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Review

Matrix metalloproteinases in inflammation ☆

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ABSTRACT

Background: Matrix metalloproteinases (MMPs) are a family of ubiquitously expressed zinc-dependent endopeptidases with broad substrate specificity and strictly regulated tissue specific expression. They are expressed in physiological situations and pathological conditions involving inflammation. MMPs regulate several functions related to inflammation including bioavailability and activity of inflammatory cytokines and chemokines. There is also evidence that MMPs regulate inflammation in tumor microenvironment, which plays an important role in cancer progression.

Scope of review: Here, we discuss the current view on the role of MMPs in the regulation of inflammation.

Major conclusions: MMPs modulate inflammation by regulating bioavailability and activity of cytokines, chemokines, and growth factors, as well as integrity of physical tissue barriers. MMPs are also involved in immune evasion of tumor cells and in regulation of inflammation in tumor microenvironment.

General significance: There is increasing evidence for non-matrix substrates of MMPs that are related to regulation of inflammatory processes. New methods have been employed for identification of the substrates of MMPs in inflammatory processes *in vivo*. Detailed information on the substrates of MMPs may offer more specific and effective ways of inhibiting MMP function by blocking the cleavage site in substrate or by inhibition of the bioactivity of the substrate. It is expected, that more precise information on the MMP–substrate interaction may offer novel strategies for therapeutic intervention in inflammatory diseases and cancer without blocking beneficial actions of MMPs. This article is part of a Special Issue entitled Matrix-mediated cell behaviour and properties.

1. Introduction

Matrix metalloproteinases (MMPs) are a family of proteolytic enzymes involved in physiological situations including tissue homeostasis, host defense and tissue repair. There is also evidence, that MMPs play a role in the pathogenesis of inflammatory diseases with focal tissue destruction, such as rheumatoid arthritis, osteoarthritis, and chronic cutaneous ulcerations, as well as in cancer progression [1–4]. The expression and activity of MMPs are under strict control in physiological situations, whereas excessive activity of MMPs is often noted in pathological conditions [5]. MMPs were initially characterized as extracellular matrix (ECM) cleaving proteolytic enzymes, but during the past years, a growing number of non-matrix substrates for MMPs have been identified [5,6].

MMPs can orchestrate the inflammatory functions at various levels [5,6]. They can regulate transmigration of inflammatory cells from vasculature to the site of inflammation in tissue. They also regulate the recruitment and influx of inflammatory cells to the site of inflammation by processing ECM components, growth factors, cytokines and chemokines. While the role of the members of ADAM family of metalloproteinases (ADAM, a proteinase with a disintegrin and a metalloprotease domain) in inflammatory processes has been well characterized, in this review we focus on the role of MMPs in inflammation.

2. Matrix metalloproteinases

MMPs belong to the metzincin superfamily, which is characterized by the presence of a highly conserved motif containing three histidine residues, which chelate a zinc ion in the catalytic site [7]. Other families in the metzincin super family are ADAMs and ADAM-TSs (ADAM with thrombospondin like motif), astacins, and serralysins. MMPs are ubiquitously expressed zinc-dependent endopeptidases with wide substrate specificities. They are produced either as soluble or cell membrane anchored proteinases that cleave proteins and proteoglycan components

Abbreviations: ADAM, a proteinase with a disintegrin and a metalloprotease domain; ADAM-TS, ADAM with thrombospondin like motif; EGF, epidermal growth factor; IL, interleukin; MMP, matrix metalloproteinase; TGF, transforming growth factor; TNF, tumor necrosis factor; ZO, zona occludens

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of ECM. In addition, MMPs cleave a multitude of non-matrix substrates including cytokines, chemokines, growth factors, growth factor receptors and cell surface adhesion receptors (Table 1). The members of the MMP family display marked differences in their tissue specific expression and substrate specificity making MMPs a diverse group of proteolytic enzymes with multiple physiological functions. Moreover, expression and activity of various MMPs has also been reported in pathological conditions, such as inflammatory diseases and cancer [1–5].

