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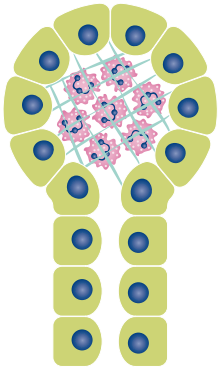
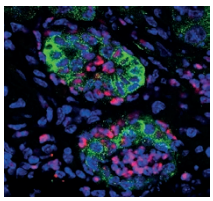
PANCREATITIS

NETs clog pancreatic ducts



IL-17A-induced pancreatitis



Inflamed pancreas showing aggregates of H3cit+ neutrophils (pink) inside the lumen of pancreatic ducts (green). Nuclei are blue. Courtesy of Moritz Leppkes.

Fibroinflammatory remodelling, typical of chronic pancreatitis, is potentially caused by the occlusion of pancreatic ducts via previously unknown agents. Now, a new model of pancreatitis driven by aggregations of neutrophil extracellular traps (NET) has been proposed.

Following on from previous work concerning intestinal inflammation, the investigators of the latest study examined the effects of IL-17A in the pancreas. First, aggregates of neutrophils expressing IL-17A were found in pancreatic ducts from human and mouse samples of inflamed pancreatic tissue. Then, using two methods of IL-17A delivery in mice, this cytokine was shown to strongly induce pancreatic neutrophilic inflammation.

"We discovered that IL-17A-induced pancreatitis strongly differs from the widely used model system of caerulein-induced pancreatitis," explains lead author Moritz Leppkes. "In response to IL-17A, neutrophils enter the pancreatic ducts and form large aggregates," he adds. Interestingly, IL-17A-induced pathological effects were initiated in the periductal areas of the pancreas and neutrophil depletion abrogated inflammation, indicating the importance of the aggregates in driving pancreatitis through ductal occlusion.

The investigators then examined the formation of decondensed chromatin NETs, which are used to trap pathogens or crystals during host defence. Neutrophils in the ductal lumens were shown to be positive for histone H3 citrullination (H3cit), which regulates chromatin decondensation via protein-arginine deiminase 4 (PADI4). By examining the components of human pancreatic juice, activation of PADI4 was found to be induced by bicarbonate and calcium carbonate *in vitro* and *in vivo*. Furthermore, using a mouse knockout model, deficiency in PADI4 strongly protected mice from IL-17A-induced pancreatitis. Thus, these findings implicate PADI4 and NETs as important factors in neutrophil aggregation and subsequent ductal occlusion.

This work clarifies a mechanism of inflammation that is broadly applicable to multiple glandular tissues. "This understanding will help in devising therapeutic concepts in multiple diseases in which ductal stasis contributes to pathology," concludes Leppkes. The researchers now plan to assess how aggregated NETs affect neighbouring epithelial cells, particularly in malignant transformation, as well as elucidating the mechanistic link between IL-17A and PADI4.

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ORIGINAL ARTICLE Leppkes, M. *et al.* Externalized decondensed neutrophil chromatin occludes pancreatic ducts and drives pancreatitis. *Nat. Commun.* http://dx.doi.org/10.1038/ncomms10973 (2016)