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Matrix Metalloproteinases: A Review of Their Structure and Role in Systemic Sclerosis

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Abstract Matrix metalloproteinases (MMPs) are the main enzymes involved in arterial wall extracellular matrix (ECM) degradation and remodeling, whose activity has been involved in various normal and pathologic processes, such as inflammation, fibrosis. As a result, the MMPs have come to consider as both therapeutic targets and diagnostic tools for the treatment and diagnosis of autoimmune diseases, including systemic lupus erythematosus and rheumatoid arthritis. Systemic sclerosis (SSc) is a rare autoimmune disease of unknown etiology characterized by an excessive over-production of collagen and other ECM, resulting in skin thickening and fibrosis of internal organs. In recent years, abnormal expression of MMPs has been demonstrated with the pathogenesis of SSc, and the association of different polymorphisms on MMPs genes with SSc has been extensively studied. This review describes the structure, function and regulation of MMPs and shortly summarizes current understanding on experimental findings, genetic associations of MMPs in SSc.

Keywords Matrix metalloproteinase · inhibitor · inflammatory · fibrosis · systemic sclerosis

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Introduction

Systemic sclerosis (SSc) is a multi-system disorder of connective tissue characterized by excessive fibrosis in the skin and various internal organs such as the lung, kidney and heart. SSc is generally divided into two categories based on the extent of skin fibrosis: diffuse cutaneous SSc (dcSSc) and limited cutaneous SSc (lcSSc) [1, 2]. Excessive accumulation of extracellular matrix (ECM) components, especially types I and III collagen, is the most prominent pathological manifestation of the disease [3, 4]. Numerous studies have shown that an abnormally increased synthesis of these constituents in SSc skin in vivo and in cells cultured form the skin of SSc patients grown in tissue culture may involve in the development of SSc [5, 6]. The tissue fibrosis in this disorder is the main features which is caused by an excessive accumulation of ECM, especially type I collagen. It reflects an imbalance between collagen production and degradation. In many studies, fibroblasts grown from SSc patients have revealed increased synthesis of collagen [4, 7].

Matrix metalloproteinases (also named matrixin or MMPs) are the main enzymes responsible for degradation of ECM components [8]. They are essential for various normal biological processes such as embryonic development, morphogenesis, reproduction tissue resorption and remodeling [9]. MMPs also have been implicated in a number of key pathologic processes including inflammation, fibrosis, arthritis, pulmonary diseases and cancer [10]. Their activity is regulated not only at the gene expression level but is also regulated by inhibitors, including an MMP-specific family, tissue inhibitors of metalloproteinases (TIMPs). MMPs are wildly studied in SSc. Up-regulated of MMPs may implicate in the process of the disease pathogenesis, and the imbalance between MMPs and the TIMPs is proposed to be crucial in the ECM deposition in SSc. Moreover, associations of MMPs and TIMPs polymorphisms

with susceptibility to SSc have been extensively reported. All these evidences indicate that MMPs may represent a novel target for the treatment of SSc.

The aim of this review is to provide an overview of the structure, function and regulation of MMPs and shortly summarize current literature on experimental findings, genetic associations of MMPs in SSc.

Structure of MMPs

The MMPs, discovered in 1962, are a family of at least 23 calcium-activated and zinc-dependent endopeptidases. They comprise a large family of protease and share several similarities in terms of their structure, regulation and function [11, 12]. More than 20 MMPs have been identified, and they are further divided into six major subfamilies based on structure and substrate specificity, including collagenases, gelatinases, stromelysins, matrilysins, membrane-type MMPs and other MMPs (Table I). The structure of all MMPs consists of three major domains: N-terminal hydrophobic signal sequence, a prodomain region and a catalytic domain [13, 14]. All MMPs except MMP-7 and MMP-22 have a C-terminal hemopexin-like domain, which determines their substrate specificity. A transmembrane domain is found in MMP-14, -15, -16, -17, -24, -25, which is important to cell-bound MMPs [15].

Regulation of MMPs

The regulation of MMPs is complex and occurs at various levels, including at gene transcription, posttranslational activation of zymogens, and endogenous inhibition [16].

