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The ectoenzyme-side of matrix metalloproteinases (MMPs) makes inflammation by serum amyloid A (SAA) and chemokines go round

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ABSTRACT

During an inflammatory response, a large number of distinct mediators appears in the affected tissues or in the blood circulation. These include acute phase proteins such as serum amyloid A (SAA), cytokines and chemokines and proteolytic enzymes. Although these molecules are generated within a cascade sequence in specific body compartments allowing for independent action, their co-appearance in space and time during acute or chronic inflammation points toward important mutual interactions. Pathogen-associated molecular patterns lead to fast induction of the pro-inflammatory endogenous pyrogens, which are evoking the acute phase response. Interleukin-1, tumor necrosis factor-α and interferons simultaneously trigger different cell types, including leukocytes, endothelial cells and fibroblasts for tissue-specific or systemic production of chemokines and matrix metalloproteinases (MMPs). In addition, SAA induces chemokines and both stimulate secretion of MMPs from multiple cell types. As a consequence, these mediators may cooperate to enhance the inflammatory response. Indeed, SAA synergizes with chemokines to increase chemoattraction of monocytes and granulocytes. On the other hand, MMPs post-translationally modify chemokines and SAA to reduce their activity. Indeed, MMPs internally cleave SAA with loss of its cytokine-inducing and direct chemotactic potential whilst retaining its capacity to synergize with chemokines in leukocyte migration. Finally, MMPs truncate chemokines at their NH_2- or COOH-terminal end, resulting in reduced or enhanced chemotactic activity. Therefore, the complex interactions between chemokines, SAA and MMPs either maintain or dampen the inflammatory response.

1. Introduction: the ectoenzyme-side of MMPs

Since the discovery of interstitial collagenase as the first matrix metalloproteinase (MMP-1) in vivo more than 55 years ago [1], several generations of researchers have contributed to understand the complexities of these molecules and have been trying to weld their knowledge of MMPs into practical uses by defining crystal structures, by making small-sized inhibitory chemicals, neutralizing antibodies and labeled probes to study MMP activities in vivo. Much of the industrial research interest on MMP inhibitors is based on the concept that these enzymes are used for cancer cell invasion and metastasis and that stopping these processes would become life-saving therapies for cancer. The success of therapies with monoclonal antibodies against cytokines, such as tumor necrosis factor and its receptors, is an illustration that such an approach may work in practice. However, natural evolution and biological systems are always more complex than we envisage. With present-day approaches of degradomics (the substrate repertoire of a specific protease) [2] and reverse degradomics (the enzyme repertoire acting on a single substrate) [3], it becomes possible to discover the complexity of natural processes involving proteolytic enzymes and the biological hierarchy of proteases in a network [4].

Our scientific focus has been on cytokines and MMPs in inflammation research, simply based on the facts that cytokines are tuners, amplifiers or dampeners of inflammation and are intrinsically connected with MMPs at three levels. First, pro-inflammatory cytokines and chemokines regulate the balances between MMPs and the tissue inhibitors of metalloproteases (TIMPs). Second, many cytokines and chemokines are processed by MMPs, as outlined below. Third and so far

Abbreviations: CRP, C-reactive protein; FLS, fibroblast-like synoviocytes; FPR, formyl peptide receptor; GPCR, G protein-coupled receptor; IL, interleukin; LPS, lipopolysaccharide; MMP, matrix metalloproteinase; SAA, serum amyloid A; TLR, toll-like receptor

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underappreciated, these processes are resolved in space and time [5]. These aspects, temporal and spatial resolution and interconnectivity of cells and molecules in hierarchical networks, which are all based on discoveries in acute inflammation, are recently being explored for better diagnosis, prognosis and therapy of chronic diseases, including autoimmune diseases and stalled chronic wounds [6,7].

MMPs are multi-domain enzymes with intrinsic functions for each protein domain [8]. The pro-domain, catalytic site and zinc ion-binding domains are involved in processing of substrates and are conserved amongst all MMPs. Other MMP domains yield additional functionalities to specific MMPs. Recently, these other structures or 'exosites' have been suggested as targets for the creation of better MMP inhibitors [9,10]. For instance, the fibronectin repeats in the gelatinases A (MMP-2) and B (MMP-9) result in high affinities for large denatured collagen substrates [8], whereas hemopexin domains are critical structures for cell surface interactions and signaling functions [11]. For structural aspects and proteolytic and non-proteolytic functions of MMPs in pathology and insights in the development of novel therapeutic inhibitors, the reader is referred to other reviews [12,13].

