Nature Reviews Gastroenterology & Hepatology | Published online 25 May 2016; doi:10.1038/nrgastro.2016.89

IBD

Sensing gene–microbiota signals in IBD

> ...IBD susceptibility genes promote disease via defects in sensing protective signals from the commensal gut microbiota

New research suggests that polymorphisms in IBD susceptibility genes promote disease via defects in sensing protective signals from the commensal gut microbiota. The findings provide more information on how gene–environmental interactions might influence the development of IBD.

Numerous IBD risk loci have been identified — most notably linked to autophagy (*ATG16L1*) and microbial sensing (*NOD2*) — and research is now trying to define their role. "This project began as we became curious if mutations in genes linked to Crohn's disease susceptibility may be involved in sensing beneficial signals from the microbiome," explains lead author Hiutung Chu. The researchers built on previous work showing that the human commensal *Bacteroides fragilis* secretes outer membrane vesicles (OMVs) that are delivered to dendritic cells (DCs) and promote the function of immunosuppressive FOXP3$^+$ regulatory T (T_{REG}) cells, protecting mice from colitis.

In a series of *in vitro* and *in vivo* experiments it was demonstrated that *B. fragilis* OMVs require IBD-associated genes *ATG16L1* and *NOD2* during protection from colitis, activating a non-canonical autophagy pathway. In the absence of these genes, *B. fragilis* OMVs did not induce T_{REG} cells *in vitro* and *in vivo*, and did not prevent mucosal inflammation.

Translating these findings to humans, monocyte-derived DCs were isolated from patients with Crohn's disease who carry the *ATG16L1* Thr300Ala risk allele and from healthy individuals with either the protective or risk allele. Crucially, immune cells from patients with Crohn's disease with the *ATG16L1* Thr300Ala risk variant had defective T_{REG}-cell responses to OMVs *in vitro*, whereas immune cells from those with the protective allele responded.

"This study reveals an entirely new function for the Crohn's-disease-associated risk genes *ATG16L1* and *NOD2*," says Chu, adding that individuals with mutations in these genes might not benefit from the protective influences of the gut microbiota.

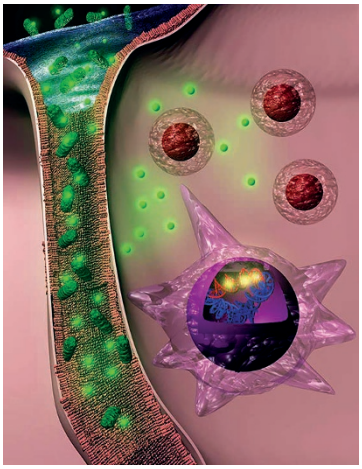

Image courtesy of N. Cruz, Caltech, USA.

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ORIGINAL ARTICLE Chu, H. *et al.* Gene–microbiota interactions contribute to the pathogenesis of inflammatory bowel disease. *Science* http://dx.doi.org/10.1126/science.aad9948 (2016)