Many regulatory factors such as cytokines (interleukin [IL], and tumor necrosis factor [TNF]), growth factors

Table I Characteristics of MMPs

Subgroup	MMP number	Chromosome location	Substrates
Collagenases	MMP-1 (collagenase 1)	11q22.3	Collagens I, II, III, VII, VIII, X, proteoglycans
	MMP-8 (collagenase 2)	11q21	Collagens I, II, III
	MMP-13 (collagenase 3)	11q22.3	Collagens I, II, III
	MMP-18 (collagenase 4)	- - - - -	Collagens I, II, III and some growth factors
Gelatinases	MMP-2 (gelatinase A)	16q21	Gelatin, collagen IV, V, VII, X, XI elastin, fibronectin
	MMP-9 (gelatinase B)	20q11.2–13.1	Gelatin, collagen IV, V, elastin, proteoglycans
Stromelysins	MMP-3 (stromelysin 1)	11q22.3	Laminin, fibronectin, elastin, proteoglycans, collagens III, IV, V, VII, IX, X
	MMP-10 (stromelysin 2)	11q22.3	Fibronectin, elastin, gelatin, collagens III, IV, V, IX, X
	MMP-11 (stromelysin 3)	22q11.2	Gelatin, fibronectin, proteoglycans
Matrilysins	MMP-7 (matrilysin 1)	11q21–q22	Laminin, fibronectin, elastin, collagen IV, X
	MMP-26 (matrilysin 2)	11q21–q22	Laminin, fibronectin, elastin, collagen IV, X
Membrane-type MMPs	MMP-14 (MT1-MMP)	14q11–q12	Laminin, fibronectin, Collagen I, III, IV
	MMP-15 (MT2-MMP)	16q13–q21	Laminin, fibronectin, Collogen I, II, IV
	MMP	8q21–q22.1	Gelatin, fibronectin, collagen III, IV
	MMP	12q24.33	Gelatin, collagen III, IV
	MMP	20q11.2	ND
	MMP	- - - - -	ND
Other MMPs	MMP-12	11q22.2–22.3	Laminin, fibronectin, elastin, vitronectin, collagen IV
	MMP-19	12q14	Fibronectin, gelatin, collagen IV
	MMP-20	11q22	Amelogenin
	MMP-21	1p 36	ND
	MMP-22	1p 36	ND
	MMP-23	1p 36	Gelatin
	MMP-27	- - - - -	ND
	MMP-28	- - - - -	Casein

ND not determined

(epidermal growth factor [EGF], transforming growth factor [TGF], and platelet-derived growth factor [PDGF]), hormones, steroids, oncogenic cellular transformations may involved in the gene expression of MMPs at the level of transcription [17, 18]. As an illustration, IL-1, IL-12, EGF, PDGF and TNF can up-regulate the expression of MMPs. However, TGF, hormones and steroids can down-regulate the expression of MMPs [19–21]. MMPs can further participate in processing and activating other MMPs. The regulatory mechanisms of MMPs induced by such stimuli may vary according to different MMPs and cell types. Furthermore, single nucleotide polymorphisms (SNPs) in gene-regulatory DNA elements may also influence MMPs transcription.

All the MMPs are synthesized and secreted in inactive forms as the latent zymogens, and are activated by the loss of a 10-kDa propeptide either extracellularly or on cell membranes. This step may occur in either intracellular or extracellular. Besides, the highly conserved cysteine residues ("cysteine switch") in the propeptide domain have the ability to bind the zinc atom in the catalytic domain, thereby rendering the enzyme inactive [22, 23].

Activation of MMPs is regulated by TIMPs which are a group of structurally related, endogenous inhibitors. They inhibit the activity of MMPs through non-covalent binding of active forms of MMPs in the extracellular space in 1:1 molar stoichiometry [24]. The dynamic equilibrium between active MMPs and TIMPs is crucial for many diverse cellular processes including proliferation, migration, adhesion and apoptosis. Besides, TIMPs also play a critical role in maintaining the balance between ECM deposition and degradation in physiological processes [25, 26]. To date, four TIMPs have been identified: TIMP-1, -2, -3, and -4 [27]. These TIMPs are secreted by a variety of cell lines including smooth muscle cells and macrophages and their activity is increased by PDGF and TGF-β and either increased or decreased by different ILs [28].

