Regulation of interferon signaling in response to gut microbes by autophagy

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ABSTRACT
The cellular degradative pathway of autophagy prevents unrestrained inflammatory signaling by removing intracellular microbes, damaged organelles, and other factors that trigger immune reactions. Consistent with this function, a common variant of the autophagy gene \textit{ATG16L1} is associated with susceptibility to inflammatory bowel disease (IBD), a disorder characterized by a chronic immune reaction directed against the gut microbiota. We recently contributed to our understanding of the link between autophagy and inflammatory signaling in the intestine by demonstrating that autophagy proteins including \textit{ATG16L1} are necessary in the epithelium to prevent a spontaneous type I interferon response to the gut microbiota. Enhanced innate immunity that occurs upon autophagy inhibition is protective in mouse models of infection by an enteric bacterial pathogen and acute epithelial injury. Although avoiding excess immune reactions towards the microbiota is necessary to prevent IBD, these observations indicate that autophagy hampers productive immunity at the intestinal epithelial barrier in certain contexts. Here, we discuss how this counterintuitive consequence of autophagy inhibition can be reconciled with the established beneficial role of the pathway.

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Introduction
A single layer of epithelial cells lies between the rest of our body and a multitude of infectious agents in the gut, including members of the microbiota that establish long-term colonization and pathogens capable of causing life-threatening disease.\textsuperscript{1} In addition to serving as a physical barrier, the intestinal epithelium relays signals back-and-forth between these microbes in the lumen and immune cells on the other side of the fence to achieve an immune response of appropriate magnitude and quality. This bidirectional communication is essential for the differentiation of immune cell subsets that promote host defense. However, maladaptive immune reactions directed towards the gut microbiota or other infectious agents can give rise to Crohn’s disease and ulcerative colitis, types of inflammatory bowel disease (IBD).\textsuperscript{2} Therefore, innate immune signaling in the gut must be controlled, which poses a challenge at the level of the epithelial barrier. Microbes are a constant source of microbe-associated molecular patterns (MAMPs) that are ligands for pattern recognition receptors (PRRs), many of which are expressed in epithelial cells to allow a swift innate immune response to invasive infections.\textsuperscript{1} What are the cell biological pathways that prevent spontaneous activation of these PRRs in the absence of a bona fide threat?

Autophagy is a cell-intrinsic mechanism by which cytosolic material is degraded. Through the coordinated action of numerous autophagy (ATG) proteins, cellular contents are engulfed in a double membrane vesicle and subsequent fusion with the lysosome leads to the breakdown and recycling of vesicle contents. In addition to countering nutritional stress, autophagy plays a critical role in cellular, tissue, and organismal homeostasis by removing protein aggregates, depolarized mitochondria, internalized microbes, and other unwanted material.\textsuperscript{3} We and others have demonstrated that ATG proteins support the intestinal epithelial barrier, likely through this cellular homeostatic function of autophagy. Inhibiting ATG proteins in the intestinal epithelium leads to accumulation of intracellular...
bacteria in enterocytes (absorptive epithelial cells), dysfunction of Paneth cells and goblet cells (secretory epithelial lineages), and overall susceptibility to cell death.\textsuperscript{4–13} Additionally, ATG protein function in the intestinal epithelium is critical for preventing inflammation following a range of enteric infections.\textsuperscript{14–17} These observations may explain the genetic association between a common polymorphism in the autophagy gene ATG16L1 (T300A allele) and susceptibility to Crohn’s disease.\textsuperscript{3,18}

To better understand the link between autophagy and mucosal immunity in the gut, we previously generated mice harboring a germ line gene-trap mutation that leads to decreased Atg16L1 expression and reduced autophagy.\textsuperscript{4} These Atg16L1 hypomorph (Atg16L1\textsuperscript{HM}) mice develop intestinal abnormalities upon infection with murine norovirus (MNV), which include lesions observed in Crohn’s disease patients such as morphological and functional defects in the antimicrobial Paneth cells that reside within the small intestinal epithelium.\textsuperscript{4,17} In a subsequent study, we showed that the immune response to the virus triggers necroptosis (programmed necrosis) in the ATG16L1-deficient epithelium, which was associated with defective autophagy-mediated removal of damaged mitochondria (mitophagy).\textsuperscript{5} Of note, we found that MNV typically establishes an asymptomatic infection and can even be a beneficial virus in other animal models of disease.\textsuperscript{19} Thus, Atg16L1 mutation leads to defects in the intestinal epithelium in response to an otherwise beneficial virus, indicating that autophagy is important for tolerating infectious threats in the gut.

