Reviewer's report

Title: Mobilization of xanthine oxidase from the gastrointestinal tract in acute pancreatitis

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Reviewer: Thierry Dugernier

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General
How what is at first a localized inflammatory process in the pancreas, which may end up in focal or diffuse necrosis, turns out into a generalized inflammatory disease with multisystem organ failure, remains obscure. A potential mechanism underlying the propagation of the inflammatory response is oxidative stress. Among other sources, activation of the xanthine dehydrogenase/oxidase pathway during acute pancreatitis may generate activated oxygen species with subsequent endothelial cell activation at remote sites from the gland.
The authors have previously shown that the circulating enzyme arose from its mobilization from the surface of endothelial cells located in the gastrointestinal system. The current study focus through a nice set of experiments on the role of amylase and ascites in the mobilization of xanthine dehydrogenase during experimental acute pancreatitis.

Discretionary Revisions (which the author can choose to ignore)
Background: line 18 - replace "adult respiratory distress syndrome" with "acute lung injury"
line 16 - delete "human"

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
Abstract: 3d line - delete "a" xanthine...
Results - correct spelling of "increase"
Conclusions - cannot understand properly last sentence, a word is missing after "circulating".
Results page 8: line 9 - "heat"

Discussion page 12: line 3 - "agrees"
line 13 - correct "therapeutical"

References page 13: n° 6 correct "Dig Dis Sci"
page 14: n° 11 correct "Heparin"

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
1) The aims of the current study were not to address the role of xanthine oxidase-generated activated oxygen species in mediating recruitment/activation of neutrophils in the lung. There are no data in this particular study to support this association as other mechanisms may be operating in acute pancreatitis. This should be taken into account in the conclusions of the abstract and the discussion.

2) Background line 18-19: ARDS is no longer the most important factor contributing to death in clinical acute pancreatitis. Studies conducted in selected patient groups originating from specialist centers reported that more than two thirds of deaths occur late in the course of the disease and are caused by secondary infection of pancreatic necrosis (see Ann Surg 2000; 5: 619-26). Population-based
reports described that 40% to 60% of all fatalities still occur within the first week of symptoms and should be ascribed to early multiple organ failure and/or comorbid disease (see Br J Surg 2002;89:298-302). Accordingly modify the statement and delete reference n°8.

3) Intestinal absorption of amylase from the ascitic fluid: agents that collect in ascites during acute pancreatitis may undergo transperitoneal absorption through either the capillary network or peritoneal lymphatics that enter the thoracic duct, and then reach the systemic circulation by-passing the splanchnic system. Although the current experiments strongly suggest a preferential uptake of amylase by the splanchnic circulation the precise anatomical pathway appears unclear. This should be tackled in the discussion.

4) Caution should be exercised when attempting to translate results of experimental studies on acute pancreatitis in human disease. The authors correctly assumed on the basis of their data that the conversion of xanthine dehydrogenase into the oxidase form takes place in the blood circulation and ascribed it to a proteolytic activity in this compartment. However, although a free protease activity in humans has been demonstrated in the peritoneal (see Hepato-gastroenterol 1984;31:277-81) and lymphatic (personal unpublished data) compartments in humans, the potency of the antiprotease defences makes very unlikely a significant proteolytic activity in blood (see Gut 1991;32:430-4).

There are considerable interspecies differences in the pathways of enzyme/toxic substances transfer from the pancreas to the systemic circulation. In humans peritoneal lavage failed to influence the amylase profile in blood during the course of the attack (see N Engl J Med 1985;312:399-404) and inflammatory mediators primarily gain access to the systemic circulation via the splanchnic blood circulation (see Am J Resp Crit Care Med 2003;168:148-57). These findings may in part account for the lack of benefit of peritoneal lavage in randomized trials. The results of the present study should be reconciled/put in perspective with these data.

5) The references should be renumbered/verified in the discussion: reference 13 should probably be read 19; ref 19 is n°20(?) and so on... as some of them are clearly irrelevant to the statement to which they refer.

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: No

Declaration of competing interests:

None