MMPs in Inflammatory Process

Numerous studies have been reported that MMPs can either promote or inhibit inflammatory process by direct proteolytic processing of inflammatory mediators including chemokines, cytokines to activate, inactivate or antagonize their functions [29, 30]. As described in a comprehensive review on the roles of MMPs in inflammatory condition by Manicone et al. [30], inflammatory cytokines are involved in the MMPs gene expression. For example, TNF-α is expressed on T-cells and macrophages as a 26 kDa membrane-bound protein (pro-TNF-α) that is activated by cleavage to a 17 kDa soluble cytokine by TNF converting enzyme (TACE), identical to ADAM17, a member of the disintegrin family of metalloproteinases [31]. Besides, IL-1β is another potent pro-inflammatory cytokine that requires proteolytic processing before activation not only by caspase-1 but also several MMPs, including MMP-2, MMP-3 and MMP-9. Interestingly, MMP-3 can degrade the mature IL-1β cytokine, suggesting potentially dual roles for MMPs in either stimulating or inhibiting IL-1β effects [32].

MMPs and Fibrosis

Organ fibrosis is a complex process that is defined as excess deposition and accumulation of ECM in the tissues including skin, heart, lung, kidney and vessels [33]. The amount of ECM in the tissue may be controlled through balance among the ECM production, the ECM degradation by MMPs and TIMPs. Too little or too much accumulation of ECM may result in different diseases such as connective tissue disorders or organ fibrosis [34]. The decreased activity of ECM-removing MMPs is mainly due to an increased expression of their TIMPs. Evidences suggest that fibrotic livers have high expression of the TIMPs, including TIMP-1 and TIMP-2, and thus the combination of low expression of MMPs and high TIMPs may prevent the degradation of the fibrillar collagens. An expert review by Iimuro et al. [35] showed that the imbalance between too few MMPs, too much ECM and too many TIMPs possibly accounted for the advanced liver fibrosis and the failure to resolve the fibrous scar. For example, MMP-9-deficient mice exhibited significantly less pulmonary fibrosis (PF) in response to bleomycin than their with MMP-9+/+ littermates [36]. In the hepatic fibrosis model infected by Schistosoma mansoni, the severity of fibrosis was most closely associated with the increased MMP-9 activity [37]. Similarly, in response to bleomycin, mice deficient in γ-glutamyl transpeptidase showed a reduction in PF, in part associated with lower MMP-9 activity in lung tissues [38]. Besides, some researches also suggest that MMP-13 may be involve in the pathogensis of PF. In rat animal models, the expression levels of MMP-13 were decreased in lung tissue of bleomycin-induced PF in contrast to normal lung tissue [39]. Selman et al. [40] demonstrated that the expression of MMP-13 was not detected in lung tissue of people with human idiopathic PF. Asano et al. [41] suggested that MMP-13 might be involved in the fibrotic process of SSc, especially in the initiation of fibrosis.

Aberrant Expression of MMPs/TIMPs in SSc

SSc is mainly characterized by microvascular damage and excess organ fibrosis. The damage is caused by a massive deposition of collagen and other connective tissue