Underestimated structural elements of many MMPs are the oligosaccharides attached as the most prominent post-translational modification. For a birds-eye view of MMP glycosylation, the reader is referred to a recent overview by Boon et al. [14]. Attached oligosaccharides contribute to correct protein folding and conformation, resistance against degradation by many proteases, abundantly present at sites of inflammation, and play important functions in molecular targeting by interactions with intracellular, pericellular and extracellular lectins, for instance galectins. In a similar way as the interactions between chemokines and the sulfated sugars of glycosaminoglycans determine leukocyte locations, interactions of MMP oligosaccharides and lectins are determinants of where proteolysis and other MMP functions are executed. Although good technologies exist to define all oligosaccharides attached to MMPs and although our structural insights are improving, we presently lack information about proven biological functions. For instance, MMP-9 contains an O-glycosylated domain, positioned between the catalytic part and the hemopexin domain [8,13]. Because of more than 10 mucin-like oligosaccharides, we assume that this part folds like a bottle brush and remains resistant against proteases thanks to the multiple sugars. However, this O-glycosylated domain has not yet been structurally resolved by any means. The definition of the crystal structure of full-sized human MMP-9 thus remains an outstanding research question.

Most MMPs are activated after secretion into the extracellular milieu and all act prominently outside cells. Three critical notes need to be made here. First, the activation of any latent pro-MMP into an active/activated MMP has been documented with many examples of in vitro biochemical assays, but not with in vivo tests. For instance, it is known that trypsin, meprins and other MMPs activate MMP-9 in vitro. However, which critical enzyme executes such an activation in specific settings in vivo remains an issue of speculation. A second remark concerns the substrate repertoires of MMPs. If MMPs are mostly activated outside cells, their primary substrates are extracellular soluble and membrane-bound proteins. Membrane-bound substrates, with inclusion of many immune receptors, are extensively discussed elsewhere [15]. A third point concerns possible intracellular substrates of MMPs. Whereas we here contemplate that MMPs are mainly destined to act as ectoenzymes, i.e. outside cells, they clearly have also an 'endo-history' inside cells. Whereas this aspect is only emerging and on the basis of intracellular/intranuclear localizations of specific MMPs, it needs some attention [16]. Recently, it was established that MMP-12 acts inside cells as a modifier of transcription [17]. Whether intracellular functions of MMPs are based on proteolysis or on non-proteolyic binding remains an open question and may be resolved in the future with the help of quenched fluorigenic substrate probes. What is sure, however, is that many intracellular substrates end up in the extracellular milieu when cells die. This aspect, the clearance function of MMPs as wreckers of ubiquitous substrates, such as actins and tubulins, and the relation with specific autoimmune diseases has been extensively dealt with previously. Data in the primary literature about the aspect that extracellular MMPs efficiently cleave intracellular protein substrates are not only convincing [18,19], but are also relevant to better understand the pathogenic mechanisms behind systemic autoimmune diseases [20].

2. The SAA-chemokine connection

Chemokines represent a large family of chemotactic cytokines, which direct leukocyte migration in vitro and in vivo in a gradient-dependent fashion. Depending on the position of conserved cysteine residues, chemokines are classified as mainly CC or CXC chemokines and activate leukocytes via signaling through G protein-coupled receptors (GPCRs), i.e. CCR and CXCR, respectively [21].

