluid mononuclear cells from patients with RA produce cytokines such as IL-1, IL-6, and TNFα in response to exposure to type-II collagen.[125] The CB11 peptide of type-II collagen can stimulate increased IL-1 production by monocytes/macrophages.[126] Jennings et al. have shown that mixed cleavage products of type-II collagen and those extracted from articular cartilage could induce proteolytic cartilage resorption at the level of proteoglycan degradation, and inhibit matrix synthesis.[127] Cyanogen bromide-cleaved fragments of type-II collagen can cause increased cleavage of type-II collagen by collagenase in chondrocyte pellet cultures.[128] Furthermore, hyaluronan hexasaccharides induce proteoglycan loss, suppression of proteoglycan synthesis, decreased aggregation of aggrecan, and gelatinase activity.[129] Hyaluronan fragments also stimulate NO production through iNOS activation in articular chondrocytes.[130]

Conclusion

Increased fragments from matrix degradation could play an important role in cartilage destruction in arthritis. These fragments activate chondrocytes and synovial fibroblasts, leading to the induction of MMPs, NO, and cytokines. Catabolic activities by FN-fs are probably mediated by cell surface receptors such as integrins that can stimulate catabolic intracellular signals, including MAPK (Fig. 3). Thorough understanding of the mechanism driven by matrix degradation products may contribute to prevention of cartilage destruction in OA and RA.

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