components. In general, tissue fibrosis reflects an imbalance between collagen production and degradation. Numerous studies have shown that MMPs and TIMPs are expressed in SSc disease processes. In one study [42], patients with SSc had higher serum concentrations of MMP-9 and TIMP-1, and a higher ratio of MMP-9 to TIMP-1 than healthy controls. Serum MMP-9 concentrations were significantly higher in the diffuse type than the limited type of SSc. Serum concentrations of MMP-9 correlated well with the degree of skin involvement, as determined by the Rodnan score and with serum concentrations of TGF-β. Moreover, dermal fibroblasts from patients with SSc produced more MMP-9 than those from healthy controls when they were stimulated with IL-1β, TNF-α, or TGF-β. As we know, SSc is frequently accompanied with interstitial lung disease (ILD) often leading to lung fibrosis. ILD may develop in both lcSSc and dcSSc and is associated with decreased survival. Andersen et al. [43] showed that bronchoalveolar fluid levels of MMP-9 were enhanced in SSc patients with signs of ILD, compared to SSc patients without ILD and healthy controls. TIMP-1 levels were elevated in both patient groups compared with healthy controls. Levels of MMP-9 and TIMP-1 were inversely associated with total lung capacity, suggesting a role in the remodelling in ILD and lung fibrosis. Circulating MMP-7 levels were significantly higher in SSc patients compared with normal controls. The negatively significant correlation of MMP-7 concentrations and the diffusion capacity of the lung for carbon monoxide value together with the significant correlation with lung fibrosis and dyspnea indicated a correlation between the MMP-7 concentration and the extent of pulmonary involvement [44]. Findings from a recent study [45] on the clinical correlations of MMP-12 with SSc suggested that serum levels of MMP-12 were significantly higher in both patients with dcSSc and lcSSc, and increased serum levels of MMP-12 were associated with the extent of skin involvement, the presence of digital ulcers and severity of nailfold capillary abnormalities. Furthermore, MMP-12 was found to be strongly expressed in different cell types of SSc skin and lung tissues including fibroblasts, microvascular endothelial cells and inflammatory cells. All of these indicated MMP-12 a critical role in the development and progression of skin sclerosis, PF and peripheral vascular damage in patients with SSc. However, another study by Kikuchi K et al. [46] showed that Serum MMP-9 activity in patients with diffuse cutaneous SSc was significantly decreased compared with that of limited cutaneous SSc or normal controls. Asano et al. [41] found that the serum levels of MMP-13 were significantly decreased in SSc patients, suggesting that the decreased expression of MMP-13 contributed to the establishment of fibrosis through reducing the degradation of ECM proteins.

Genetic Polymorphisms of MMPs and SSc

It has now been established that sequence variation in the promoter regions of MMP genes may alter the level of gene expression and thus influence MMP/TIMP balance within the ECM. The association of MMPs gene SNPs with SSc has been extensively studied, but the controversial results exist. Marasini et al. [47] showed that individuals who carried 6A allele of MMP-3 might be relevant for susceptibility to and pathogenesis of SSc. For MMP-12 promoter region, the SNP rs2276109, has been studies in Italian population with SSc [48]. A significant difference was observed in MMP-12 rs2276109 genotype distribution between patients with SSc and controls (P=0.0003), and between lcSSc and dcSSc (P=0.003). This gene polymorphism might contribute to susceptibility to SSc, and in particular to dcSSc and PF. In a large cohort of European Caucasian, Wipff et al. [49] investigated six SNPs (rs-1306, rs-790, rs-735, rs1292301, rs7201, rs243849) of the MMP-2 gene, two SNPs (rs17576, rs2274756) of MMP-9 and two SNPs (rs743257, rs1042703) of MMP-14 genes with the susceptibility to SSc. They did not find any association between the investigated polymorphisms and SSc susceptibility nor with the major SSc clinical subsets. Skarmoutsou et al. [50] showed that the presence of the polymorphism −1562 C/T (rs3918242) of MMP-9 was not associated with the susceptibility to SSc in the Italian population, but it seemed to suggest that the C/T genotype of the MMP-9 −1562 C/T polymorphism might be associated with a smaller risk for susceptibility to developing skin ulcers only in male SSc patients. A same polymorphism in the MMP-1 promoter resulting from a guanine insertion at −1607 bp had been identified in different populations. Johnson et al. [51] failed to detect any association with the development and clinical manifestations of SSc in Caucasians, African-Americans, and Hispanics. Similar results were also found on this issue, but the high activity promoter genotype of MMP-1 seemed to significantly correlate with the limited subset of Korean SSc patients [52]. Besides, Indelicato et al. [53] analyzed three polymorphisms of the TIMP-1 gene (−19A/G, +261 C/T and +372 T/C) in Italian population. Their findings suggested that the +372 T/C polymorphism was associated with SSc in male individuals, but no association with the clinical characteristics of SSc Italian patients and TIMP-1 gene polymorphisms was observed.