Serum amyloid A (SAA) is one of the major acute phase proteins in humans, together with C-reactive protein (CRP). SAA production is highly up-regulated during the acute phase response, triggered by any inflammatory event, during infection, trauma or cancer. In humans, SAA comprises SAA1 (with the subtypes SAA1α, -β and -γ), SAA2 (SAA2α and -β), SAA3 and SAA4 [22]. In contrast to serum concentrations of SAA1 and SAA2, which increase up to 1000-fold during the acute phase response, serum levels of SAA4 remain relatively stable. Therefore, SAA1/2 are denominated 'acute phase SAA' (A-SAA), whereas SAA4 is named 'constitutive SAA' (C-SAA). Human SAA3 has only been detected at very low levels in supernatants of stimulated mammary epithelial cells [23]. Since SAA is highly conserved through evolution, it probably plays a crucial biological role, which is still not fully understood. In the past decades, several biological activities have been attributed to SAA, including antiviral and antibacterial properties [24–28] and effects on cholesterol transport [29]. It has been suggested that SAA takes part in the pathogenesis of several diseases, including rheumatoid arthritis, obesity and cancer [30–32]. Just recently, it became clear that important activities of SAA include chemotactic effects and cytokine, chemokine and matrix degrading enzyme inducing capacities [22]. SAA is directly chemotactic for monocytes, neutrophils, immature dendritic cells and T cells at low concentrations (10–1000 ng/ml) [33–37]. Like for chemokines, its attractant activity is exerted through activation of a GPCR, i.e. formyl peptide receptor 2 (FPR2) [38]. Although its direct chemotactic activity is generally weak compared to chemokines, human SAA1α is able to greatly enhance the migration of monocytes and neutrophils by inducing chemokines in monocytes through binding to TLR2 and by synergizing with these induced chemokines [35,36,39]. Indeed, very rapidly (within 2–3 h) after stimulation with SAA1α, monocytes produce significant amounts of CXCL8 and CCL3. Within the duration of a chemotaxis assay ($\leq$ 2 h), the subsequent cooperation of these induced chemokines was proven by a significant decrease in monocyte migration after treatment of the cells with antagonists for the CCL3 receptors CCR1/5 or with antibodies against CXCL8 and/or CCL3 [36]. Moreover, in vivo, the recruitment of neutrophils toward SAA1α injected into the peritoneal cavity is significantly reduced when mice are co-injected with a CXCR2 antagonist, blocking the synergistic effect of SAA1α-induced CXCR2 agonists (e.g. CXCL8 or CXCL6). Indeed, synergy between SAA1α and CXCL8 in in vitro neutrophil chemotaxis has been demonstrated [39]. Such an indirect chemotactic activity, by inducing chemokines, has also been demonstrated for other inflammatory mediators. For instance, the TGF-β cytokine family member activin A induces immature dendritic cell migration via the rapid (within 1 h) secondary production of CXCL12 and CXCL14 by migrated cells [40,41].

Not only monocytes, but also a variety of other cell types produce chemokines upon stimulation with SAA1/2 [35,36,42–45]. SAA1/2 also induces chemokines in macrophages and immature monocyte-derived dendritic cells [36,45]. Further, endothelial cells, fibroblasts and chondrocytes are reported to produce chemokines when stimulated with SAA1/2 [30,32,46–50]. All these SAA-induced chemokines

Table 1
Co-expression of chemokines and MMPs.

Chemokines	MMP	Cell/tissue/disease	Reference
CXCL8	MMP-1	Fibroblasts + copper	[58]
		Rheumatoid FLS	[56]
CCL2	MMP-1	Tuberculosis	[54]
CCL2, CCL3	MMP-1	Rheumatoid arthritis	[57]
CXCL1, CXCL2, CCL2, CCL3, CCL5, CCL20, CX_3CL1	MMP-2	Astrocytes + plasminogen activator	[60]
CCL2	MMP-2	Prostate cancer	[61]
CXCL1, CXCL2, CXCL6, CCL2	MMP-3	Fibroblasts + IL-17	[59]
CXCL1, CCL2	MMP-3	Cryptococcus infection	[55]
CXCL8	MMP-3	Rheumatoid FLS	[56]
CCL2, CCL3	MMP-3	Rheumatoid arthritis	[57]
CXCL8	MMP-7 MMP-9	Sputum / fibrosis	[52]
CXCL1, CXCL2, CCL2, CCL3, CCL5, CCL20, CX_3CL1	MMP-9	Astrocytes + plasminogen activator	[60]
CXCL1, CXCL2, CXCL6, CCL2	MMP-9	Fibroblasts + IL-17	[59]
CCL2	MMP-9	Cerebral aneurysm	[62]
CXCL8, CXCL10, CXCL11, CCL20	MMP-9	Lung epithelium / asthma	[53]
CXCL12	MMP-9	Multiple myeloma cells	[63]
CXCL8, CCL2	MMP-9	THP-1 cells + IFN-γ	[64]
CXCL8	MMP-9	Myeloid leukemia cells	[65]
CXCL1, CCL2	MMP-12	Cryptococcus infection	[55]
CXCL1, CXCL2, CXCL6, CCL2	MMP-13	Fibroblasts + IL-17	[59]
CXCL12	MMP-14	Multiple myeloma cells	[63]

Abbreviations: FLS, fibroblast-like synoviocytes.

contribute to an extensive SAA-chemokine network, consisting of SAA, on one hand, which elicits a chemotactic response on leukocytes by itself, and chemokines on the other hand, induced by SAA and other inflammatory mediators, which further enhance the chemotactic response of leukocytes by synergizing with each other and also with SAA.

