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A novel role for leucocytes in determining the severity of acute pancreatitis

Julia Mayerle

For more than a century autodigestion has been regarded as the principal mechanism underlying pancreatitis. The modern version of this concept implies that a premature and intrapancreatic activation of pancreatic proteases occurs very early in the disease, and then overwhelms a multitude of protective mechanisms that physiologically prevent or inhibit digestive enzymes activity outside the small intestine. Novel treatments that target protease activity have, unfortunately, not been shown to be consistently beneficial in clinical pancreatitis. This is probably because they either target the wrong proteases or because they are administered too late in the disease process.

Another line of experimental evidence suggests that, while initial protease activation may be a triggering event, the ultimate disease severity depends on the balance between pro- and anti-inflammatory responses of the affected patient and cellular and humoral factors have been shown to be involved in the process. While activities of pancreatic enzymes in the blood, ie, parameters of local damage such as amylase and lipase, can be used to determine the presence or absence of pancreatitis, they do not reflect disease severity in humans and the extent of their elevation is of no prognostic value. Parameters reflecting the inflammatory response, such as C-reactive protein, procalcitonin or polymorphonuclear (PMN)-elastase, on the other hand, have been found to correlate rather well with disease severity and are commonly used to triage patients to intensive care surveillance and treatment.

Parameters reflecting the inflammatory response, such as C-reactive protein, procalcitonin or polymorphonuclear (PMN)-elastase, on the other hand, have been found to correlate rather well with disease severity and are commonly used to triage patients to intensive care surveillance and treatment. Based on this "inflammation concept" of pancreatitis a number of experimental studies have been conducted in order to modulate the inflammatory response and to attain a beneficial therapeutic effect. Inhibiting pro-inflammatory mediators (eg, platelet activating factor (PAF), interleukin 6 (IL6), intracellular adhesion molecule (ICAM), S100A9, toll-like receptor 4 (TLR4)) or enhancing anti-inflammatory mechanisms (eg, IL10) or modulating cellular immune responses, have all been found to be beneficial in experimental pancreatitis models. Unfortunately, and until the present day, they have failed spectacularly at finding their way into clinical routine, with the possible exception of preventing post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis. Post-ERCP pancreatitis, however, is an issue of preventing pathophysiological events and not one of treating disease-affected patients. In this setting even inhibiting protease activity may have some beneficial affect although this positive initial finding is increasingly being questioned.

One of the most promising new drugs that targets the pro-inflammatory response, and one that was used in the most carefully conducted (and expensive) clinical trials on acute pancreatitis to date, is the platelet activating factor antagonist Lexipafant. In a randomised, double blinded trial on 290 patients with severe acute pancreatitis (APACHE II score >6) intravenous Lexipafant for 7 days did not reduce the rate of multi-organ failure. This result was particularly disappointing because multiple prior studies employing experimental animal models suggested that Lexipafant is highly effective in reducing the systemic inflammatory response syndrome (SIRS) associated with acute pancreatitis.

The question is why was there no beneficial effect in the clinical setting? Again, targeting the wrong cytokines or the wrong type of immune cells is a possible answer. Another explanation would be that it is not the initial systemic (pro-) inflammatory response syndrome, but the subsequent compensatory anti-inflammatory response syndrome (CARS, fig 1), which leaves the patient prone to bacterial translocation and infected pancreatic necrosis, which needs to be targeted to prevent complications and death from severe pancreatitis. A significant number of patients in the Lexipafant trial may thus have received a potentially beneficial treatment for the initial phase of the disease, while they were already in a more advanced stage where immune-stimulation, rather than immuno-suppression, would have been called for.

In the current issue of Gut, Ryschich and co-workers (see page 1508) put forward a different, and rather unexpected explanation. They used a mouse strain in which leucocytes and monocytes carry a fluorescent marker that allows these cells to be observed. The circulation and migration of the cells were recorded during experimental pancreatitis by in vivo video microscopy. Using time-lapse intravital fluorescent imaging on these lys-EGFP-ki mice the authors employed models of experimental pancreatitis ranging from mild to severe. Their principal finding is that neutrophils and monocytes accumulate in pancreatic capillaries (intra-capillary leucocyte accumulation) and that this accumulation prevents capillary...
haemorrhage in a time- and concentration-dependent manner. In other words, intracapillary leucocyte accumulation must be regarded as a protective mechanism that prevents the transition from mild oedematous to haemorrhagic necrotising pancreatitis. Interestingly, this process preceded leucocyte extravasation from venules, an event that is thought to mediate pancreatic injury and increase disease severity. Intracapillary leucocyte accumulation was further found to depend on pro-inflammatory chemotactic stimuli such as IL8 and formyl-methionyl-leucyl-phenyalanine (FMLP) and on the ability of leucocytes to adhere to the endothelium of capillaries via lymphocyte function associated antigen-1 (LFA-1), CD11c/CD18 or ICAM. On the other hand, intracapillary leucocyte accumulation was almost absent in Mac-1-deleted animals (CD11b/CD18).

A number of important conclusions arise from this interesting experimental study. First, the protective effect of intracapillary leucocyte accumulation could explain how pancreatic haemorrhage, an event that depends on the local effect of vascular mediators such as bradykinin, is physiologically prevented in the initial disease phase and thus why the majority of patients never develop haemorrhagic necrotising pancreatitis. Second, intracapillary leucocyte accumulation is also a process distinctly different from thrombus formation. The latter event would have been a more expected observation given the activated serum protease cascade in pancreatitis and the known relationship between thrombosis and haemorrhage. Third, while the well established mechanisms of leucocyte recruitment to the pancreas during the early disease phase are not disputed in the present study, leucocyte transmigration into the pancreatic tissue and thus reduce severity. The quest for a cure for severe acute pancreatitis has not necessarily become easier with this study from Heidelberg.

In conclusion, the manuscript by Ryschich et al proposes an intriguing new hypothesis based on evidence for a protective role of neutrophils and monocytes in acute pancreatitis. The study is also a strong reminder of the complex immune system alterations that develop during different phases of the disease process. It also challenges us to further explore the tight balance between a systemic (pro-)inflammatory response syndrome (SIRS), a compensatory anti-inflammatory response syndrome (CARS) and possibly also a mixed inflammatory response syndrome (MARS) during different phases of acute pancreatitis. Modulating the immune system in order to treat pancreatitis appears to require a much better understanding of these different phases than we currently have, and a much more individualised approach to a patient than we can presently employ. What may help one patient in one phase of pancreatitis may aggravate the disease in another. Finding the markers that allow us to predict the correct time point for an appropriate intervention will certainly keep us busy for while.

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