Given the complexity of the mechanisms driving SSc and the heterogeneity of the studied populations, further studies will be necessary. However, upon validation and confirmatory mechanistic studies, MMP polymorphisms may be a valuable tool for clinical stratification of SSc patients.

Therapeutic Value of MMPs in SSc

As described above, the discovery of MMPs may be a new field of investigation for the development of new therapeutics in the treatment of SSc. Sato et al. [54] showed that anti-MMP-1 autoantibody contributed to the development of fibrosis by inhibiting MMP-1 collagenase activity and reducing the ECM turnover, and anti-MMP-1 autoantibody might also contribute to SSc vasculopathy through inhibition of angiogenesis as well as vascular damage due to fibrosis. As a result, they pointed out that MMP inhibitors, including anti-MMP-1 antibody, would be potential therapeutic targets for SSc. Nishijima et al. [55] also found similar results, and suggested that anti-MMP-3 antibody might be related to various aspects of SSc disease expression, including skin sclerosis, lung fibrosis, renal vasculopathy and autoimmunity. Apart from these, Serrati et al. [56] suggested that MMP-12 over-production in SSc fibroblasts and SSc endothelial cells might have a critical pathogenic role in SSc-associated vascular alterations, and MMP-12 could be therapeutically effective in SSc by blocking angiogenesis. In addition, over-production of MMP-12 by SSc microvascular endothelial cells might contribute to reduced angiogenesis in SSc patients, suggesting clinical relevance in therapeutic attempts to reverse the process of anti-angiogenesis [57, 58].

Conclusion

SSc has the highest case fatality rate among the connective tissue diseases. Although clinical outcomes have improved in recent years, no current therapy is able to reverse or slow the natural progression of this disease [59]. Thus, SSc is considered incurable, and so determining the mechanisms underlying the disease is a priority for research efforts. As all we known, MMPs play an important role in both physiological and pathological condition. The degree of this involvement can be modulated either by increasing or decreasing MMP expression and activity. Their role in SSc is unfolding as we obtain more information implicating their presence in inflammatory and fibrosis process. We propose that MMPs may play an important role in the etiology of SSc. In spite of the presence of few conflicting data regarding MMPs in SSc, generally this enzyme can be regarded as participating in crucial steps in the pathogenesis of autoimmune diseases. Therefore, it should be considered a target for therapy in SSc.

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Conflict of Interest None.