3. Induction of MMPs by SAA and chemokines

MMPs can process numerous substrates, including a series of inflammatory mediators such as interacting chemokines and SAAs, thereby creating the third dimension of the MMP-SAA-chemokine network. To make this theoretical model physiologically relevant, MMPs must be co-expressed simultaneously with their substrates in the same cells or tissues during disease. Such co-production of SAAs and chemokines has already been evidenced.

3.1. Co-expression of MMPs and chemokines during inflammation

During infection or inflammation, several MMPs have been detected in tissues or body fluids, together with various chemokines (Table 1). Co-expression occurs when both the chemokine and the MMP genes have similar responsive promotor/enhancer elements. For instance, interleukin-1 (IL-1) induces simultaneously the expression of CXCL8 and MMP-9 [51] in macrophages (vide infra). Sputum from idiopathic pulmonary fibrosis patients contains raised levels of CXCL8, MMP-7 and MMP-9 [52], whereas asthmatic bronchial epithelial cells co-express MMP-9 and both neutrophil and lymphocyte chemoattractants (CXCL8, CXCL10, CXCL11, CCL20) [53]. In pulmonary tuberculosis, MMP-1 and CCL2 expression are linked [54], whereas during pulmonary inflammation due to Cryptococcus infection, MMP-3, MMP-12 and CCL2, CXCL1 are co-regulated [55].

Rheumatoid fibroblast-like synoviocytes (FLS) co-produce CXCL8, MMP-1 and MMP-3 [56], whereas synovial co-expression of CCL2, CCL3, MMP-1 and MMP-3 is reduced upon rheumatoid arthritis remission [57]. Co-production of MMP-1, MMP-3, MMP-9, MMP-13 and CXCL1, CXCL2, CXCL6, CXCL8, CCL2 has been reported in fibroblasts stimulated with IL-17 or with copper [58,59].

Table 2
Induction of MMPs by chemokines.

Chemokine	MMP	Cell/tissue/disease	Receptor	References
CXCL8	MMP-2	Endothelial cells	CXCR1,2	[67]
CXCL8	MMP-2,-9	Cultured neurons		[68]
CXCL8	MMP-9	Neutrophilic granulocytes		[51,66]
CXCL12	MMP-1,-2,-3,-9,-10,-11,-14	Prostate cancer	CXCR4	[69]
CXCL12	MMP-2	Smooth muscle cells	CXCR4	[71,74]
CXCL12	MMP-9	Lung epithelium / asthma	CXCR4	[72]
CXCL12	MMP-9	Ovarian carcinoma	CXCR4	[71]
			CXCR7	[70]
CXCL12	MMP-9	Osteoclast precursors		[81]
CXCL12	MMP-9	Megakaryocytes	CXCR4	[73]
CXCL12	MMP-13	Squamous cell carcinoma	CXCR4	[75]
CCL1	MMP-2	Smooth muscle cells	CCR8	[76]
CCL2	MMP-1	Fibroblasts		[77]
CCL2	MMP-9	Macrophages		[78]
CCL11	MMP-2	Smooth muscle cells	CCR3	[74]

3.2. Induction of MMPs by chemokines

The co-expression of MMPs and chemokines can also be explained by the fact that the latter inflammatory mediators induce MMPs in a variety of cell types (Table 2). For instance, the CXC chemokine CXCL8 has been reported as a potent stimulator of MMP-9 secretion by neutrophils [51,66]. This CXCR1/2 agonist also induces MMP-2 in endothelial cells [67], whereas both MMP-2 and MMP-9 are induced in cultured neurons by CXCL8 [68]. CXCL12 stimulates MMP-1, MMP-2, MMP-3, MMP-9, MMP-10, MMP-11 and MMP-14 expression by prostate cancer cells in a CXCR4-dependent manner [69], but MMP-9 expression by CXCL12 in ovarian cancer cell invasion is induced through both CXCR4 and CXCR7 [70,71]. CXCR4 is also involved in the induction of MMP-9 in lung epithelium [72] and megakaryocytes [73], as well as in the induction of MMP-2 in smooth muscle cells [74] and MMP-13 in carcinoma cells [75] in response to CXCL12.