Atg16L1\textsuperscript{HM} mice display exacerbated disease in response to other inflammatory triggers such as Staphylococcus aureus infection and allogeneic bone marrow transplantation.\textsuperscript{20,21} However, Atg16L1\textsuperscript{HM} mice are resistant to uropathogenic E. coli (UPEC) in a model of urinary tract infection and display decreased vertical transmission of Zika virus,\textsuperscript{22,23} demonstrating that reducing ATG16L1 function does not unilaterally compromise the immune system. Also, we found that Atg16L1\textsuperscript{HM} mice are extraordinarily protected from disease following oral inoculation with Citrobacter rodentium.\textsuperscript{24} This finding was unexpected because C. rodentium is a model of intestinal infection by enteropathogenic E. coli (EPEC), representing a striking contrast from our results with MNV. This protection from C. rodentium was associated with decreased colonic inflammation (which occurs due to binding of C. rodentium to the epithelial surface) and a striking reduction in bacterial burden. While CD4+ T cells and neutrophils were not required for enhanced C. rodentium resistance, we found monocytes play a crucial role in the mechanism of protection. Atg16L1 deficiency was associated with a hyperimmune transcriptional response characterized by increased expression of interferon-stimulated genes (ISGs) in the colon that precedes infection and becomes exacerbated in the presence of C. rodentium. These observations led us to question if ATG16L1 and autophagy were regulating inflammatory responses at the gut mucosal surface.

**Autophagy proteins suppress protective type I interferon signaling**

In our recent manuscript, we make progress in elucidating the mechanism by which Atg16L1 mutation enhances antimicrobial immunity in the gut.\textsuperscript{25} Using cell type-specific knockout mice, we demonstrate that loss of ATG16L1 in the epithelium is sufficient to confer resistance to C. rodentium infection. Thus, ATG16L1 function in the intestinal epithelium prevents an adverse immune response to an enteric commensal-like virus (i.e., MNV), while suppressing a protective response to an enteric bacterial pathogen (i.e., C. rodentium). Autophagy can inhibit immune responses by mediating the degradation of PRRs (or their downstream signaling intermediates), MAMPs, and mitochondria that release reactive oxygen species (ROS). The two most established examples are autophagy-mediated inhibition of IL-1β production downstream of the NLRP3 inflammasome and IFN-I signaling following nucleic acid sensing.\textsuperscript{3} We found that removing the IFN-I receptor (IFNAR1) in Atg16L1\textsuperscript{HM} mice, but not NLRP3, abrogated the resistance to C. rodentium conferred by Atg16L1 mutation. Resistance to C. rodentium upon autophagy inhibition, therefore, is mediated by an enhanced IFN-I response, reflected by the increased ISG expression in the colon. These results are reminiscent of findings by other groups showing that certain viruses promote mitophagy to inhibit IFN-I signaling.\textsuperscript{26–28} Our results suggest that dampening the local IFN-I response through mitophagy may also increase susceptibility to extracellular bacterial pathogens of the gut.
We found that Atg16L1<sup>HM</sup> mice display an increase in MAVS, a mitochondria-associated signaling molecule involved in viral RNA sensing, which suggests that reduced ATG16L1 function leads to inhibition of mitophagy and associated proteins in the intestine. We further found that mice deficient in another ATG protein (ATG4B) were also resistant to <i>C. rodentium</i> and displayed a similar increase in ISG expression. Our observations are consistent with a model in which the enhanced resistance conferred by Atg16L1 mutation reflect suppression of IFN-I signaling through mitophagy. One point of caution, however, is that ATG proteins function in cellular processes other than autophagy that contribute to immunity. An increase in MAVS can be secondary to other defects downstream of ATG inhibition, and thus, we cannot rule-out the contribution of autophagy-independent pathways. As discussed below, identifying the exact upstream trigger of IFN-I activity may clarify this issue.