References

1. Gilliam AC. Scleroderma. Curr Dir Autoimmun. 2008;10:258–79.
2. Randone SB, Guiducci S, Cerinic MM. Systemic sclerosis and infections. Autoimmun Rev. 2008;8:36–40.
3. LeRoy EC. Increased collagen synthesis by scleroderma skin fibroblasts in vivo. J Clin Invest. 1974;54:880–9.
4. Uitto J, Bauer EA, Eisen AZ. Scleroderma: increased biosynthesis of triple-helical type I and type III procollagens associated with unaltered expression of collagenase by skin fibroblasts. J Clin Invest. 1979;64:921–30.
5. Peltonen J, Kahari L, Uitto J, Jimenez SA. Increased expression of type VI collagen genes in systemic sclerosis. Arthritis Rheum. 1990;33:1829–35.
6. Kuroda K, Shinkai H. Gene expression of types I and III collagen, decorin, matrix metalloproteinases and tissue inhibitors of metallopro-teinases in skin fibroblasts from patients with systemic sclerosis. Arch Dermatol Res. 1997;289:567–72.
7. Fleischmajer R, Perlish JS, Krieg T, Trimpl R. Variability in collagen and fibronectin synthesis by scleroderma fibroblasts in primary culture. J Invest Dermatol. 1981;76:400–3.
8. Clutterbuck AL, Asplin KE, Harris P, Allaway D, Mobasheri A. Targeting matrix metalloproteinases in inflammatory conditions. Curr Drug Targets. 2009;10:1245–54.
9. Szarvas T, vom Dorp F, Ergün S, Rübben H, vom Dorp F, Ergün S. Matrix metalloproteinases and their clinical relevance in urinary bladder cancer. Nat Rev Urol. 2011;8:241–54.
10. Amălinei C, Căruntu ID, Giuşcă SE, Bălan RA. Matrix metalloproteinases involvement in pathologic conditions. Rom J Morphol Embryol. 2010;51:215–28.
11. Nagase H, Woessner Jr JF. Matrix metalloproteinases. J Biol Chem. 1999;274:21491–4.
12. Bode W, Maskos K. Structural studies on MMPs and TIMPs. Methods Mol Biol. 2001;151:45–77.
13. Nagase H. Activation mechanisms of matrix metalloproteinases. Biol Chem. 1997;378:151–60.
14. Visse R, Nagase H. Matrix metalloproteinases and tissue inhibitors of metalloproteinases: structure, function, and biochemistry. Circ Res. 2003;92:827–39.
15. Gaggar A, Hector A, Bratcher PE, Mall MA, Griese M, Hartl D. The role of matrix metalloproteinases in cystic fibrosis lung disease. Eur Respir J. 2011;38:721–7.
16. Galis ZS, Khatri JJ. Matrix metalloproteinases in vascular remodeling and atherogenesis: the good, the bad and the ugly. Circ Res. 2002;90:251–62.
17. Yan C, Boyd DD. Regulation of matrix metalloproteinase gene expression. J Cell Physiol. 2007;211:19–26.
18. Fanjul-Fernández M, Folgueras AR, Cabrera S, López-Otín C. Matrix metalloproteinases: evolution, gene regulation and functional analysis in mouse models. Biochim Biophys Acta. 2010;1803:3–19.
19. Hozumi A, Nishimura Y, Nishiuma T, Kotani Y, Yokoyama M. Induction of MMP-9 in normal human bronchial epithelial cells by TNF-alpha via NF-kappa B-mediated pathway. Am J Physiol Lung Cell Mol Physiol. 2001;281:L1444–52.
20. Alper O, Bergmann-Leitner ES, Bennett TA, Hacker NF, Stromberg K, Stetler-Stevenson WG. Epidermal growth factor receptor signaling and the invasive phenotype of ovarian carcinoma cells. J Natl Cancer Inst. 2001;93:1375–84.
21. Mengshol JA, Vincenti MP, Brinckerhoff CE. IL-1 induces collagenase-3 (MMP-13) promoter activity in stably transfected

