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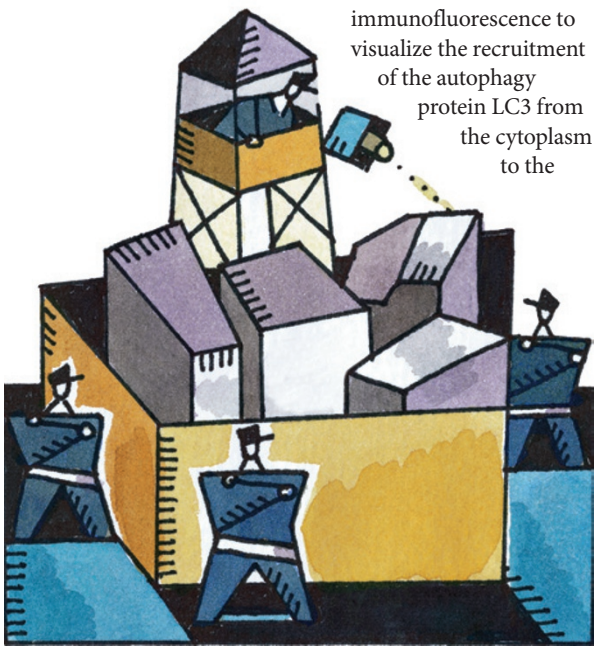
MUCOSAL IMMUNOLOGY

Autophagy helps man the barriers

> autophagy in intestinal epithelial cells protects against the dissemination of invasive bacteria

Autophagy has a central role in maintaining cell homeostasis, and polymorphisms in autophagy-related gene 16-like 1 (*ATG16L1*) are associated with susceptibility to Crohn's disease in humans. However, these polymorphisms affect the autophagy-independent functions of *ATG16L1* that result in defective granule formation in Paneth cells. Therefore, it remains unknown whether autophagy has a direct role in maintaining intestinal homeostasis *in vivo*. Reporting in *Cell Host & Microbe*, Hooper and colleagues show that autophagy in intestinal epithelial cells protects against the dissemination of invasive bacteria.



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The authors used immunofluorescence to visualize the recruitment of the autophagy protein LC3 from the cytoplasm to the autophagosomes, which is a classical assay of autophagy activation. They showed that LC3-positive autophagosomes formed in intestinal epithelial cells following oral infection of germ-free or conventionally raised mice with the invasive intestinal pathogen *Salmonella enterica* subsp. *enterica* serovar Typhimurium. In addition, autophagy in epithelial cells was activated following infection of germ-free mice with the opportunistically invasive commensal bacteria *Enterococcus faecalis*. LC3-positive autophagosome formation occurred rapidly (within 24 hours) after infection, was highest in epithelial cells of the distal small intestine (ileum) and was lower in the middle and proximal regions (jejunum and duodenum).

Further analysis showed that infection of germ-free mice with mutant strains of *S.* Typhimurium that cannot invade gut epithelial cells, or with the non-invasive bacteria *Lactobacillus salivarius*, did not result in the induction of autophagy in intestinal epithelial cells. This indicates that autophagy activation depends on bacterial entry into epithelial cells.

Previous studies have shown there to be a requirement for innate immune signals in the bacterial induction of autophagy in macrophages. Similarly, expression of the innate immune adaptor protein MYD88 (myeloid differentiation primary-response protein 88) specifically in epithelial cells was shown to be required for autophagy activation by invasive bacteria. By contrast, autophagy activation in intestinal epithelial cells was independent of the adaptor protein TRIF (TIR-domain-containing adaptor protein inducing IFNβ; also known as TICAM1) and the intracellular pattern recognition receptor NOD2 (nucleotide-binding oligomerization domain protein 2).

Finally, mice that have an epithelial cell-specific deletion of the essential autophagy gene *Atg5* (*Atg5*$^{\Delta IEC}$ mice) were orally infected with *S.* Typhimurium, which resulted in decreased numbers of autophagosomes and in increased numbers of intracellular bacteria in intestinal epithelial cells. Furthermore, these mice had increased numbers of bacteria in their spleen and liver compared with littermate controls. This increased bacterial dissemination was not observed in *Atg5*$^{\Delta IEC}$ mice infected with a non-invasive *S.* Typhimurium strain.

Together, these data show that autophagy is an epithelial cell-intrinsic innate immune mechanism that protects against the dissemination of invasive intestinal bacteria.

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ORIGINAL RESEARCH PAPER Benjamin, J. L. *et al.* Intestinal epithelial autophagy is essential for host defense against invasive bacteria. *Cell Host Microbe* **13**, 723–734 (2013)
FURTHER READING Kamada, N. *et al.* Role of the gut microbiota in immunity and inflammatory disease. *Nature Rev. Immunol.* **13**, 321–335 (2013)