2.1. MMP structure and function

To date, 23 human MMPs have been identified. According to their structure, substrate specificity, and function, MMPs can be classified to different subgroups: *collagenases* (MMP-1, -8, and -13), *gelatinases* (MMP-2 and -9), *stromelysins* (MMP-3, and -10), *stromelysin-like* MMPs (MMP-11 and -12), *matrilysins* (MMP-7, and -26), *transmembrane* MMPs (MMP-14, -15, -16, and -24), glycosyl-phosphatidyl-

Table 1
Non-matrix substrates of MMPs.

MMP	Substrate	Response	Reference
MMP-1	α1-antitrypsin/α1-antichymotrypsin	Inactive serpins	[60,143]
	IL-1β	Inactivation of IL-1β	[61]
	Latent TNF-α	Bioavailable TNF-α	[60]
	MCP-1, -2, -3, -4	CC chemokine receptor antagonists	[58]
	IGFBP-2, -3	Bioavailable IGF	[87,88]
	SDF-1	Inactive chemokine	[57]
	VEGF	Activation	[89]
MMP-2	IL-1β	Inactivation of IL-1β	[61]
	Pro-IL-1β	Activation of IL-1β	[55]
	SDF-1	Inactive chemokine	[57]
	MCP-3	CC chemokine receptor antagonists	[58]
	IGFBP-3	Bioavailable IGF	[88]
	Latent TGF-β	Activation	[90]
	Latent TNFα	Bioavailable TNFα	[60]
	FGFR1	Bioactive FGFR1 ectodomain	[91]
	Pleiotrophin	Mobilization of VEGF	[92]
	CTGF	Mobilization of VEGF	[92]
MMP-3	α1-antitrypsin/α1-antichymotrypsin	Inactive serpins	[93]
	IL-1β	Inactivation of IL-1β	[61]
	Pro-IL-1β	Activation of IL-1β	[55]
	MCP-1, -2, -3, -4	CC chemokine receptor antagonists	[58]
	SDF-1	Inactive chemokine	[57]
	IGFBP-1, 3	Bioavailable IGF	[88,94]
	Latent TGF-β	Activation	[95]
	Pro-HB-EGF	Activation	[96]
	Latent TNFα	Bioavailable TNFα	[60]
	Osteopontin	Increased bioactivity	[97]
	VEGF	Activation	[89]
MMP-7	α1-antitrypsin	Inactive serpinA1	[93]
	Pro-HB-EGF	Activation	[98,99]
	Latent TNFα	Bioavailable TNFα	[59]
	Syndecan-1	CXC1-chemokine gradient	[62]
	Osteopontin	Increased bioactivity	[97]
	Cellular membrane bound FasL	Active/inactive soluble FasL	[100,101]
MMP-8	α1-antitrypsin	Inactive serpinA1	[60]
	CXCL5	Increased bioactivity	[54]
	IL-8	Activation	[102]
MMP-9	α1-antitrypsin	Inactive serpinA1	[52]
	IL-1β	Inactivation of IL-1β	[61]
	Pro-IL-1β	Activation of IL-1β	[55]
	CXCL5	Inactivation	[54]
	IL-8	Potentiates the activity of IL-8	[65]
	SDF-1	Inactive chemokine	[57]
	Latent TGF-β	Activation	[90]
	Latent TNFα	Bioavailable TNF-α	[60]
	IL-2Rα	Cleavage of IL-2Rα	[80]
	IGFBP-1	Bioavailable IGF	[94]
	VEGF	Activation	[89]
MMP-11	α1-antitrypsin	Inactive serpinA1	[103]
	IGFBP-1	Bioavailable IGF	[94]
MMP-12	Latent TNFα	Bioavailable TNFα	[104]
MMP-13	α1-antichymotrypsin	Inactive serpin	[60]
	Latent TNFα	Bioavailable TNFα	[39]
	Latent TGF-β	Activation	[105]
	MCP-3	CC chemokine receptor antagonists	[58]
	SDF-1	Inactive chemokine	[57]
MMP-14	MCP-3	CC chemokine receptor antagonists	[58]
	SDF-1	Inactive chemokine	[57]
MMP-16	VEGF	Activation	[89]
MMP-17	TNFα	Bioavailable TNFα	[60]
MMP-19	VEGF	Activation	[89]
MMP-26	α1-antitrypsin	Inactive serpinA1	[102]

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