Inflammatory bowel disease (IBD) is a complex, multifactorial disease with genetic, microbial and environmental risk factors combining to result in recurrent inflammation of the intestine. Genetic analyses have uncovered a cluster of IBD risk genes, which regulate a cell stress response called autophagy. Functional studies of these autophagy-related genes highlight contributions of disease-associated dysregulation to several aspects of IBD pathology, which include alterations in microbiome composition and bacterial responses (xenophagy), antimicrobial peptide production by Paneth cells (crinophagy), enhanced levels of proinflammatory cytokines and enhanced T-cell subset responses. This suite of autophagy-gene regulated responses is modulated not only by the cell type or stimulus, but also by environmental context, with the overall balance of responses critical to the maintenance of health or induction of disease. These findings have opened up new avenues for the development of IBD therapeutics and increased understanding of disease mechanisms to facilitate a more personalised approach to the treatment of IBD.

Introduction

Inflammatory bowel disease (IBD) is characterised by recurrent inflammation of the gastrointestinal tract. The exact cause of this disease remains elusive; however, it is now understood that it is a complex and multifactorial disease where a combination of genetics, environmental exposures and abnormal immune responses to microbes results in disease development. A major breakthrough in the elucidation of the underlying disease processes occurred with the application of advanced genetic analyses to IBD (Lees et al., 2011). Initial genome-wide association screens (GWAS) identified a cluster of IBD risk genes involved in autophagy, a cellular stress response (Hampe et al., 2007; Rioux et al., 2007; Wellcome Trust Case Control C., 2007). Subsequent comprehensive meta-analyses have replicated these findings and continued to increase the number of autophagy-related genes associated with IBD susceptibility (Franke et al., 2010; Anderson et al., 2011). Functional studies demonstrate that disease-associated genetic variants in autophagy-related genes primarily impair their function and suggest several distinct, but related roles for dysfunctional autophagy in IBD pathogenesis. These autophagy-dependent processes include intracellular bacterial killing by xenophagy, antimicrobial peptide secretion by Paneth cells regulated by crinophagy, proinflammatory cytokine production by macrophages, antigen presentation by dendritic cells (DCs) and endoplasmic reticulum (ER) stress responses in enterocytes. Our current understanding of the autophagic response, the IBD-associated genes involved in this pathway and how autophagy gene-dependent processes are involved in IBD pathology are described in this article.

See also: Inflammatory Bowel Disease, Genetics of

Autophagy: The Process and Players

Autophagy (meaning ‘self-eating’) is an evolutionarily conserved catabolic pathway occurring in virtually all eukaryotic organisms (Mizushima, 2007). This degradative pathway permits cells to remove protein aggregates,
intracellular microbes and defective organelles via capture of these components in multilamellar vesicles for destruction by lysosomal processes. The diverse roles played by autophagy in various physiological activities, including adaptation to starvation, degradation of aberrant structures, innate and adaptive immunity, and programmed cell death, make it an integral player in maintaining cellular homeostasis. Autophagy can be mechanistically subdivided into several subtypes based on their physiological functions and mode of delivery to the lysosomes. For the purposes of this article, the authors will focus on processes related to macroautophagy, hereafter referred to as autophagy.

Autophagy is a multistep process that results in the formation of a double membrane-bound vacuole (autophagosome) and degradation of the vesicular cargo through lysosomal fusion (see Figure 1). This process involves the concerted activity of various protein complexes that are themselves tightly regulated by a series of post-translational modifications (Ravikumar et al., 2010). Initiation of autophagy requires two evolutionarily conserved protein kinase complexes: the phosphatidylinositol-3-kinase (PI3K) and unc-51-like kinase (ULK) complexes. The PI3K complex is essential for the recruitment of effector proteins to sites of autophagosome formation. A second macromolecular complex, the ULK complex, is tightly regulated by a series of phosphorylation and dephosphorylation events driven by the autophagy-inducing kinases, mammalian target of rapamycin and adenosine monophosphate (AMP)-activated protein kinase. Once activated, the ULK complex translocates from the cytosol to an autophagosome nucleation site for the recruitment of additional proteins mediating autophagosomal membrane elongation.

