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Is MMP-8 Activity in the Mucosal Barrier a Requirement for Leakage of Cecal Material in Peritonitis?

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Matrix metalloproteinases (MMP) participate in a variety of structural and immunological functions. They are present in many cell types including the epithelial mucosal barrier of a normal intestine. Based on previous evidence suggesting a role of MMP-8 (a collagenase) in survival of pediatric septic patients as well as survival in a cecal ligation model (1,2), Dr. Atkinson and her colleagues (3) focus on MMP-8 in the intestine and in myeloid cells. Detailed analysis of physiological and pathophysiological functions of MMPs in-vivo is, however, hampered by the lack of specific inhibitors without off target effects. Thus to gain further mechanistic insight these investigators present an interesting proposal with an experimental design that uses a genetic approach in combination with organ/tissue exchanges with a wild type mouse. Using a MMP-8 gene knockdown mouse the authors report that the MMP-8 inherent to the cecum, and less the MMP-8 in myeloid cells (e.g. neutrophils), plays a role in survival after cecal ligation puncture (CLP)-induced peritonitis.

Using additional organ transfer experiments with cecal pouches between a wild type and a MMP-8 null mouse the authors report that MMP-8 in these tissues is a critical component of septic CLP-mediated peritonitis secondary to intestinal compromise. Intraperitoneal implantation of a punctured MMP8 null cecum provides a survival advantage as compared to a wild type cecum. In other words, the MMP-8 in the cecum is involved in the lethal progression of peritonitis. MMP-8 may be serving as a proinflammatory mediator. But this hypothesis is not uniformly supported by the literature in which MMP-8 has been observed to enhance and in some cases reduce markers for inflammation (4). Thus the mechanism(s) by which MMP-8 in the intestine may mediate a lethal progression in CLP-induced peritonitis remains unknown. If a soluble form of MMP-8 itself causes inflammation and the lethal progression in peritonitis, then a MMP-8 deletion model should provide a robust protection from its lethal course. But this is only in part the case and one needs to consider that MMP-8 may control other processes, e.g. the important mucosal barrier functions.

In the experiment by Atkinson et al. the protection by MMP-8 deletion is statistically significant, but according to the survival curves provides only a temporary delay in death. This raises the question whether MMP-8 serves to *modulate* the lethal event that causes organ failure in peritonitis as compared to being primarily responsible for it. A typical cecal slurry consists of a mixture of fully or partially digested food items, the powerful digestive

enzymes, enteral bacteria and viruses, each needs to be contained in the cecum and the intestine to avoid peritoneal cell injuries and inflammation. The containment of these cytotoxic and proinflammatory materials in the cecum or in the lumen of the intestine requires an intact mucosal epithelial barrier (5) and therefore there is a possibility that MMP-8 may be involved in the maintenance of barrier properties.

Indeed, MMP-8 is expressed in the mucosal epithelium of normal intestine and is located in close proximity to the tight junctions in the intestinal epithelium. Thus MMP-8 may play a role in breakdown of the mucosal barrier properties in epithelium when the intestine is exposed from its outside at the serosa to cecal slurry in the peritoneum (e.g. after cecal slurry injection or leakage from a transplanted cecum pouch in the exchange experiments by Atkinson et al.). A pro-MMP-8 conversion into an active protease may be achieved by even low concentrations of a protease, such as trypsin, leaking from a cecal slurry, as seen in the case of MMP-9 (6). Active MMP-8 may clip the extracellular domain of tight junction proteins in mucosal epithelium and thereby compromise the barrier properties. In line with this mechanism, a MMP-8 gene deletion model may enjoy protection of its epithelial barrier properties and thereby reduces escape of cecal cytotoxic mediators into the peritoneum, as reported by the authors.

The question arises whether intervention against MMP-8 should be tested in patients. The presence of soluble MMP-8 in patients may suggest such a consideration and the results by Atkinson et al. provide further support. But the benefit of MMP-8 inhibition is so far only documented over relatively short study periods and may need to be investigated in preclinical studies with longer endpoints. Other protease may be present in the mucosal epithelium with an ability to clip tight junction barrier proteins, e.g. other MMPs, cathepsins (7). Understanding these proteases on a larger (and eventually omic) scale and over longer periods of time is paramount to optimally block leakage of cecal material in sepsis. The role of proteases needs to be identified not only in the cecum but also in the small intestine from which considerable cytotoxicity can be derived (8). Last but not least the issue needs to be investigated in human tissue, since mouse mucosal epithelium may have a different proteolytic profile. Identification and delineation of the proteolytic “degratome” in peritonitis will open an important opportunity to preserve mucosal barrier properties and minimize escape of cytotoxic materials from the cecum and lumen of the intestine.

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