The CC chemokines CCL1 [76] and CCL11 [74] stimulate MMP-2 expression in smooth muscle cells via their proper receptors CCR8 and CCR3, respectively. CCL2 can induce MMP-1 [77] and MMP-9 [78] in fibroblasts and macrophages, respectively. Finally, in the opposite direction, MMP-8 and MMP-12 have been described to induce CXCL8 in breast cancer cells [79] and airway epithelial cells [80], respectively.

3.3. Co-expression of MMPs and SAA

Besides co-regulation of chemokines and MMPs, some MMPs are expressed together with SAA (Table 3). In serum of patients with psoriatic arthritis [82] and rheumatoid arthritis [82,83], SAA is co-expressed with MMP-3, whereas levels of SAA and MMP-2 are elevated in serum of patients with lung cancer metastasis [84]. Both SAA and MMP-9 are increased in serum of cows injected intravenously with lipopolysaccharide (LPS) [85]. MMP-2, MMP-3 and SAA1, SAA3 are also simultaneously up-regulated in corneas with inflammatory neovascularization [86]. Further, after long-term exposure to cigarette smoke, the expression of both SAA and MMP-12 remained elevated in mouse lungs [87].

3.4. Induction of MMPs by SAA

Like chemokines, SAA is a potent inducer of MMPs in various cell

Table 3
Co-expression of SAA and MMPs.

MMP	Cell/tissue/disease	Reference
MMP-1	Plasma / Strongyloides stercoralis infection	[88]
MMP-2	Serum / lung cancer metastasis	[84]
	Cornea / inflammatory neovascularization	[86]
MMP-3	Serum / inflammatory arthritis	[82]
	Serum / rheumatoid arthritis	[83]
	Cornea / inflammatory neovascularization	[86]
MMP-9	Appendicitis	[89]
	Serum / intravenous LPS challenge	[85]
MMP-12	Lungs / COPD	[87]

Abbreviations: COPD, chronic obstructive pulmonary disease; LPS, lipopolysaccharide.

Table 4
Induction of human MMPs by SAA.

MMP	Cell type	SAA (μg/ml)	Receptor	References
MMP-1	Chondrocytes	0.1-2.5		[82,94]
			TLR4	[90]
	FLS	0.1-2.5		[82,92]
			TLR4	[90]
MMP-2	Chondrocytes	10		[82]
	FLS	5-50		[82,91]
MMP-3	Chondrocytes	2.5-50		[82]
			TLR4	[90]
	FLS	1-10		[82,91–93]
			TLR4	[90]
MMP-9	FLS	10		[82]
	Hepatic stellate cells			[96]
	Monocytes	1.2-24	GPCR (FPR2?)	[95]
	Renal cell carcinoma	10	None-GPCR	[97]
MMP-10	Chondrocytes	2.5		[90]
	HUVEC, HCAEC	20		[98]
MMP-13	Chondrocytes	2.5-10		[82]
			TLR4	[90]
	FLS	1-2.5		[82]
			TLR4	[90]

Abbreviations: FLS, fibroblast-like synoviocytes; HCAEC, human coronary artery endothelial cells; HUVEC, human umbilical vein endothelial cells.

types (Table 4). At relatively low concentrations (0.1 to 2.5 μg/ml), A-SAA induces MMP-1, MMP-3 in FLS from inflammatory arthritis patients [82,90–93]. In contrast, higher SAA levels (5–50 μg/ml) are needed to stimulate the production of MMP-2, MMP-9 in these cells [82,91]. MMP-1, MMP-3, MMP-10, MMP-13 are secreted from chondrocytes treated with A-SAA from 0.1 to 2.5 μg/ml onwards [82,90,94]. Although primary chondrocytes stimulated with SAA (10 μg/ml) express MMP-2 [82], no up-regulation of MMP-2, MMP-8, MMP-9 was observed in SAA-treated (5 μg/ml) osteoarthritis chondrocytes [90]. de Seny et al. [90] demonstrated that TLR4 is involved in SAA-mediated MMP production by FLS and chondrocytes from osteoarthritis patients, whereas other SAA receptors, i.e. FPR2, CD36 and 'CD36 and LIMPII analogous-1' (CLA-1), are not implicated. In monocytes, MMP-9 induction is mediated by signaling of SAA through a GPCR (possibly FPR2) [95].