Cargo selection and maturation of the autophagosome is less well understood. A growing list of cargo adaptors include sequestosome 1 (SQSTM1/p62), neighbour of BRCA1 gene 1 (NBR1) and nuclear dot protein 52 kDa (NDP52), which appear to bind to ubiquitinated substrates and traffic them to LC3-II. Once the autophagosomal membrane closes around the cargo, the autophagosome traffics via microtubules to fuse with lysosomes to form autophagolysosomes and degrade the enclosed cargo. The fate of the resulting degradation products depends on the autophagosomal cargo and cell type, and may include transport to the cytosol for recycling as nutrients by the cell, crosspresentation of peptides to stimulate adaptive immune responses or secretion from the cell.

See also: Autophagy

Elongation of the autophagosomal membrane is driven by two different ubiquitin-like conjugation systems (Atg12 and light chain 3 (LC3) systems) and facilitated by membrane trafficking by the transmembrane protein, Atg9. The Atg12 system acts to conjugate Atg12 to Atg5 and stimulate the formation of a macromolecular complex with Atg16L1 that assists in the insertion of microtubule-associated protein 1A/1B-LC3 family proteins into the forming autophagosomal membrane. The second ubiquitin-like system modifies LC3 family proteins to convert them from a cytosolic form (LC3-I) to a lipid-modified, membrane-associated form (LC3-II). In contrast to yeast that has only one LC3 protein, mammals have at least seven homologues of which the function of LC3B is the best characterised. The lipidated LC3-II inserts into the autophagosomal membrane to facilitate membrane curvature and cargo recruitment.

### Table: Stress sensor, Nucleation, Elongation and cargo selection, Maturation

<table>
<thead>
<tr>
<th>Stress sensor</th>
<th>Nucleation</th>
<th>Elongation and cargo selection</th>
<th>Maturation</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOD2</td>
<td>ULK1</td>
<td>ATG16L1</td>
<td>LRRK2</td>
</tr>
<tr>
<td>RIP2</td>
<td>DAP1</td>
<td>ATG4</td>
<td>IRGM</td>
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<tr>
<td>IRGM</td>
<td></td>
<td>MAP1LC3A</td>
<td></td>
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<tr>
<td>SMURF1</td>
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<tr>
<td>NCF4</td>
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<td>VDR</td>
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<td>XBP1</td>
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Figure 1 The process of autophagy and autophagy-related genes associated with inflammatory bowel disease. Autophagy is a stepwise process where cellular stressors (such as bacterial infection) are sensed by stress sensor proteins to induce nucleation of an autophagosome via the action of the ULK and PI3K complexes. The forming membrane is elongated through the actions of the Atg12 and LC3 systems. Cargo is tagged with cargo adaptor proteins and targeted to LC3-II in the autophagosome membrane. The autophagosome matures through fusion with the lysosome and the contents degraded by lysosomal enzymes. The IBD risk genes associated with autophagy are indicated under the step at which they are thought to act.
Autophagy-related Genes Linked to IBD

IBD susceptibility is associated with genetic variants in a spectrum of autophagy-related genes directly involved in multiple stages of formation and maturation of autophagosomes, as well as regulatory proteins controlling this process (see Figure 1 and Table 1 (Gardet and Xavier, 2012). The majority of risk variants in autophagy-related genes are associated with Crohn’s disease (CD) and not the other major form of IBD, ulcerative colitis (UC). Sensor proteins that trigger autophagy in response to diverse stimuli, such as microbial infection (nucleotide-binding oligomerisation domain 2 (NOD2), receptor-interacting protein 2 (RIP2), immunity-related guanosine triphosphatase family M (IRGM) and Smad-ubiquitin regulatory factor 1 (SMURF1)), reactive oxygen species (neutrophil cytosolic factor 4 (NCF4)), vitamin deficiency (vitamin D receptor (VDR)) or ER stress (X-box binding protein 1 (XBP1)), are all linked to IBD susceptibility. Additional disease-associated variants are found in the core autophagy components ULK1, ATG4, MAP1LC3A and ATG16L1. Finally, genes that negatively regulate or regulate multiple steps of the autophagic process have been linked to IBD as well and include death-associated protein 1 (DAP1), leucine-rich repeat kinase 2 (LRRK2), tyrosine-protein phosphatase nonreceptor type 2 (PTPN2) and NOD-like receptors (NLR) family, pyrin domain containing 3 (NLRP3). As more becomes known about the function of genes encoded by other IBD-associated loci, this list is likely to increase. Moreover, under active investigation is how disease-associated variants in autophagy-related genes impact intestinal homeostasis and result in IBD pathophysiology. A number of cellular processes regulated by autophagy-related genes have been implicated in IBD pathogenesis, which include intracellular bacterial clearance by xenophagy, Paneth cell antimicrobial peptide secretion by crinophagy, macrophage proinflammatory cytokine secretion, antigen presentation and epithelial cell ER stress responses (see Figure 2). See also: Molecular Genetics of Crohn Disease

