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Metalloproteinase-7 contributes to joint destruction in *Staphylococcus aureus* induced arthritis

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Abstract

Septic arthritis induced by *Staphylococcus aureus* causes a rapid destruction of joint cartilage and periarticular bone. The mechanisms behind this phenomenon are not fully understood. Earlier studies have shown that cytokines and metalloproteinases are of importance in bone metabolism. Matrix metalloproteinase-7 (MMP-7) has pleiotropic function including facilitating migration of both macrophages and neutrophils. The aim of this study has been to investigate the significance of MMP-7 expression in septic arthritis. MMP-7 deficient mice and congeneic controls were intravenously inoculated with an arthritogenic dose of *S. aureus* LS-1. This study shows that MMP-7 deficient mice exposed to *S. aureus* developed significantly less severe arthritis both clinically and histologically. Despite this finding, bacterial growth in the deficient animals was significantly increased. In vitro responses to staphylococcal antigens and superantigens did not differ between MMP-$7^{+/+}$ and MMP-$7^{-/-}$ mice with respect to cytokine production and if anything increased the production of certain chemokines. In addition MMP-$7^{-/-}$ mice exhibited decreased numbers of peripheral blood mononuclear cells before and one day after bacterial inoculation, but increased numbers of peripheral granulocytes on day 1. In conclusion, MMP-7 contributes to the development of a destructive course of septic arthritis despite decreased bacterial load. In addition, expression of MMP-7 is of importance for the distribution of peripheral leukocytes.

Keywords: *S. aureus*; MMP-7; Arthritis; Mice

1. Introduction

Septic arthritis induced by *Staphylococcus aureus* has a rapid and highly destructive course. The mechanisms behind this phenomenon are not fully understood. The issue has up to recently mainly been investigated in the context of cytokine production and invasion of joints by inflammatory cells. These studies have shown that there are complex interactions between the clearance of bacteria and the severity of arthritis [1].

Earlier studies have shown that the severity of *S. aureus* induced arthritis is dependent on T cells [2], macrophages [3] and granulocytes [4]. Macrophage-depletion leads to less severe arthritis while granulocyte-depletion aggravates it [3]. Cytokines influence the development of septic arthritis both directly and indirectly. The Th1 cytokines TNF/LTA aggravate the arthritis but facilitate bacterial clearance [5] while the Th2 type cytokine IL-10 both ameliorates the arthritis and improves bacterial clearance [6]. In contrast, the B cell compartment does not significantly influence survival or the outcome of arthritis [7].

It is a well known fact that proteases e.g. serine, thiol and cystein proteases in addition to matrix metalloproteinases (MMP) [8–10] contribute to degradation of extracellular matrix (ECM) in aseptic arthritides. Yoshihara et al. [11] recently demonstrated that several MMPs are upregulated in synovial fluid originating from patients with rheumatoid arthritis as compared to synovial fluid from osteoarthritic controls.

There are now around 26 known members of the MMP-family all of which having the capacity to degrade specific

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components of ECM in an overlapping pattern. MMP-7/matrilysin is the smallest member with a molecular weight of 19 kDa in its active form. MMP-7 has a broad specificity and cleaves a number of matrix substances including proteoglycans and collagen III/IV/V/IX/X/XI [12]. In addition, it activates pro-MMP-1, 2 and 7 which further broadens the matrix components cleaved. Beside these traditional substrates MMP-7 also displays other properties: e.g. it activates pro-α-defensin to α-defensin, decorin to bioavailable TGFβ, and cell bound FasLigand (FasL) to active or inactive soluble FasL (sFasL). It releases B4 integrin and the bioactive E-cadherin ectodomains (reviewed in [12]). MMP-7 is also expressed in a variety of tumors where it is involved in tumor formation as well as in tissue degradation which accompanies tumor cell extravasation (reviewed in [13]). MMP-7 cleaves membrane-bound TNF on macrophages but with 100–1000 fold slower rate than TNF alpha converting enzyme (TACE) and with 30 times lower specificity [14]. Recently Li et al. [15] elegantly showed that MMP-7 is required for neutrophil invasion into an injured area and Haro et al. [16] have shown that the invasion of macrophages, required for resorption of a herniated disc in vitro is dependent on MMP-7 induced TNF release from macrophages.