4. Processing of SAA and chemokines by MMPs

4.1. NH_2- and COOH-terminal truncation of chemokines by MMPs

The chemokine family represents a major target for MMPs since most of the inflammatory chemokines are sensitive substrates for these proteinases. Post-translational processing of chemokines has already been reviewed extensively in the past [99–101], in particular by the ectoenzyme CD26/dipeptidyl peptidase IV. CD26 rapidly and efficiently cleaves inflammatory CXC and CC chemokines at the penultimate NH_2-teminal position with drastic consequences for their receptor usage and hence chemotactic activity. These include the CXCR3 ligands (CXCL9, CXCL10, CXCL11), losing their lymphocyte chemotactic but not their angiostatic potential, and CD26-cleaved CXCL12 lacking CXCR4-binding and anti-HIV activity. Some CC chemokines, such as the monocyte chemotactic proteins CCL2, CCL7, CCL8, are protected from cleavage by an NH_2-terminal pyroglutamic acid, whereas CCL3 and CCL5 processed by CD26 show more potent and decreased CCR1-mediated monocyte chemoattraction, respectively.

Table 5
NH_2- and COOH-terminal processing of chemokines by MMPs.

MMP	Human chemokines	Truncation site (No. of deleted aa)	Chemotactic activity
MMP-1	CXCL5	NH_2 (-5,-7)	Increased
	CXCL8	NH_2 (-6)	Increased
	CXCL2, CXCL12, CCL2, CCL7, CCL8, CCL13	NH_2 (-4)	Reduced
	CCL8	COOH (-3)	Reduced
MMP-2	CXCL12, CCL2, CCL7, CX_3CL1	NH_2 (-4)	Reduced
MMP-3	CXCL12, CCL2, CCL7, CCL8, CCL13	NH_2 (-4)	Reduced
	CCL8	COOH (-3)	Reduced
MMP-7	CXCL9, CXCL10, CXCL11	COOH (-4 to -15)	Reduced
MMP-8	CXCL5	NH_2 (-7)	Increased
	CXCL6	NH_2 (-5,-6)	No effect
	CXCL8	NH_2 (-6)	Increased
	CXCL9, CXCL10, CXCL11	COOH (-4 to -15)	Reduced
	CXCL11, CCL2	NH_2 (-4)	Reduced
MMP-9	CXCL2, CXCL12, CCL2	NH_2 (-4)	Reduced
	CXCL5	NH_2 (-5,-6,-7)	Increased
	CXCL6	NH_2 (-5,-6)	No effect
	CXCL8	NH_2 (-6)	Increased
	CXCL9, CXCL10, CXCL11	COOH (-4 to -15)	Reduced
MMP-12	CXCL1, CXCL3	NH_2 (-6)	Reduced
	CXCL2	NH_2 (-4,-6)	Reduced
	CXCL5	NH_2 (-5)	Increased
		NH_2 (-10)	Reduced
	CXCL6	NH_2 (-14)	Reduced
	CXCL7	COOH (-20)	Reduced
	CXCL8	NH_2 (-6)	Increased
		NH_2 (-9)	Reduced
	CXCL9, CXCL10, CXCL11	COOH (-4 to -15)	Reduced
	CXCL11, CCL2, CCL7, CCL8, CCL13	NH_2 (-4)	Reduced
	CCL8	COOH (-3)	Reduced
MMP-13	CXCL8	NH_2 (-5)	Increased
	CXCL12, CCL7	NH_2 (-4)	Reduced
	CCL2	NH_2 (-5)	Reduced
MMP-14	CXCL8	NH_2 (-5)	Increased
	CXCL12, CCL7	NH_2 (-4)	Reduced

Abbreviations: aa, amino acids.

MMPs exert a broad proteolytic cleavage pattern on chemokines, ranging from both NH_2- and COOH-terminal processing (Table 5) to internal chemokine cleavage and degradation. Truncation of four NH_2-terminal residues from CXCL2, CXCL12 as well as CCL2, CCL7, CCL8 and/or CCL13 by MMP-1, MMP-2, MMP-3, MMP-9, MMP-12, MMP-13 and/or MMP-14 causes impaired chemokine activity [18,101]. Similarly, cleavage of four to 15 COOH-terminal residues from CXCL9, CXCL10 and CXCL11 by MMP-7, MMP-8, MMP-9 and MMP-12 results in reduced lymphocyte chemotactic activity. In sharp contrast, deletion of five to seven NH_2-terminal residues from CXCL5 and CXCL8 by MMP-1, MMP-8, MMP-9, MMP-12, MMP-13 and/or MMP-14 yields an increase in their neutrophil chemotactic activity via CXCR2. A similar NH_2-terminal truncation (five or six residues) by MMP-8 or MMP-9 has no effect on the neutrophil chemotactic potency of CXCL6, whereas cleavage of 14 residues by MMP-12 does impair its activity. Taken together, post-translational processing of chemokines by MMPs predominantly dampens the inflammatory response.