chondrocytic cells: requirement for Runx-2 and activation by p38 MAPK and JNK pathways. Nucleic Acids Res. 2001;29:4361–72.
22. Rouis M. Matrix metalloproteinases: a potential therapeutic target in atherosclerosis. Curr Drug Targets Cardiovasc Haematol Disord. 2005;5:541–8.
23. Van Wart HE, Birkeda-Hansenl H. The cysteine switch: a principle of regulation of metalloproteinase activity with potential applicability to the entire matrix metalloproteinase gene family. Proc Natl Acad Sci USA. 1990;87:5578–82.
24. Beaudeux JL, Giral P, Bruckert E, Foglietti MJ, Chapman MJ. Matrix metalloproteinases, inflammation and atherosclerosis: therapeutic perspectives. Clin Chem Lab Med. 2004;42:121–31.
25. Hulboy DL, Rudolph LA, Matrisian LM. Matrix metalloproteinases as mediators of reproductive function. Mol Hum Reprod. 1997;3:27–45.
26. Vu TH, Werb Z. Matrix metalloproteinases: effectors of development and normal physiology. Genes Dev. 2000;14:2123–33.
27. Cruz-Munoz W, Khokha R. The role of tissue inhibitors of metalloproteinases in tumorigenesis and metastasis. Crit Rev Clin Lab Sci. 2008;45:291–338.
28. Jones CB, Sane DC, Herrington DM. Matrix metalloproteinases: a review of their structure and role in acute coronary syndrome. Cardiovasc Res. 2003;59:812–23.
29. Van Lint P, Libert C. Chemokine and cytokine processing by matrix metalloproteinases and its effect on leukocyte migration and inflammation. J Leuk Biol. 2007;82:1375–81.
30. McGuire JK, Manicorne AM. Matrix metalloproteinases as modulators of inflammation. Semin Cell Dev Biol. 2008;19:34–41.
31. Black RA, Rauch CT, Kozlosky CJ, Peschon JJ, Slack JL, Wolfson MF, et al. A metalloproteinase disintegrin that releases tumour-necrosis factor-alpha from cell. Nature. 1997;385:729–33.
32. Ito A, Mukaiyama A, Itoh H, Nagase H, Thorgersen IB, Enghild JJ, et al. Degradation of interleukin 1 beta by matrix metalloproteinases. J Biol Chem. 1996;271:14657–60.
33. Jinnin M. Mechanisms of skin fibrosis in systemic sclerosis. J Dermatol. 2010;37:11–25.
34. Uitto J, Kouba D. Cytokine modulation of extracellular matrix gene expression: relevance to fibrotic skin diseases. J Dermatol Sci. 2001;24 Suppl 1:S60–9.
35. Iimuro Y, Brenner DA. Matrix metalloproteinase gene delivery for liver fibrosis. Pharm Res. 2008;25:249–58.
36. Betsuyaku T, Fukuda Y, Parks WC, Shipley JM, Senior RM. Gelatinase B is required for alveolar bronchiolization after intratracheal bleomycin. Am J Pathol. 2000;157:525–35.
37. Vaillant B, Chiaramonte MG, Cheever AW, Soloway PD, Wynn TA. Regulation of hepatic fibrosis and extracellular matrix genes by the Th response: new insight into the role of tissue inhibitors of matrix metalloproteinases. J Immunol. 2001;167:7017–26.
38. Pardo A, Ruiz V, Arreola JL, Ramirez R, Cisneros-Lira J, Gaxiola M, et al. Bleomycin-induced pulmonary fibrosis is attenuated in gamma-glutamyl transpeptidase-deficient mice. Am J Respir Crit Care Med. 2003;167:925–32.
39. Ruiz V, Ordóñez RM, Berumen J, Ramírez R, Uhal B, Becerril C, et al. Unbalanced collagenases/TIMP-1 expression and epithelial apoptosis in experimental lung fibrosis. Am J Physiol Lung Cell Mol Physiol. 2003;285:L1026–36.
40. Selman M, Ruiz V, Cabrera S, Segura L, Ramírez R, Barrios R, et al. TIMP-1, -2, -3, and -4 in idiopathic pulmonary fibrosis. A prevailing nondegradative lung microenvironment? Am J Physiol Lung Cell Mol Physiol. 2000;279:L562–74.
41. Asano Y, Ihn H, Kubo M, Jinnin M, Mimura Y, Ashida R, et al. Clinical significance of serum levels of matrix metalloproteinase-13 in patients with systemic sclerosis. Rheumatology (Oxford). 2006;45:303–7.
42. Kim WU, Min SY, Cho ML, Hong KH, Shin YJ, Park SH, et al. Elevated matrix metalloproteinase-9 in patients with systemic sclerosis. Arthritis Res Ther. 2005;7:R71–9.