The histological picture of *S. aureus* induced arthritis is dominated by heavy infiltration of macrophages, granulocytes and lymphocytes and severe bone and cartilage destruction [17]. Little is known about the role of proteases participating in bone and cartilage destruction. The role of matrix metalloproteinases, particularly MMP-7 has not been previously addressed regarding infectious arthritis.

The aim of this study has been to investigate the contribution of MMP-7 in *S. aureus* arthritis. Our results clearly demonstrate that MMP-7 is of significant importance for the joint destruction but also for bacterial clearance in systemic infection. Finally, we also report that the presence of MMP-7 significantly influences the composition of peripheral leukocytes and their chemokinetic properties.

2. Results

2.1. MMP-7 contributes to the development of S. aureus induced arthritis

The MMP-7$^{-/-}$ mice ($n=26$) developed a clinically significantly less severe arthritis late during the infection as compared to the congeneic MMP-7$^{+/+}$ controls ($n=24$) (Fig. 1). In addition, the frequency of arthritis was lower in the MMP-7$^{-/-}$ but did not reach statistical significance following bacterial inoculation (Table 1). The clinical findings were confirmed with histology of hind- and forepaws, which showed that both synovitis, and bone and cartilage destruction were significantly reduced in the MMP-7 deficient mice ($p=0.03$ and $p<0.05$, respectively) (Fig. 2). In contrast, no significant differences were found between MMP-7$^{-/-}$ ($n=10$) and wild-type ($n=10$) mice with regard to synovitis and cartilage/bone destruction when the bacteria were inoculated intraarticularly (Fig. 3), indicating that expression of MMP-7 is of importance during hematogenous spreading of bacteria.

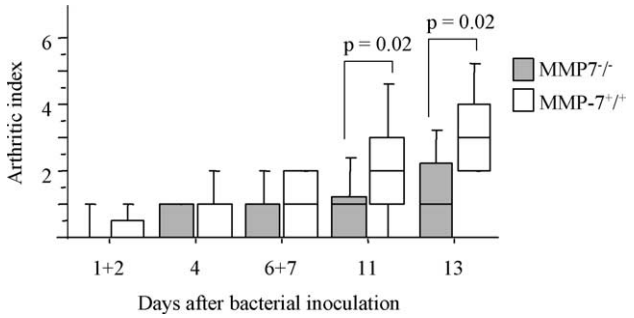

Fig. 1. Clinical evaluation showed MMP-7$^{-/-}$ mice ($n=26$) developed a significantly milder septic arthritis as compared to congeneic controls ($n=24$). Data are pooled from two in vivo experiments when *S. aureus* was i.v. oculated, and are expressed as median and IQR.

2.2. MMP-7 increases the in vivo clearance of S. aureus

Staphylococci home to several different body compartments but resides mainly in joints and kidneys [18]. The technique used to recover bacteria from the joints is crude and probably explains why growth of *S. aureus* was detected only in 2/8 MMP-7$^{-/-}$ mice and 3/8 control mice joints (n.s.). On the other hand, the bacterial load in kidneys at days 11+13 was significantly increased ($p=0.04$) in the MMP-7 knock-out mice ($n=22$) as compared to wild-type controls ($n=21$), giving a more accurate mirror of the general bacterial burden (Fig. 4).

Table 1
Frequency of arthritis following systemic inoculation with *S. aureus*

	Day 1+2	Day 4	Day 6+7	Day11	Day 13
MMP-7$^{-/-}$ (%)	11	32	52	59	66
MMP-7$^{+/+}$ (%)	25	45	57	85	100

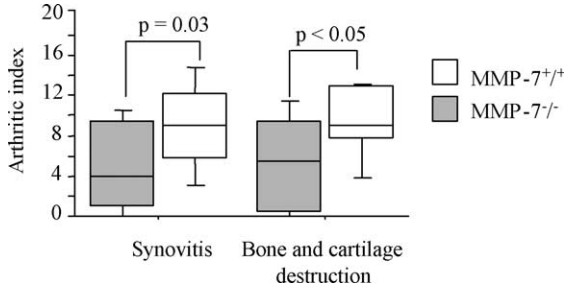

Fig. 2. Histological changes at day 13 following staphylococcal inoculation i.v. regarding synovitis and bone/cartilage destruction showing that both processes are significantly aggravated in the MMP-7$^{-/-}$ mice ($n=12$) during the disease process as compared to control mice ($n=13$). Data are expressed as median and IQR.