Acute pancreatitis

Activation of nuclear factor κB in acinar cells does not provoke acute pancreatitis

Roland M Schmid

Acute pancreatitis does not result from nuclear factor κB activation in the pancreas but could inhibition of nuclear factor κB activation be of some benefit in the course of acute pancreatitis?

Acute pancreatitis is a common disease, mostly self-limiting, but in some cases an acute abdominal emergency which lacks specific therapy. Our understanding of the mechanistic processes that initiate acute pancreatitis and mediate the pathobiological responses is rapidly evolving. The discovery of mutations in the genes encoding cationic trypsinogen (PRSS1) and the pancreatic secretory trypsin inhibitor (SPINK1), which are associated with chronic pancreatitis, have supported the concept that intrapancreatic activation of digestive enzymes is a key event in the initiation of acute pancreatitis. In severe cases a systemic inflammatory response is induced resulting in multiorgan failure. Although the relationship between pancreatic injury and the uncontrolled systemic inflammatory response is unclear, several lines of evidence suggest the participation of proinflammatory cytokines, including tumour necrosis factor α (TNF-α) and interleukin (IL)-1. One key transcription factor which is activated by these proinflammatory cytokines is nuclear factor κB (NFκB). NFκB is central for the regulation of immune and inflammatory responses, proliferation, survival and tumorigenesis. The family is composed of NFκB (1 and 2) and Rel proteins (RelA, RelB and c-Rel). NFκB exists in the cytoplasm of resting cells but enters the nucleus in response to various stimuli, including proinflammatory cytokines such as TNF-α and IL-1. Activation is controlled by inhibitory subunits such as IκBα und IκBβ, which retain NFκB dimers in the cytoplasm. The IκB kinase (IKK) complex is composed of two catalytic subunits (IKK1 or α and IKK2 or β) and a regulatory subunit (IKKγ or NEMO) among other proteins forming the IKK signalosome. IκB kinase activity phosphorylates IκBα and IκBβ with subsequent ubiquitination and degradation of IκB as well as consequent exposure of a nuclear localisation signal on NFκB. In the nucleus, NFκB dimers activate numerous target genes, including inflammatory chemokines, cytokines, mitogens, adhesion molecules and immune receptors.

As NFκB is activated in numerous inflammatory diseases it was not a surprise to find IKK and NFκB activation in animal models of acute pancreatitis, information which is not available from patients, because it is too difficult to access the organ and obtain biopsy specimens.[1–3] The first study demonstrating activation of NFκB in acute pancreatitis was undertaken in the cerulein model of acute pancreatitis. NFκB was induced as early as 10 minutes after cerulein application within acinar cells. Activity peaked at 30 and subsided by 90 minutes. One way to analyse the function of NFκB during pancreatitis is to compare the course of pancreatitis with and without blocking its activation. Inhibition of NFκB activation using non-specific chemicals, natural compounds, peptides or viral recombinant inhibitors revealed attenuation of severity or even improved survival in different experimental models of acute pancreatitis.[4–6] Therefore, one might come to the conclusion that inhibition of this pathway might be the novel secret treatment for acute pancreatitis. However, one other study suggested a protective mechanism mediated by NFκB.[3] In this study two different non-specific inhibitors inhibited nuclear translocation of NFκB during the course of pancreatitis which enhanced tissue injury and inflammation, demonstrating that NFκB mediated induction of genes prevented a higher degree of damage of pancreatic tissue. This study supports the protective role of NFκB in acute phases of inflammation demonstrated in other systems. The difficulty with all of these studies is the use of inhibitors which are not totally specific.

Another experimental approach is activation of NFκB in acinar cells to determine whether NFκB activation results in deterioration of the course of pancreatitis or even can induce pancreatitis per se. Aleksic *et al*,[7] in this issue of *Gut*, describe a very elegant approach to shed light on the role of NFκB activation ***(see page 227)***. They aimed to investigate the consequence of activation of the NFκB signalling pathway using a constitutively active mutant of an IKK subunit. The exact mechanism of IKK activation is not clear but all inducers of NFκB show autophosphorylation of IKK. Both IKK1 and IKK2 contain a canonical MAP kinase kinase activation loop motif in which phosphorylation of both Ser residues is necessary for activation.[8] Mutation of both Ser to Glu mimics the effect of P-Ser and generates a highly active kinase activity. Aleksic *et al* used an inducible system (rtTA/tetO) to express the constitutively active kinase in mice. In this system, a mouse line, where rtTA expression is driven by the CMV promoter, was crossed with a mouse line with a construct composed of a bidirectional promoter driving luciferase as reporter and the active IKK mutant. Animals transgenic for both transgenes were exposed to doxycycline by adding the drug to the drinking water. The transgene was induced up to 200-fold resulting in moderate activation of IκB kinase and nuclear translocation of RelAp65. Although transgene expression was detected early on in the thymus and in the kidney, its expression seemed to be limited to the pancreas after 8–12 weeks. Histological analysis revealed leucocyte infiltrates in the pancreas starting 3–4 weeks after induction of the transgene but no signs of acute pancreatitis. These infiltrates were characterised as B-lymphocytes and macrophages, and displayed a patchy pattern. TNF-α and RANTES were detected in pancreas acinar cells and proposed to be responsible for the observed phenotype. The authors conclude that acute pancreatitis does not result from NFκB activation in the pancreas, which is an important finding.

