The first MMP in sepsis

Roosmarijn E. Vandenbroucke1,2, Lien Dejager1,2, Claude Libert1,2*

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Systemic inflammatory response syndrome (SIRS) is the number one killer in intensive care units. It is a collective name referring to an exaggerated inflammatory response that can have several etiologies and can be observed, for example, after poly trauma, burns or in post-operative patients. The most reputed condition of SIRS, however, is sepsis, which is the result of a — usually microbial infection. Sepsis associated with organ failure is called severe sepsis, and sepsis associated with persistent blood pressure loss, despite fluid resuscitation, is called septic shock. In the USA, some 900,000 new cases of sepsis are counted yearly, which increases by 1.5% per year. In Europe, about 27% of sepsis, 32% of severe sepsis and 54% of septic shock patients will not survive their admission. Despite decades of intensive research, the list of new therapeutics for the treatment of sepsis is very short. Hence, sepsis has been called ‘the graveyard for pharmaceutical companies’ (Riedemann et al, 2003).

But what makes sepsis such a difficult condition to deal with? First, it is usually an acute condition and patients arriving at the ICU are already infected. Second, many infectious agents have developed antibiotic resistances. Third, the response of patients is very complex and differs significantly depending on the infectious agent, but also depending on patient-specific aspects, such as age, gender and genetic background. Moreover, the host response seems to develop from an initially hyper-inflammatory phase to a hypo-inflammatory phase. Infectious agents activate the innate immune system and inflammation through several mechanisms. The inflammatory condition of the host has been considered as dangerous and many clinical trials using anti-cytokine therapies have failed, probably because these cytokines are rather protective and necessary to build sufficient immunity. Finally, many molecules have emerged as potential drug targets for sepsis using mouse models, which have their value, but certainly also their limitations. There are significant differences in response of small rodents compared to primates in sepsis. Nevertheless, the validated mouse septic peritonitis model known as the cecal ligation and puncture (CLP) model has proven a reliable mouse model (Dejager et al, 2011).

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Using the CLP model in mice, Tressel et al have found that a member of the family of matrix metalloproteinases (MMPs), namely MMP1, is an interesting new drug target (Tressel et al, 2011).

Indeed, circulating MMP1 levels were found to be elevated in human sepsis patients, and the levels of active MMP1 directly correlate with worse survival chances. MMP1 is the MMP that was first discovered in 1962, as a protease responsible for the drop of the tail of tadpoles during metamorphosis. The mammalian MMP family now comprises 24 members (Fanjul-Fernandez et al, 2010). The proteases are Zn2+- and Ca2+-dependent and share sequence similarity in their active centre. Most MMPs are secreted as zymogens and need an activation step. The MMP family is divided in subfamilies and MMP1, together with MMP8 and MMP13, forms the collagenase family, because they display increased substrate specificity for collagen. Typically, however, MMPs have a poor substrate specificity and will cleave many substrates in vitro assays. In the mouse CLP sepsis model, Tressel et al, found MMP1 appearing in circulation, just a few hours after CLP initiation. An MMP inhibitor, which blocks MMP1 but also MMP8 with equal IC50, was able to protect mice from CLP-induced lethality. This result was reproduced, although much less impressively, using an MMP1-specific antibody, which makes us wonder to what extent MMP8 is involved in mouse CLP. Indeed, using MMP8-knockout mice, Tester et al already described that MMP8 plays a mediating role in a model of local inflammation (Tester et al, 2007). CLP experiments with MMP1 knockout and MMP8 knockout mice will hopefully answer this burning question.

As to the mechanism by which MMP1 contributes to sepsis, Tressel et al found a very interesting link with the coagulation system. Sepsis is clearly associated with
activation of several complex systems, such as inflammation, complement, but also coagulation. In fact, coagulation is held responsible for the damage of the microvasculature and the inactivation of organ functioning during sepsis. It is not a coincidence that the only approved therapeutic agent in the clinic is activated protein C (APC), which is an inhibitor of coagulation. The molecular target of APC is PAR1 or protease-activated receptor 1. PAR1 is activated by several proteases, but the default PAR1 agonist is thrombin, which is activated during coagulation. Although the overall therapeutic benefit of APC is rather limited, it is clear that PAR1 is an interesting drug target and the identification of other PAR1 activating proteases than thrombin is a priority. By a combination of immunohistochemistry and in vitro assays, Tressel et al describe that MMP1 is such a PAR1 activator. MMP1 is expressed by unstressed endothelial cells and secreted by these cells during sepsis. This release causes loss of endothelial integrity, which leads to PAR1 dependent permeability. Activation of PAR1 signals to endothelial cells via activation of Rho GTPases resulting in actin-skeleton-dependent contraction of the cells. Interestingly, in the mouse sepsis model, it was now described for the first time that MMP1 is responsible for the majority of the PAR1 activation. As expected, the MMP1 inhibitor (with MMP8 inhibitory activity) protected mice against CLP, but failed to protect PAR1 knockout mice against CLP, which would suggest that the activities of MMP1 are strictly PAR1 mediated. The MMP-inhibitor protected mice against lethality, lung vascular permeability, clotting abnormalities and production of cytokines (Fig 1).

Collectively, the data are supportive for an important function of MMP1 in sepsis. Several questions are now emerging. What causes the release of MMP1 from endothelial cells during sepsis? This question has to be addressed. Is MMP1 a potential drug target in sepsis patients? The answer to this question is difficult to predict. Clinical trials might be suggested. Since thrombin inhibition and APC bear dangerous risks for bleeding in sepsis patients, one could speculate that MMP1 inhibition might be a safer alternative. However, the paper of Tressel et al describes that the MMP inhibitor protects mice when given at the start of the CLP protocol, but no longer when given just 4 h after. Is MMP1 mediating other forms of SIRS besides sepsis? It is difficult to predict whether MMP1 also mediates SIRS induced by ischemia/reperfusion, trauma or burns, but it would certainly increase the therapeutic value of MMP1-specific blockers. Is MMP1 the only MMP mediating sepsis? This is very unlikely. The fact that the MMP1 antibody protected much less than the (non-selective) MMP1 inhibitor suggests that other MMPs play important roles in sepsis too. Indeed, in sepsis, the levels of several MMPs have been found to correlate with outcome (Vanlaere & Libert, 2009). Detailed studies using several MMP knockout mice will reveal their individual functions in sepsis. Finally, the development of MMP-specific inhibitors should be high on the list of pharmaceutical companies, because the currently available broad-spectrum MMP blockers might inhibit both the bad...
MMPs as well as the protective MMPs leading to suboptimal therapeutic approaches. MMP-specific blockers might pave the way to efficient inhibitors of sepsis, and perhaps sepsis may become attractive again for the pharmaceutical industry.

The authors declare that they have no conflict of interest.

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