Table 6
Cleavage of human SAA by MMPs.

MMP	Human SAA source	Generated peptides	Activity[b]	Reference
MMP-1	Plasma-derived SAA	1-57	ND	[104]
		58-104	ND	
		7-29/8-30/9-31 (20 aa)	ND	
	rSAA1α	1-57	ND	[105]
		58-104	ND	
	rSAA1β	24-104	ND	
		30-104	ND	
		58-104	ND	
MMP-2	Plasma-derived SAA	1-51	ND	[104]
		52-104	ND	
		8-55	ND	
	rSAA1α (300-53, Peprotech)	52-104[a]	Synergy in chemotaxis =	[102]
MMP-3	Plasma-derived SAA	57-104	ND	[104]
		58-104	ND	
		74-104	ND	
		8-55	ND	
MMP-9	rSAA1α (300-53, Peprotech)	1-51[a]	Direct chemotaxis ↘ Synergy in chemotaxis ↘ Chemokine induction ↘	[103]
		52-104[a]	Direct chemotaxis ↘ Chemokine induction ↘	
		57-104[a]	ND	
		58-104[a]	Direct chemotaxis ↘ Synergy in chemotaxis = Chemokine induction ↘	

Abbreviations: ND, not determined; rSAA, recombinant serum amyloid A.
[a] For determination of biological activity, synthetic peptide has been used.
[b] ↘: decreased; =: unchanged.

4.2. Proteolytic processing of SAA by MMPs

Human SAA is also post-translationally modified by MMPs, but reports dealing with this matter are scarce (Table 6). MMP-1, MMP-2, MMP-3, MMP-9 are known to cleave SAA and predominantly generate the COOH-terminal peptides 52–104, 57–104 and/or 58–104 [102–105]. Further, the complementary NH_2-terminal SAA peptides 1–57 and 1–51 are detectable after treatment of SAA with MMP-1 [104,105] and with MMP-2 or MMP-9 [103,104], respectively. Shorter (74–104) and longer (24–104, 30–104) COOH-terminal peptides of SAA have also been detected after incubation of plasma-derived SAA1 and/or SAA2 with MMP-3 [104] or of SAA1β with MMP-1 [105], respectively. MMP-1, MMP-2, MMP-3 can also internally cleave SAA, leading to the formation of SAA(8–55) or a peptide containing only 20 amino acids (Table 6; [104]).

The influence of post-translational modification of SAA by MMPs on its biological activities has barely been investigated (Table 6). In comparison to intact SAA1α, the peptides 52–104 and 58–104 lack the ability to directly chemoattract monocytes and neutrophils and to induce chemokines in leukocytes. However, these COOH-terminal peptides retain their capability to synergize with chemokines in monocyte and neutrophil migration [102,103]. In contrast, the NH_2-terminal peptide 1–51 lacks all of these three activities [103]. In such ways, post-translational cleavage of SAA by MMPs fine-tunes the inflammatory response, leading to a prolonged, but tempered state of inflammation.

5. The complex interrelationship between MMPs, SAA and chemokines

During infection, an inflammatory response is evoked by microbial products, such as bacterial LPS, inducing various primary cytokines such as IL-1, tumor necrosis factor and interferon [106]. These exogenous and endogenous pyrogens, also including IL-6 [107], mediate the acute phase response by acting as hepatocyte-stimulating factors inducing a series of acute phase proteins in the liver, such as CRP and SAA [108]. Together with LPS and inflammatory cytokines, SAA stimulates the production of several chemokines, e.g. CXCL8 [109], in monocytes (Fig. 1) and in various other cell types, such as fibroblasts