**ATG16L1 inhibits spontaneous nucleic acid sensing in the presence of the gut microbiota**

Chronic low levels of IFN-I are notoriously difficult to detect in situ, but we could infer its presence based on the genetic evidence of its activity (the observation that Atg16L1<sup>HM Ifnar1</sup>–/– double mutant mice lose resistance to <i>C. rodentium</i>), the presence of phospho-STAT1 (p-STAT1) in the epithelium, and local ISG expression. p-STAT1 and ISG expression were observed in Atg16L1<sup>HM</sup> mice prior to <i>C. rodentium</i> infection. Germ-free Atg16L1<sup>HM</sup> mice did not display these markers of IFN-I activity, indicating that intestinal microbes were necessary for spontaneous signaling. We also found that resistance to <i>C. rodentium</i> infection required MAVS and STING, which mediate IFN-I production in response to cytosolic RNA and DNA, respectively. Hence, ATG16L1 suppresses a protective nucleic acid sensing response that is dependent on the gut microbiota (Figure 1).

A simple model would be one in which direct sensing of bacterial nucleic acid in the cytosol of intestinal epithelial cells occurs upon inhibition of autophagy. MAVS and STING can act in parallel or regulate each other’s activity in this scenario. An alternative model would involve other MAMPs derived from the microbiota that indirectly trigger the release of RNA and DNA from damaged mitochondria or neighboring cells. While we were revising our manuscript, an important study was published demonstrating that ATG16L1 inhibits IFN-I production downstream of LPS recognition by TLR4 through autophagy-mediated degradation of TRIF. Such a role for the TLR4-TRIF pathway is not mutually exclusive from the role of MAVS and STING that we identified, and may also contribute to the enhanced IFN-I response we observe in the Atg16L1 mutant conditions. An important future direction would be to identify the specific microbes in the gut that are responsible for the spontaneous IFN-I response observed in Atg16L1<sup>HM</sup> mice.

**Atg16L1 mutation enhances monocyte competence for wound repair**

In the above experiments, autophagy inhibition increased epithelial proliferation in a manner dependent on the microbiota and IFN-I signaling. Macrophages responding to enhanced IFN-I production increase epithelial turnover and improve wound repair, which led us to examine this cell type in our model. Following local activation of the PRR NOD2, monocytes are recruited to the gut during <i>C. rodentium</i> infection and differentiate into macrophages to contribute to the ongoing immune response. In our previous study, we found that removing NOD2 on the Atg16L1<sup>HM</sup> background reversed the protection independently of CD4<sup>+</sup> T cells. In our more recent manuscript, we found that removing the monocyte chemokine receptor CCR2 in Atg16L1<sup>HM</sup> mice led to a similar loss in resistance towards <i>C. rodentium</i>. RNAseq analysis, combined with additional functional analyses, indicated that monocytes isolated from the colon of <i>C. rodentium</i>-infected Atg16L1<sup>HM</sup> mice display increased expression of cell cycle genes and markers of activation and phagocytosis compared with their counterparts harvested from wild-type control mice. These isolated monocytes also displayed a gene expression signature indicative of increased fatty acid β-oxidation associated with wound-healing macrophages. These various properties of the recruited monocytes and macrophages are consistent with enhanced resolution of the infection and would repair.
In these experiments, we did not separate specialized myeloid subsets to be examined individually, such as the recently characterized Ym1"Ly6c+ monocytes that plays a role in resolving colitis. This limitation in our approach likely explains why we observe gene expression-level changes that are not representative of a single monocyte or macrophage population. Also, the exact relationship between IFN-I signaling and monocytes is unclear. Because ATG16L1-deficiency in the intestinal epithelium is sufficient to confer resistance to C. rodentium, and monocytes are not recruited until the infection is underway, we favor a model where higher basal IFN-I responses creates a local environment that is permissive for enhanced monocyte and macrophage function. However, monocytes and macrophages are not only targets of IFN-I, they can be the source of IFN-I during C. rodentium infection that can enhance resistance when amplified. Also, in addition to directly producing effector molecules, IL-1β production following caspase-11 inflammasome activation in monocytes induces IL-22 production by innate lymphoid cells (ILCs) during C. rodentium infection. We also observed a role for caspase-1 and caspase-11 in C. rodentium resistance in Atg16L1HM mice (in our study, we genetically deleted the caspases together). When our results are taken in the context of this literature, a complex feedback loop involving multiple cell