These data are in contrast with adenoviral mediated transfer of RelA which was able to provoke pancreatitis and a systemic inflammatory response.[9] However, the difficulty with this study approach is the use of adenoviral infection. Adenoviral infection per se generates expression of chemokines and cytokines and therefore the use of an inducible genetic system can be regarded as ''cleaner''. Although Aleksic *et al* did not find that IKK/NFκB activation in acinar cells provoked acute pancreatitis, they suggest that IKK activity is sufficient to worsen the course of cerulein pancreatitis. They found increased vacuolisation, oedema and infiltration of leucocytes in the pancreas using histological analysis following cerulein application in mice overexpressing the constitutively active form

of IKK. These findings are not supported by biochemical data and are certainly not very impressive. This leaves us with more questions than answers.

What is the relationship between trypsinogen and NFκB activation?

Trypsinogen activation is considered the key event in the initiation of acute pancreatitis. Whether NFκB activation participates in the activation of trypsin is unclear. Interestingly, NFκB is induced with a kinetic similar to activation of trypsin.[10–12] Is there a cell type specific role for NFκB activation in the course of acute pancreatitis? Inhibition of NFκB in acinar cells might be harmful and extend tissue injury whereas blocking NFκB activity in inflammatory cells might be beneficial and prevent the uncontrolled systemic response. What are the NFκB dependent "protective genes"? It could even be possible that NFκB activation contributes to the pancreatic defence programme and triggers the synthesis of proinflammatory cytokines within the acinar cells simultaneously. Is slight inhibition of NFκB beneficial? Acinar cells might need a small dose of NFκB activation to be able to turn on a defence program. The use of genetically defined knockout mice will help to answer these questions. The possibility to inactivating genes in a tissue and time specific fashion will allow analysis of the consequence of inhibition of different components of NFκB signalling in different cellular compartments.

In summary the study by Aleksic *et al* clearly shows that activation of NFκB in acinar cells is not deleterious to the pancreas per se. Induced NFκB activity for months resulted in infiltrates composed of B-lymphocytes and macrophages without destroying the organ. The key question for the future is whether inhibition of NFκB activation will be of some benefit in the course of acute pancreatitis. What cell type has to be targeted? What time course of inhibition is best? And finally, will this approach work in our patients suffering from acute pancreatitis?

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Correspondence to: Dr Roland M Schmid, 2nd Department of Internal Medicine, Technical University of Munich, Klinikum rechts der Isar, Ismainger Strasse 22, D-81675 München, Germany; roland.schmid@lrz.tum.de

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Gastrointestinal disease

The burden of gastrointestinal disease: implications for the provision of care in the UK

M D Hellier, J G Williams

Gastroenterology involves many disciplines, including physicians, surgeons, radiologists, pathologists, nurses, dieticians, clinical scientists and general practitioners, who need to work together closely to deliver the best care. Gastrointestinal and liver disorders are common, but the specialty is poorly understood and has attracted little attention from a policy perspective. Thus, it has no National Service Framework, was not included in the "Quality and Outcome Framework" for general practice and does not attract significant charitable research funding, in comparison with many other disciplines. Yet the burden of disease relating to gastroenterology and hepatology is very considerable. Gastrointestinal disease is the third most common cause of death, and cancer of the gastrointestinal tract is the leading cause of cancer death. Including day case investigations, gastrointestinal disorders account for as many hospital admissions as respiratory illnesses, and both are second only to circulatory disorders. In the past few decades there have been increases in the incidence of most gastrointestinal diseases that have major implications for future healthcare needs. These include hepatitis C, acute and chronic pancreatitis, alcoholic liver disease, gallstone disease, upper gastrointestinal haemorrhage, diverticular disease, Barrett's oesophagus and oesophageal and colorectal cancers. The impairment of quality of life is substantial in terms of symptoms, activities of daily living and employment. Conditions with a particularly high level of disruption to the lives of sufferers include gastro-oesophageal reflux disease, dyspepsia, irritable bowel syndrome, anorectal disorders, gastrointestinal cancers and chronic liver disease.

The evidence underpinning these conclusions can be found in a document commissioned by the British Society of Gastroenterology (BSG) and published this month as a supplement to *Gut*.[1] It is accompanied by a strategic view of the future care of patients with gastrointestinal disorders from the BSG.[2] These two documents are intended to fill the void created by the absence of a National Service Framework for Gastroenterology and Hepatology. This omission seriously disadvantages the specialty and patients who have gastrointestinal disorders at a time when there are unprecedented pressures to improve healthcare services. There is an urgent need for such improve-