43. Andersen GN, Nilsson K, Pourazar J, Hackett TL, Kazzam E, Blomberg A, et al. Bronchoalveolar matrix metalloproteinase 9 relates to restrictive lung function impairment in systemic sclerosis. Respir Med. 2007;101:2199–206.
44. Moinzadeh P, Krieg T, Hellmich M, Brinckmann J, Neumann E, Müller-Ladner U, et al. Elevated MMP-7 levels in patients with systemic sclerosis: correlation with pulmonary involvement. Exp Dermatol. 2011;20:770–3.
45. Manetti M, Guiducci S, Romano E, Bellando-Randone S, Conforti ML, Ibba-Manneschi L, et al. Increased serum levels and tissue expression of matrix metalloproteinase-12 in patients with systemic sclerosis: correlation with severity of skin and pulmonary fibrosis and vascular damage. Ann Rheum Dis. 2012;71:1064–72.
46. Kikuchi K, Kubo M, Hoashi T, Tamaki K. Decreased MMP-9 activity in the serum of patients with diffuse cutaneous systemic sclerosis. Clin Exp Dermatol. 2002;27:301–5.
47. Marasini B, Casari S, Zeni S, Turri O, Biondi ML. Stromelysin promoter polymorphism is associated with systemic sclerosis. Rheumatology (Oxford). 2001;40:475–6.
48. Manetti M, Ibba-Manneschi L, Fatini C, Guiducci S, Cuomo G, Bonino C, et al. Association of a functional polymorphism in the matrix metalloproteinase-12 promoter region with systemic sclerosis in an Italian population. J Rheumatol. 2010;37:1852–7.
49. Wipff J, Dieude P, Avouac J, Tiev K, Hachulla E, Cracowski JL, et al. Association of metalloproteinase gene polymorphisms with systemic sclerosis in the European Caucasian population. J Rheumatol. 2010;37:599–602.
50. Skarmoutsou E, D'Amico F, Marchini M, Stivala F, Malaponte G, Scorza R, et al. Analysis of matrix metalloproteinase-9 gene polymorphism -1562 C/T in patients suffering from systemic sclerosis with and without ulcers. Int J Mol Med. 2011;27:873–7.
51. Johnson RW, Reveille JD, McNearney T, Fischbach M, Friedman AW, Ahn C, et al. Lack of association of a functionally relevant single nucleotide polymorphism of matrix metalloproteinase-1 promoter with systemic sclerosis (scleroderma). Genes Immun. 2001;2:273–5.
52. Joung CI, Na YI, Shin ES, Sung YK, Yoo DH, Jun JB. The single nucleotide polymorphisms of matrix metalloproteinase-1 in patients with systemic sclerosis. Rheumatol Int. 2008;28:1183–5.
53. Indelicato M, Chiarenza V, Libra M, Malaponte G, Bevelacqua V, Marchini M, et al. Analysis of TIMP-1 gene polymorphisms in Italian sclerodermic patients. J Clin Lab Anal. 2006;20:173–6.
54. Sato S, Hayakawa I, Hasegawa M, Fujimoto M, Takehara K. Function blocking autoantibodies against matrix metalloproteinase-1 in patients with systemic sclerosis. J Invest Dermatol. 2003;120:542–7.
55. Nishijima C, Hayakawa I, Matsushita T, Komura K, Hasegawa M, Takehara K, et al. Autoantibody against matrix metalloproteinase-3 in patients with systemic sclerosis. Clin Exp Immunol. 2004;138:357–63.
56. Serratì S, Cinelli M, Margheri F, Guiducci S, Del Rosso A, Pucci M, et al. Systemic sclerosis fibroblasts inhibit in vitro angiogenesis by MMP-12-dependent cleavage of the endothelial cell urokinase receptor. J Pathol. 2006;210:240–8.
57. D'Alessio S, Fibbi G, Cinelli M, Guiducci S, Del Rosso A, Margheri F, et al. Matrix metalloproteinase 12-dependent cleavage of urokinase receptor in systemic sclerosis microvascular endothelial cells results in impaired angiogenesis. Arthritis Rheum. 2004;50:3275–85.
58. Margheri F, Manetti M, Serratì S, Nosi D, Pucci M, Matucci-Cerinic M, et al. Domain 1 of the urokinase-type plasminogen activator receptor is required for its morphologic and functional, beta2 integrin-mediated connection with actin cytoskeleton in human microvascular endothelial cells: failure of association in systemic sclerosis endothelial cells. Arthritis Rheum. 2006;54:3926–38.
59. Au K, Khanna D, Clements PJ, Furst DE, Tashkin DP. Current concepts in disease-modifying therapy for systemic sclerosis-associated interstitial lung disease: lessons from clinical trials. Curr Rheumatol Rep. 2009;11:111–9.