Intracellular Bacterial Clearance via Xenophagy

Inappropriate immune responses to microbes and microbial products in the intestine play a critical role in the initiation and progression of IBD (Friswell et al., 2010). The fact that antibiotics improve clinical outcome in IBD patients highlights a central role for bacteria and the dysregulation of antibacterial responses in disease pathogenesis (Wang et al., 2012). Several autophagy-related genes are clearly linked to antibacterial responses in IBD, suggesting a central role for the clearance of bacteria by a specialised type of autophagy, termed xenophagy. Defective xenophagy is thought to lead to ineffective bacterial clearance resulting in the initiation and/or perpetuation of chronic inflammation observed in IBD. Xenophagy targets multiple bacterial strains linked to IBD, such as Mycobacteria spp., Salmonella typhimurium and adherent invasive Escherichia coli (AIEC) strains isolated from CD patients (Lapaquette and Darfeuille-Michaud, 2010). The CD-associated risk genes, ATG16L1, IRGM, NOD2, RIP2 and PTPN2 mediate xenophagy, with disease-associated variants impairing this process. ATG16L1 is one of the first autophagy-related CD risk genes identified by GWAS (Hampe et al., 2007; Rioux et al., 2007). ATG16L1 plays an essential role in xenophagy in both epithelial cell lines (Homer et al., 2010) and macrophages (Lapaquette et al., 2012), as ribonucleic acid interference (RNAi)-mediated decrease in Atg16L1 expression facilitates replication of intracellular AIEC and

Table 1  Autophagy-related gene variants associated with IBD. Autophagy process affected by disease-associated variant indicated by X (xenophagy), C (crinophagy), CS (cytokine secretion), Ag (antigen presentation) or ER (ER stress)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Major variant(s)</th>
<th>Autophagy process</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATG16L1</td>
<td>p.Thr300Ala</td>
<td>X, C, CS and Ag</td>
<td>Hampe et al., 2007; Rioux et al., 2007</td>
</tr>
<tr>
<td>IRGM</td>
<td>c.313C&gt;T</td>
<td>X and Ag</td>
<td>Parkes et al., 2007</td>
</tr>
<tr>
<td>NOD2</td>
<td>p.Arg702Trp</td>
<td>X, CS and Ag</td>
<td>Hugot et al., 2001; Ogura et al., 2001</td>
</tr>
<tr>
<td>NLRP3</td>
<td>g.41134913G&gt;A</td>
<td>CS</td>
<td>Villani et al., 2009</td>
</tr>
<tr>
<td>PTPN2</td>
<td>g.12799346A&gt;G</td>
<td>X</td>
<td>Scharl et al., 2012</td>
</tr>
<tr>
<td>RIPK2</td>
<td>g.4149467T&gt;C</td>
<td>X</td>
<td>Jostins et al., 2012</td>
</tr>
<tr>
<td>XBP1</td>
<td>g.9629T&gt;C</td>
<td>ER</td>
<td>Kaser et al., 2008</td>
</tr>
</tbody>
</table>
S. typhimurium. The only disease-associated ATG16L1 allele encodes an alanine instead of threonine at amino acid position 300 (p.Thr300Ala) in the C-terminal Trp-Asp (WD) repeat domain (Kuballa et al., 2008; Fujita et al., 2009). Although basal autophagy is unaffected by the ATG16L1 p.Thr300Ala polymorphism, the targeting of internalised S. typhimurium by xenophagy in human epithelial cell lines and DCs derived from CD patients is impaired (Kuballa et al., 2008; Cooney et al., 2010; Homer et al., 2010; Travassos et al., 2010). However, this xenophagic defect of ATG16L1 p.Thr300Ala appears to be cell-type dependent, and was not observed in mouse embryonic fibroblasts and human macrophages from healthy individuals (Fujita et al., 2009; Homer et al., 2010). As the ATG16L1 p.Thr300Ala risk variant is highly prevalent in healthy population (Hampe et al., 2007), these discrepancies suggest other risk factors, such as environment, carriage of additional genetic variants and microbes, may contribute significantly to the ultimate development of CD in individuals with an ATG16L1 risk genotype.