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**Figure 1.** Autophagy in the intestinal epithelium can be harmful or protective during injury depending on the type of perturbation and the presence of the microbiota. (A) Autophagy (ATG) proteins prevent spontaneous triggering of the type I interferon (IFN-I) pathway by restraining the activity of cytosolic nucleic acid sensors MAVS and STING. In the absence of ATG proteins in the intestinal epithelium, enhanced IFN-I signaling increases resistance to infection by the bacterial pathogen *Citrobacter rodentium* or chemical injury by dextran sodium sulfate (DSS) treatment. These consequences of ATG protein inhibition are absent in germ-free mice lacking intestinal microbes. (B) Murine norovirus (MNV) infection is typically innocuous because ATG proteins promote epithelial homeostasis and viability. In the absence of ATG proteins, MNV infection triggers structural and functional abnormalities in Paneth cells. DSS treatment in this setting exacerbates epithelial defects by promoting necroptosis signaling through the RIPK1-RIPK3-MLKL complex, leading to loss of Paneth cells and mortality. Depletion of the microbiota reduces MNV infection and restores resistance to intestinal injury.
types and cytokines appears to explain how an increase in IFN-I above the normal amount results in protection from an enteric bacterial pathogen. Although we have not completely addressed these important questions surrounding how cell–cell interactions are rewired when ATG16L1 is inhibited, we were able to demonstrate that the enhanced IFN-I signaling and monocyte response improve intestinal injury. Atg16L1HM mice displayed increased survival in the dextran sodium sulfate (DSS) model of chemical injury to the gut, and this improved response was nullified upon inhibition of MAVS, STING, or CCR2. Germ-free Atg16L1HM mice were not protected from DSS, again implicating factors derived from the microbiota. This enhanced intestinal injury response likely contributes to the protection from C. rodentium that occurs upon Atg16L1 mutation.

Outlook: ATG16L1 function in intestinal disease susceptibility and treatment

The ATG16L1 T300A risk allele is present in 40–50% of individuals with 15% homozygosity in certain populations. It is unclear why this variant was maintained in the human population. The threonine to alanine coding change increases the cleavage of ATG16L1 by caspase-3 and leads to reduced autophagy in the presence of TNFα, internalized bacteria, or metabolic stress.5,36–39 To determine the impact of this variant on C. rodentium infection, we used Atg16L1T316A knock-in (KI) mice that harbor the equivalent of the human T300A mutation in the endogenous Atg16L1 locus. We found that treating homozygous KI mice with PAC1, a chemical activator of caspase-3, reduced amounts of full-length ATG16L1 and increased ISG expression in the colon. Pre-treatment of Atg16L1T316A KI mice with PAC1 also boosted protection against C. rodentium infection. PAC1 treatment was necessary for this protection, and did not improve resistance to infection in wild-type mice. Similar, but mechanistically distinct, observations have been made in models of urinary tract infection and Salmonella dissemination.23,30 Given that diarrheal pathogens such as pathogenic E. coli remain a major contributor to early childhood mortality, a provocative implication of our observation and these other findings from the field is that ATG16L1T300A was maintained in the population because its presence leads to improved defense against certain types of bacterial pathogens, even if autophagy is generally beneficial in other circumstances.