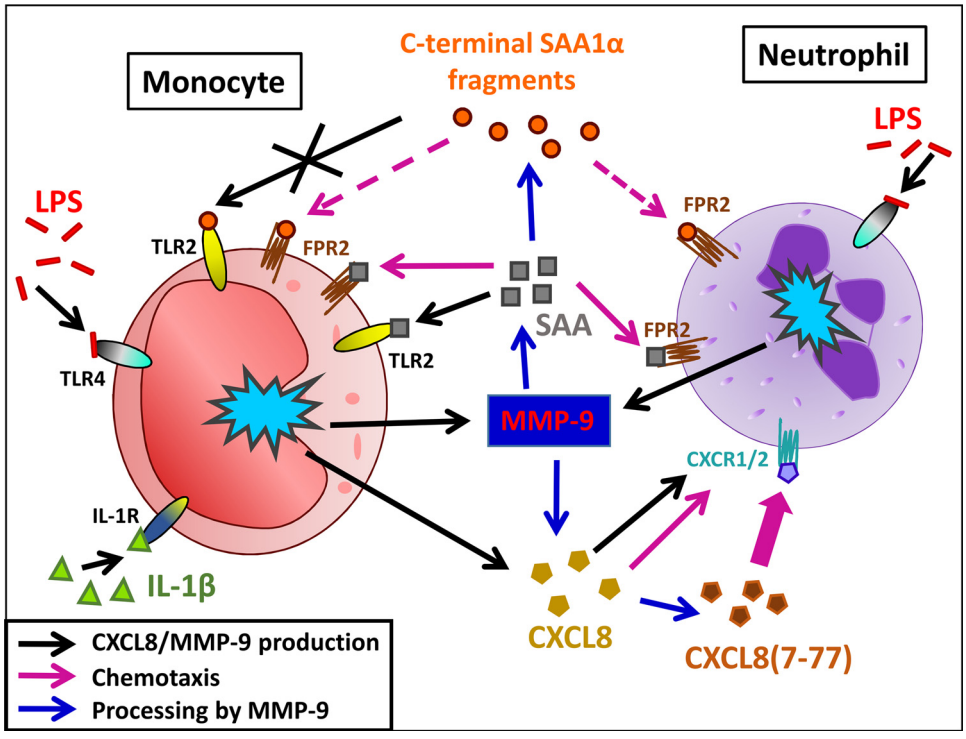

Fig. 1. The complex interrelationship between MMPs, SAA and chemokines. Full, bold or dashed arrows indicate cytokine/protease inducing capacity (black arrow) or chemotactic capacity (pink arrow) of intact SAA1, CXCL8 or MMP-9-generated SAA1/CXCL8 fragments (blue arrow). The figure shows the complexity of interactions between SAA1, chemokines and MMPs. The acute phase protein SAA1 induces MMP-9 in monocytes, which enzymatically cleaves SAA1 into COOH-terminal fragments. In contrast to intact SAA1, the fragments lack direct chemotactic (dashed pink arrow) and cytokine-inducing capacity (crossed black arrow). Furthermore, both MMP-9 and chemokines (e.g. CXCL8) are co-induced in monocytes by SAA1 and by other endogenous (e.g. IL-1β) and exogenous (e.g. LPS) inflammatory mediators. Chemokines, such as CXCL8, stimulate neutrophils to secrete proteases such as MMP-9 which in turn cleaves CXCL8 into a more active neutrophil chemoattractant CXCL8(7–77) (bold pink arrow). In addition, truncated CXCL8 can synergize with SAA1 or its COOH-terminal fragments (dashed pink arrow) in leukocyte chemotaxis (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

[110] and endothelial cells [111], to chemoattract different leukocyte types to the inflammatory site. Moreover, SAA synergizes with chemokines to enhance the chemotactic response [36,39]. Simultaneously, cytokines (IL-1 induces MMP-9 in various cell types; [51,112]), chemokines (MMP-9 release from neutrophils by CXCL8; Table 2; [51]), and SAA (Table 4) induce the production of MMPs by leukocytes and tissue cells. Subsequently, SAA and chemokines are post-translationally processed by MMPs (Tables 5 and 6), resulting in enhanced or decreased chemotactic activity, thereby fine-tuning the inflammatory response. For example, MMP-9 NH_2-terminally cleaves CXCL8 into a more potent neutrophil activator and chemoattractant [113], whereas SAA is internally cleaved by MMP-9 with loss of chemokine inducing capacity, but preserved potential to synergize with chemokines (Fig. 1) [103].

6. Conclusions: the ecto-side of MMPs makes the inflammatory response go round

MMPs were discovered as matrix degrading proteases. We have demonstrated that MMPs are critical processing enzymes for both chemokines and acute phase molecules. Because SAA1 at low concentrations synergizes with chemokines and because processed forms of SAA and chemokines retain or loose specific biological effects in inflammation, the outcome of MMP action is time- and space-resolved and thus complex. This information illustrates the difficulties for the systemic application of MMP inhibition in inflammatory diseases.

Declarations of interest

None.

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