IRGM is another gene identified by GWAS that was identified as an autophagy-related IBD risk gene based on studies describing its roles in xenophagic elimination of intracellular Mycobacterium tuberculosis (Singh et al., 2006; Massey and Parkes, 2007; Rioux et al., 2007; Barrett et al., 2008). Further studies determined a requirement for IRGM expression in epithelial cells and macrophages (Lapaquette et al., 2012) for clearance of intracellular AIEC. Several CD-associated IRGM single-nucleotide polymorphisms (SNPs) have been identified (Parkes et al., 2007; Wellcome Trust Case Control C., 2007; McCarroll et al., 2008; Brest et al., 2011). One pair of IRGM polymorphisms in strong linkage disequilibrium maintains IRGM expression during inflammation and results in dysregulated xenophagy (McCarroll et al., 2008). These polymorphisms include a common 20-kb deletion polymorphism (rs13361189) immediately upstream of IRGM and a synonymous SNP (c.313C>T) in the coding region. The c.313T risk allele was determined to be the causal variant in this pair, as carriage of c.313T interfered with normal downregulation of IRGM expression by a specific family of microRNAs (miRNA-196) in the inflamed intestinal epithelium. This dysregulated IRGM expression compromised xenophagic control of AIEC intracellular replication (Brest et al., 2011).

NOD2 is the first identified IBD risk gene and encodes for an intracellular bacterial sensor (Hugot et al., 2001; Ogura et al., 2001). This component of the innate immune response triggers the production of proinflammatory mediators, antibacterial peptides, as well as activates xenophagy. Three main risk variants (p.Arg702Trp, p.Gly908Arg and p.Leu1007fs) and numerous rare alleles have been identified in NOD2 and homozygous/compound heterozygous carriage of these alleles increases the risk of developing CD by up to 40-fold. NOD2 physically and functionally interacts with Atg16L1 to mediate xenophagy (Cooney et al., 2010; Homer et al., 2010; Travassos et al., 2010). CD-associated variants of NOD2 or ATG16L1 interfere with xenophagy in a number of cell types including epithelial, lymphoblastoid and DCs. NOD2 recruits...
Atg16L1 to bacterial entry sites to facilitate capture of bacteria in autophagosomes and stimulates xenophagy induction through the activation of another IBD risk gene, RIP2 kinase (Travassos et al., 2010; Homer et al., 2012). Macrophages carrying NOD2 risk variants are defective in this recruitment and RIP2 kinase activation, indicating a critical role for NOD2 in xenophagy induction (Travassos et al., 2010). Finally, NOD2 signalling and autophagy induction is also regulated by the phosphatase PTPN2, which has genetic variants associated with both CD and UC. In intestinal cells with CD-associated PTPN2 variants, intracellular killing of Listeria monocytogenes via xenophagy was impaired, potentially through alterations in autophagy-related gene expression (Scharl and Rogler, 2012). These results highlight how xenophagy is an important mediator of intestinal homoeostasis and genetic dysfunction in any of a number of autophagy-related genes, which impair this response and contribute to IBD.

Regulation of Paneth Cell Antimicrobial Peptide Secretion by Crinophagy

Paneth cells are ileal epithelial cells found at the base of the crypt of Lieberkühn. These cells contain large granules enriched with antimicrobial peptides and lysosomes. The broad-spectrum antimicrobial peptides secreted by Paneth cells, termed α-defensins, act as endogenous antibiotics and play an important role in the control of intestinal microbiota and modulation of host response to enteric commensals (Porter et al., 2002). Paneth cell-secreted human defensin-5 (HD-5) and HD-6 are the most prominent antimicrobial peptides in the intestine. Dysfunction of Paneth cells has been related to the pathogenesis of CD (Simms et al., 2008; Bevins et al., 2009; Perminow et al., 2010).

Multiple studies indicate that alterations in autophagy-related genes contribute to the loss of Paneth cell function in CD through defective crinophagy. Crinophagy is a process related to autophagy that targets secretory vesicles for degradation and when impaired results in an accumulation of secretory vesicles in these cells. This type of Paneth cell abnormality has been observed in ATG16L1 p.Thr300Ala homozygous CD patients and a mouse strain with reduced expression of Atg16L1 (Atg16L1H/M) (Cadwell et al., 2008). These alterations in Atg16L1 function lead to disruption of the Paneth cell granule exocytosis pathway. Similar findings were observed in epithelial cell-specific knockouts of either Atg5 or Atg7 in mice, implicating an autophagy-dependent pathway in this type of Paneth cell dysfunction. Interestingly, further analysis of the Atg16L1H/M mice uncovered a requirement for specific norovirus (MNV CR6) infection for these Paneth cell abnormalities to develop and result in the development of CD-like ileitis in an experimental colitis model (Cadwell et al., 2010). Further study of these mice may provide insights into how genetics, environmental factors, and microbes work together to contribute to the pathogenesis of CD.

