It may not be intestinal, but tissue non-specific alkaline phosphatase


*Gut* 2010 59: 560
doi: 10.1136/gut.2009.191957

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The interesting study by Tuin et al in a recent issue of Gut uncovers a hitherto unrecognised protective role of alkaline phosphatase (AP) in intestinal inflammation. These authors measured AP activity (including lipopolysaccharide (LPS) as a substrate) and mRNA level of the intestinal isoenzyme (IAP) in inflamed and non-inflamed mucosa of patients with inflammatory bowel disease. IAP expression and AP activity were virtually non-existent in the colon when compared to the ileum.

These researchers follow up on a recent paper by Richard Hodin’s group1 which describes how intestinal AP knockout mice are less well suited than wild-type counterparts against bacterial translocation in the context of ischaemia–reperfusion injury. The physiological role of AP in the intestine has been an open question for decades, but the realisation that AP can remove a terminal phosphate group from LPS, thus greatly diminishing its damaging potential, meant that it may serve a protective role. Thus, Tuin et al went on to show quite nicely that oral treatment of dextran sodium sulfate (DSS) colitic rats with IAP administered as gastric resistant tablets has a beneficial effect on inflammation.

It is intriguing to note that a colonic protective protein is barely expressed in this intestinal segment. Moreover, colonic inflammation further downregulates IAP expression in both ulcerative colitis and Crohn’s disease, as shown by Tuin et al themselves. This observation clashes with their reporting of augmented AP activity in histological sections from DSS colitic rats, involving both the inflammatory infiltrate and the epithelium (figure 6).2 In their paper.1 Although IAP mRNA measurements from the animal study were not included in the article, we have previously shown that AP activity is markedly upregulated in multiple models of colitis,3 including DSS colitis. At least in the trimethoprim-sulfamethoxazole acid model the isoenzyme expressed by the inflamed intestine is not IAP but tissue non-specific AP. As in the study by Tuin et al, AP is increased both in infiltrating leukocytes and in epithelial cells. However, the isoenzyme of the colitic tissue is more sensitive to inhibition by levamisole, homo-arginine and heat, and there are changes in glycosylolation involved. We have also established that oxidative stress reproduces this effect in epithelial cell lines.

Therefore, it appears that, while IAP expression fades in the inflamed colon, IAP expression of tissue non-specific AP increases. Does this mean anything functionally? It is too soon to tell, but it is tempting to speculate that the latter covers the absence of the former.

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Funding Other Funders: CIBER-EHD, Ministry of Science and Innovation, Junta de Andalucía.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

Gut 2010;59:560. doi:10.1136/gut.2008.191957

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Authors’ response

As mentioned by Martinez-Augustin et al, we found reduced levels for intestinal alkaline phosphatase (AP) mRNA in rats with dextran sulfate sodium (DSS)-induced colitis and in patients with ulcerative colitis.1 In the same paper we show a reduced enzyme activity along the intestinal epithelium in sections from rats with DSS-induced colitis (figure 6K of Tuin et al). There is no contradiction in this. However, as also noted by Martinez-Augustin et al, this decline in intestinal AP was associated with an increased staining for AP in infiltrating cells. It is indeed tempting to speculate that the augmentation of one isoenzyme serves to compensate the loss of another one. If this is the case, the function of AP must be important. In 1997 we proposed that AP plays an important role in the defence system against lipopolysaccharide (LPS); we found that AP can dephosphorylate the lipid A moiety of LPS, thereby detoxifying this bacterial product.2 We suggested that this activity might even be a physiological role for this enzyme, this suggestion being based in part on the fact that AP dephosphorylated LPS at physiological pH levels (pH 7.4) in contrast to the dephosphorylation of all other substrates (pH optimum >10) and that the localisation of the enzyme in most cases perfectly fits with its proposed role. In particular the co-localisation of AP with the LPS receptor CD14 within neutrophils3 provides fuel for this notion. Recent publications by Goldberg and Hodin et al support this hypothesis.4 So, accumulating evidence suggests that AP plays a key role in the intestinal wall. It would be an important step to definitely unravel a role for this enzyme that has been extensively studied ever since 1954, whose presence is so ubiquitous in nearly all organs of the body, whose activity profoundly changes during various diseases, yet whose function is so utterly obscure.

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Competing interests None.

Provenance and peer review Not commissioned; not externally peer reviewed.

Gut 2010;59:560. doi:10.1136/gut.2009.191186

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