Induction and rescue of Nod2-dependent Th1-driven granulomatous inflammation of the ileum

JAN WEHKAMP
Germany

Biswas A, Liu YJ, Hao L, Mizoguchi A, Salzman NH, Bevins CL, Kobayashi KS

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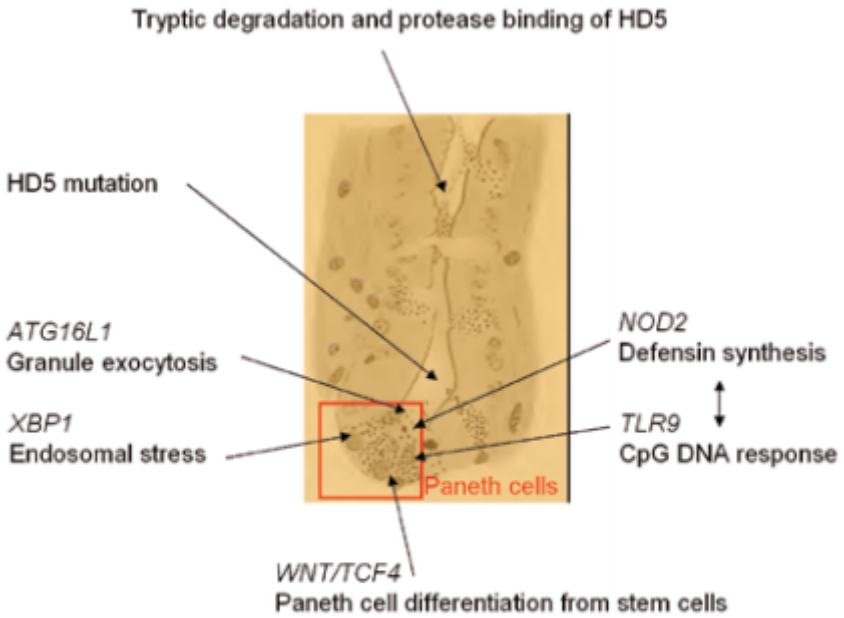
Reflecting the programme of the 2011 ECCO Congress in Dublin there are different lines of current understanding and research. The classical and probably most established investigation line is the role of the adaptive immune system including the role of Th-1 driven inflammation. The more recent but already very dominant area of interest is the role of the microbiota, which is generally accepted to trigger the inflammation in both Crohn's Disease and Ulcerative Colitis. Another translational research driven achievement of the past years is the acknowledgment of different clinical phenotypes and disease locations, most importantly the understanding that ileal inflammation is likely due to different factors than inflammation in the colon. The newest and – by some – still controversially discussed field is the understanding of host antimicrobial defense and especially the understanding that – at least – different types of IBD are caused by a barrier problem. In the lines of a barrier problem, different mechanisms including NOD2 mutations, stem cell differentiation WNT signaling defects, Autophagy as well as endosomal stress pinpoint to an important role of the small intestinal crypt – epithelial Paneth cell, especially in case of small intestinal disease involvement.

The paper by Biswas et al. elegantly addresses all these different aspects and nicely demonstrates that these different arms of host immunity as well as non host microbiota can not be viewed as separate and independent. As shown before (in patients and rodent models) the authors demonstrate the link between NOD2 and Paneth cell antimicrobial host defense. The authors report that Nod2-deficient mice treated with an opportunistic pathogenic bacterium, developed granulomatous inflammation of the ileum, which was characterised by an increased expression of Th1-related genes and inflammatory cytokines. Accordingly, this resulted in an enlargement of Peyer's patches and mesenteric lymph nodes and more specifically expansion of IFN-γ–producing CD4 and CD8 T cells. Rip2-deficient mice exhibited a similar phenotype, suggesting that Nod2 function likely depends on the Rip2 kinase in this model. Transferring wild-type bone marrow cells into irradiated Nod2-deficient mice did not rescue the phenotype.



Different genetic mechanisms are linked with ileal disease phenotype and pinpoint to an important role of the small intestinal Paneth cell. The authors demonstrate that restoring Paneth cell antimicrobial function can rescue the ileal TH1 inflammation phenotype. (Paneth's disease. Source: reproduced with permission of the authors: J Crohns Colitis. 2010 Nov;4(5):523-31)

Key finding

However, restoring Paneth cell crypt antimicrobial function of Nod2-deficient mice by transgenic expression of α-defensin in Paneth cells rescued the Th1 inflammatory phenotype. Thus the authors demonstrate that through the regulation of intestinal microbes, Nod2 function in Paneth cells of the small intestinal crypts is critical for protecting mice from a Th1-driven ileal inflammation. This could (and hopefully will) be future therapy!

In summary, why clinicians and scientists should be aware of this:

This paper demonstrates a close link between microbiota, adaptive and innate antimicrobial host defense in a disease model of ileal inflammation. Importantly it suggests the therapeutic potential of restoring defective antimicrobial host defense. I am convinced that understanding especially the interplay of these different aspects will open up – hopefully many – therapeutic avenues in the near future.