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Crohn's Disease, Autophagy, and the Paneth Cell

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Because of its very nature, the gastrointestinal tract is potentially subject to inflammation and infection. Much of its surface is designed to be highly exposed and absorptive, yet it faces a tremendous microbial population. Therefore, it is not surprising that various gastrointestinal disorders are linked to microbial infection or toxins. For example, peptic ulcers, affecting approximately 10% of the population in the United States, are caused in part by infection with *Helicobacter pylori*. Accordingly, treatment for this type of ulcer includes antibiotics.

Unfortunately, less success has been achieved in managing another often debilitating disorder, Crohn's disease, an inflammatory disease affecting the small intestine. There is no cure for Crohn's disease, and treatment is focused on limiting the recurrence and severity of the symptoms. Genomewide association studies have shown that Crohn's disease is associated with at least 30 mutant loci,¹ a finding that suggests that it may actually represent a spectrum of disorders that present with similar gross phenotypes. Three recent studies^{2–4} have linked Crohn's disease with cellular autophagy, providing new insights that may eventually lead to therapeutic intervention.

To understand the role of autophagy (literally, “self-eating”) in the pathogenesis of Crohn's disease, it is necessary to consider the mechanism of this process. The type of autophagy that is relevant to Crohn's disease is macroautophagy (hereafter referred to as autophagy). The morphologic hallmark of this type of autophagy is the formation of double-membrane cytosolic vesicles, called autophagosomes, that sequester cytoplasmic contents and deliver them to the lysosome for subsequent degradation. The autophagosome does not bud off from preexisting organelles but, rather, is formed by a dynamic process of membrane expansion. This allows the autophagosome to sequester cargoes of almost any size, a capacity that is critical to many aspects of autophagic function, including the elimination of microbial pathogens from host cells. The ability to sequester invasive bacteria and deliver them to the lysosome would seem to be a potentially important role for epithelial and immune cells that encounter a heavy microbial load. The finding that a variant of *ATG16L1*, an orthologue of the yeast autophagy-related *ATG16*, is associated with Crohn's disease¹ suggests that the inability to eliminate intestinal microbes via autophagy might account for some types of this disease. The situation, however, appears to be more complex.

The three studies^{2–4} show that *ATG16L1* mediates autophagy. The variation (T300A) in *ATG16L1* associated with Crohn's disease lies outside the region of homology with the yeast orthologue, and accordingly, when the mutant protein is over-expressed, it is not associated with defects in basal, nonselective autophagy (increased nonselective autophagy is a starvation response in yeast). Indeed, in vivo studies in mice suggest that rather than compromising the ability of the cell to sequester bacteria, T300A induces an autophagy-associated defect in Paneth cells, specialized cells in the crypts of Lieberkühn within the small intestine that secrete

lysozyme and antimicrobial peptides (Fig. 1). The mutant Paneth cells show defects in the exocytic pathway. They also have degenerating mitochondria and an abnormal endoplasmic reticulum, which may reflect the loss of organelle degradative capacity associated with the autophagy defect, since autophagy plays an important role in removing damaged or dysfunctional organelles. These defects, which are also observed in mice engineered to lack either of the autophagy genes *Atg5* or *Atg7* in the intestinal epithelium,^{2,5} correlate with the absence of lysozyme in the protective mucus layer of the ileum. Furthermore, microarray profiling indicates that genes associated with the inflammatory response, including leptin and adiponectin, are up-regulated in the autophagy-deficient Paneth cells. Analysis of tissue sections from human patients with the *ATG16L1* risk allele confirms the presence of abnormal Paneth cells.

ATG16L1-dependent autophagy also mediates the endotoxin-induced inflammatory response.⁴ Mice with ATG16L1-deficient macrophages produce higher levels of the inflammatory cytokine interleukin-1 β and are susceptible to acute colitis in response to the chemical damaging agent dextran sodium sulfate. The increased production of cytokines may reflect failure of an autophagic stress response.

All three studies suggest that a defect in autophagy may be the primary cause of ATG16L1-associated Crohn's disease. It will be important to determine whether induction or up-regulation of autophagy, in particular in Paneth cells or macrophages, reverses the phenotypic abnormalities; restoration of their normal homeostasis may ameliorate the disease symptoms. From a clinical standpoint, treatment with neutralizing antibodies to inflammatory cytokines⁴ such as interleukin-1 β or possibly the oral administration of an encapsulated (protease-protected) preparation that mirrors the contents of Paneth-cell secretory granules may help restore the microbial biota and intestinal milieu to its normal disease-free state.

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Figure 1. Autophagy and the Intestinal Epithelium

Recent studies have indicated that defects in macroautophagy contribute to Crohn's disease.²⁻⁵ Macroautophagy can sequester cytoplasmic components, including organelles or (as depicted here) an invasive microbe, within double-membrane autophagosomes (Panel A). Fusion with the lysosome allows the breakdown of the cargo and elimination of the pathogen. Through exocytosis of granules, Paneth cells in the crypts of Lieberkühn secrete antimicrobial peptides and lysozyme, which regulate microbial status in the intestine and protect against pathogenic invasion (Panel B). Studies in mice²⁻⁴ have indicated that genetic variation in *ATG16L1*, which was previously associated with Crohn's disease, results in defective

autophagy in Paneth cells, a diminution of lysozyme in the intestinal lumen, and an increase in intestinal inflammation.