In contrast to these findings, other studies describe abnormal activation of crinophagy in CD patients as demonstrated by significant LC3 accumulation and a decrease in the number of secretory granules in Paneth cells (Thachil et al., 2012). It is unknown at this time as to which autophagy-related genes are involved in this process, as the hyperactivation of crinophagy in these patients did not correlate with ATG16L1, IRGM or NOD2 risk variants. However, the combination of these observations suggests that a delicate balance of crinophagy activation is required to achieve effective antimicrobial peptide secretion to maintain intestinal homoeostasis.

Macrophage Proinflammatory Cytokine Production

Macrophages are major players in the innate immune system to produce an initial, immediate response against pathogens. One response mechanism used by these cells to control pathogens is the production of proinflammatory cytokines. Levels of these cytokines must be tightly regulated to transiently deliver effective amounts to clear infection, but not cause tissue damage due to prolonged exposure. It is thought that enhanced cytokine production or ineffective downregulation of cytokine levels may contribute to the increased levels of proinflammatory cytokines and chronic inflammation observed in IBD. See also: Cytokines as Mediators of Disease

The autophagy-related genes, ATG16L1 and NOD2, have been demonstrated to regulate the production of proinflammatory cytokines in response to bacterial products. Atg16L1-deficient macrophages produce significantly higher amounts of IL-1β and IL-18 in response to lipopolysaccharide (LPS) (Saitoh et al., 2008). Similar enhancement of LPS-stimulated IL-1β production was also observed in Ag7-deficient macrophages, indicating an autophagy-dependent mechanism. In vivo, this enhanced proinflammatory cytokine response in macrophages translated to exacerbated experimental colitis in mice with haematopoietic cell deficiency of Atg16l1 (Fujita et al., 2008). Treatment of these mice with antibodies to IL-1β and IL-18 was effective in decreasing disease activity, indicating a crucial regulatory role for the autophagy-related gene Atg16L1 in macrophage-driven intestinal inflammation.

Further studies link disease-associated variants of autophagy-related genes in the regulation of macrophage proinflammatory cytokine production. Peripheral blood mononuclear cells from healthy individuals homozygous for ATG16L1 p.Thr300Ala have a significantly higher production of IL-1β and IL-6 upon stimulation with muramyl dipeptide (MDP), a component of the bacterial cell wall and NOD2 ligand (Plantinga et al., 2011). This
effect is dependent on a functional NOD2, as MDP-induced IL-1β production was ablated in the same cell type from CD patients homozygous/compound heterozygous for NOD2 disease-associated variants. These findings reinforce the concept that NOD2 and ATG16L1 are components of the same autophagic pathway, which also functions to regulate the production of proinflammatory cytokines.

The mechanism by which proinflammatory cytokine production in macrophages is controlled by autophagy is not well understood, but one major player in this process is the inflammasome. The inflammasome is a multiprotein complex containing at least one member of the cytosolic innate immune sensor family, the NLRs and the protease caspase-1. Several different NLR family members can form inflammasomes, with the best characterised being the NLRP3 inflammasome. Inflammasomes are activated in response to infection, cellular stress or metabolic dysregulation to trigger caspase-1 activation, the cleavage of pro-IL-1β and pro-IL-18 and subsequent secretion of mature IL-1β and IL-18 (Schroder and Tschopp, 2010). Interestingly, the same cellular stressors that stimulate inflammasome activity can also activate autophagy (Leemans et al., 2012).

Autophagy and inflammasomes have complex, cross-regulatory interactions, which are still under investigation. The ‘yin–yang’ relationship between autophagy and inflammasomes is described in an elegant study by Shi et al. (2012), that shows if autophagy is inhibited, inflammasome activity increases and vice versa. This finding is supported by several other studies in macrophages demonstrating that chemical or genetic inhibition of autophagy results in enhanced inflammasome activity measured by increased caspase-1 activation and IL-1β production (Saitoh et al., 2008; Harris et al., 2011; Shi et al., 2012). Autophagy is thought to keep inflammasome activity in check through selectively targeting inflammasome components, such as NLRP3, caspase-1 and pro-IL-1β (Harris et al., 2011; Shi et al., 2012). The opposite has also been demonstrated in macrophages deficient in NLRC4 or caspase-1 expression, where autophagy induction in response to Shigella is enhanced (Suzuki et al., 2007). Some NLR family members may bind to and downregulate the activity of Beclin-1 in the autophagy initiating PI3K complex (Jouan et al., 2011). Counterintuitive to these findings, genetic variants that decrease the expression of NLRP3 have been associated with CD in a small cohort of individuals of European descent (Villani et al., 2009). Therefore, it may be the balance between autophagy and inflammasome activation, which is critical to maintain intestinal homeostasis.