In the mouse model we describe above, we artificially induced ATG16L1T300A cleavage with a chemical. What factors activate caspase-3 to process ATG16L1 in humans? As mentioned above, the presence of another infectious agent or malnutrition can lead to processing of ATG16L1T300A in vitro. Whether infection or nutritional stress have similar effects at the whole organism level remains to be determined. For modern humans, short-term treatment of NSAIDs induces caspase-3 activation.40,41 This observation is relevant to the link between this allele and disease because NSAIDs are associated with IBD flares in mice and humans.42,43 Also, cigarette smoke is associated with Paneth cell defects in Atg16L1T316A KI mice and Crohn’s disease patients harboring the ATG16L1T300A allele.44 Thus, multiple environmental triggers may induce ATG16L1 processing in the epithelium, and depending on the surrounding circumstances, the outcome can be beneficial (infection by an enteric bacterial pathogen) or detrimental (sustained inflammation directed against the gut microbiota).

With this dichotomy in mind, it is interesting to note that MNV infection induces disease outcomes in the same Atg16L1T316A mice and other autophagy mutant models we discuss in this addendum. Notably, DSS treatment leads to severe histopathology in Atg16L1 mutant mice in a manner dependent on MNV infection, which is reversed by antibiotics.17 There are several potential explanations for this opposing consequence of ATG protein dysfunction. First, our findings could reflect differences in the consequence of disrupting autophagy in the small intestine versus colon. MNV infection primarily leads to defects in Paneth cells, which are found in the small intestine, and ATG16L1T300A is predominantly associated with small intestinal Crohn’s disease in humans.18 In contrast, the highest burden of C. rodentium during the course of infection is observed in the cecum and colon. Another difference in the two infection models is that the MNV strain we have been examining establishes a persistent infection while C. rodentium is transient. It stands to reason that an enhanced immune
response may be beneficial during a self-resolving infection, but that chronic stimulation of the mucosal immune system may be undesirable. Consistent with this idea, a non-persistent strain of MNV fails to induce disease in Atg16L1HM mice. The reason depletion of the bacterial microbiota has opposite results during DSS treatment of MNV-infected versus naïve Atg16L1 mutant mice is likely due to the impact of bacteria on the viral life cycle; intestinal bacteria promote MNV infection by facilitating attachment to host cells and dampening immune signaling.\textsuperscript{19,45,46}

It will be important to determine whether the enhanced IFN-I signaling that protects against C. rodentium contributes to MNV-induced disease in Atg16L1 mutant mice. A recent study showed that IL-22, which promotes epithelial wound repair and is essential for defense against C. rodentium, mediates necroptosis in mice harboring a loss of ATG16L1 in the intestinal epithelium.\textsuperscript{12} The authors also found a spontaneous IFN-I signature that was dependent on STING. It is possible that excess IFN-I may have a pathologic role in our virally-triggered IBD model despite its protective effect during bacterial infection. Although counterintuitive because IFN-I is typically associated with inhibiting viral replication, we found that IFNAR1 is necessary for promoting the beneficial effects of persistent MNV infection with a relatively minor role in controlling viral burden.\textsuperscript{19} Recent findings help explain this observation. In contrast to MNV strains that establish a self-limiting infection controlled by IFN-I, persistent MNV infection can be detected in the epithelium and is sensitive to type III IFN (IFN-λ) instead.\textsuperscript{47–49} Interestingly, the gut microbiota facilitates MNV persistence by inhibiting IFN-λ activity,\textsuperscript{45} reinforcing the idea that IFN-I and IFN-λ have significantly divergent regulation and function in the gut despite activating similar transription factors.

Clinical trials for IBD are examining the therapeutic efficacy of blocking JAK/STAT molecules, which function downstream of multiple cytokine receptors including IFNAR1. It is tempting to speculate that one mechanism by which this class of drugs can ameliorate intestinal disease is through inhibiting IFN-I signaling and other pathways that are problematic when the epithelium is autophagy-deficient. However, great care must be taken before considering therapy that targets autophagy, IFN-I signaling, or any of the players mentioned here. IBD patients may be vulnerable to enteric infections by inflammatory microbes such as adherent invasive E. coli (AIEC). It is unknown whether individuals who are positive for these pathogens should be treated differently from other patients during flares.\textsuperscript{50} Segregating IBD patients based on their autophagy activity or their genetic status together with screening for enteric infections may help determine the conditions under which therapeutically targeting signaling pathways is safe and effective.

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