## Autophagy and Antigen Presentation

Autophagy contributes to antigen processing and presentation through both major histocompatibility complex class I (MHC I) and class II (MHC II) molecules (Munz, 2010). In the context of IBD, the role of autophagy in antigen presentation in DCs for the generation of MHC II-specific CD4+ T-cell responses is best described. Defects in extracellular microbial antigen processing and MHC II presentation have been observed in cells with Atg5 expression knocked down by RNAi (Lee et al., 2010) and DCs from CD patients carrying NOD2 or ATG16L1 risk alleles (Cooney et al., 2010). In addition, autophagy regulates the termination of the immunologic synapse formed between DCs and T cells during antigen presentation. Suppression of autophagy by RNAi-mediated knockdown of either ATG16L1 or IRGM resulted in hyperstable synapses between DCs and T cells, increased activation of T cells and stimulation of a T-helper 17 cell response. Similarly, the immunologic synapses formed with DCs from CD patients homozygous for ATG16L1 pThr300Ala are also hyperstable (Wildenberg et al., 2012). These findings demonstrate how autophagy genes may shape the increased T-cell responses observed in IBD through altering antigen presentation and enhancing the activation of T-cell subsets. See also: Antigen Presentation to Lymphocytes

## ER Stress, Autophagy and IBD

Autophagy induction by ER stress is another mechanism under intensive investigation that has recently been implicated in IBD pathogenesis. Increased markers of ER stress have been identified in the ileal and colonic mucosa from IBD patients (Kaser et al., 2008). ER stress is triggered by increased levels of misfolded or unfolded proteins within the ER. The unfolded protein response (UPR) mediates the cellular response to ER stress and has been shown to induce autophagy to reduce ER stress levels. The three major UPR pathways include inositol-requiring enzyme 1α and β (IRE1α and β), pancreatic ER kinase (PERK) and activating transcription factor 6 (ATF6) (Schroeder and Kaufman, 2005). Among these pathways, the IRE1 pathway is associated with both IBD and autophagy.

XBP1, a key component of the IRE1 pathway, is required for the development and maintenance of secretory cells. An intronic genetic variant of XBP1, which decreases its expression has been associated with both CD and UC, further suggesting that the ER stress pathway may be involved as a common genetic contributor to IBD (Kaser et al., 2008). XBP1 deletion (Xbp1−/− mice) in intestinal epithelial cells leads to ER stress, Paneth cell depletion and development of spontaneous enteritis (Kaser et al., 2008). These changes in Xbp1−/− mice impair mucosal defence against L. monocytogenes and increases susceptibility to dextran sulfate sodium-induced colitis, presumably through ineffective xenophagy induction. XBP1 deficiency in macrophages has been found to impair resistance to infection with Francisella tularensis (Martinon et al., 2010). Altogether, these results suggest an important role for UPR and ER stress in xenophagy and Paneth cell function, two autophagy-related functions that altered the context of IBD.
Conclusions

The application of state-of-the-art genetic tools to IBD has resulted in a paradigm shift in the understanding of disease mechanisms. The field has progressed from the analysis of single genes in isolation to disease-associated pathways of which one is autophagy. Several autophagy-dependent processes are now linked to IBD pathogenesis, which include xenophagy, crinophagy, proinflammatory cytokine secretion, antigen presentation and ER stress responses. Each process affects a different aspect of IBD pathology – alterations in microbiome composition and bacterial response (xenophagy), antimicrobial peptide production by Paneth cells (crinophagy), enhanced levels of proinflammatory cytokines and enhanced T-cell subset responses. The overall effect of this suite of responses is modulated not only by cell type or stimulus, but is also to be critical. These findings have opened up new avenues for the development of IBD therapeutics and increased understanding of disease mechanisms to facilitate a more personalised approach to the treatment of IBD.

References


Further Reading


