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AUTOPHAGY AS AN IMPORTANT PROCESS IN GUT HOMEOSTASIS AND CROHN'S DISEASE PATHOGENESIS

RAMNIK J. XAVIER[‡], **ALAN HUETT**[‡], and **JOHN D. RIOUX**[*]

[‡]Center for Computational and Integrative Biology and Gastrointestinal Unit, Massachusetts General Hospital, Harvard Medical School, 185 Cambridge Street, Boston, MA 02114, USA

[*]Université de Montréal and the Montreal Heart Institute, Research Center, 5000 Bélanger Street, Montreal, Quebec H1T 1C8, Canada

Abstract

Recent genome-wide association studies in Crohn's Disease have identified genetic variation within two genes involved in a biological process known as autophagy. These genetic findings reveal an important role for autophagic processes in both gut homeostasis and in the development of chronic inflammation of the gastrointestinal tract.

Keywords

Crohn's disease; genetics; autophagy; inflammation

Recent genetic studies have implicated autophagy as playing an essential role in Crohn's disease pathogenesis

Crohns disease (CD) is a complex polygenic trait whereby multiple genetic and non- genetic risk factors contribute to disease susceptibility. Association testing is a statistical approach commonly used for identifying genetic risk factors for complex/multigenic disease, which typically compares the allele frequency of a selected marker, most often a bi-allelic single nucleotide polymorphism (SNP), for differences between patient and control populations. SNPs represent most of the common genetic variation, with an estimated 10 million SNPs found in the human genome[1]. Although a powerful statistical approach, until recently, the majority of association studies were limited to the examination of a small number of candidate genes, the selection of which will inevitably be biased by the current knowledge of disease pathogenesis. Following some key developments in our understanding of genetic variation within the human genome, as well as technological advances that have enabled affordable genotyping of 300,000-1,000,000 SNPs per study subject (and therefore approximately one billion genotypes or more per genetic study), association testing can now be applied genome-wide in order to search for genetic risk factors in an unbiased manner [2-4].

In one of the first genome-wide association studies (GWAS) we and our colleagues of the NIDDK IBD Genetics Consortium tested approximately 300,000 SNPs in one thousand

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patients with Crohn's disease (CD) and in one thousand healthy individuals, and identified association with variants in the autophagy related 16-like 1 (*S. cerevisiae*) or ATG16L1 gene [5]. The ATG16 gene product is part of a multimeric protein complex that is essential for autophagy, a biological process that mediates the bulk degradation of cytoplasmic components in lysosomes and vacuoles [6]. This recent GWAS specifically identified an associated SNP that encodes a nonsynonymous amino acid change – an alanine to threonine substitution in exon 8 (a.k.a. Ala197Thr) – in the human equivalent of the ATG16 gene. In all of the populations examined, the threonine allele is the minor allele and has a protective effect. The same causal variant in ATG16L1 had also been identified in an independent screen of ~7000 common non-synonymous coding variants in a German CD study [7]. Alone or combined, these two studies provide incontrovertible evidence that a protein involved in the autophagic machinery is also involved with a chronic inflammatory disease of the digestive tract.

In a subsequent study of Crohn's disease that was part of the landmark Wellcome Trust Case Control Consortium (WTCCC) GWAS, ATG16L1 association was confirmed. In addition, this study identified a second autophagic gene in disease susceptibility [8]. Specifically, multiple SNPs flanking and within the IRGM gene, located on chromosome 5q33, were found to be highly associated with Crohn's disease. Sequencing of this gene in samples from CD patients and healthy controls, however, did not identify any causal amino acid changes and therefore the authors speculated that the genetic variation conferring susceptibility to CD could operate via modulation of IRGM gene expression [9]. The IRGM gene belongs to an emerging family of genes encoding for interferon inducible guanosine triphosphatases (IRGs) involved in newly recognized forms of pathogen clearance [10]. Specifically, it has recently been demonstrated that IRGM induces autophagy in order to efficiently eliminate intracellular mycobacteria [11]. Although much work remains to be done to understand the mechanisms by which the variants in the IRGM and ATG16L1 genes are acting, these recent discoveries strongly imply that autophagy is an important biological pathway in Crohn's disease pathogenesis and further understanding of the relevant autophagic processes should provide clues to their role in mucosal immune responses in health and disease.

Autophagy and the role of ATG16L1 and IRGM gene products

Autophagy is a fundamental biological process defined as a cytoplasmic homeostasis pathway whereby cytoplasmic portions become sequestered by a membrane for delivery to lysosomes and has been previously implicated in both health promoting and disease associated states [6]. Initial studies of autophagy in yeast focused upon its role in the starvation response and in the removal of damaged or surplus organelles [12-14]. More recently it has been demonstrated to play essential roles in the clearance of long-lived proteins as a complementary function to that of the ubiquitin proteasome system (mainly for short-lived proteins), removal of aggregated and misfolded proteins such as Huntingtin, and in the control of intracellular pathogens [11, 15-18]. Furthermore, autophagy has been demonstrated to play a protective role in infectious disease - a previously unrecognized weapon in the innate immune system's armamentarium. Just as with many other innate immune processes, autophagy is linked to adaptive immunity; both by the delivery of ligands via pattern-recognition receptors to promote inflammation and by delivery of cytoplasmic antigen to HLA class II molecules for the cross-presentation necessary for immune recognition [19-21]. Recent studies have also demonstrated that autophagy plays an important role in clearance of apoptotic bodies [22]. Persistence of apoptotic bodies as a result of incomplete autophagy in complex tissues such as the intestinal mucosa in turn could contribute to persistent inflammation and autoimmunity seen in CD.

The basic mechanisms of the autophagic process seem to be highly conserved amongst eukaryotes. Upon induction of autophagy, a membrane cisterna, known as the isolation membrane, appears and, by the addition of new membrane of unknown origin, curves around

part of the cytoplasm (elongation). Sealing of the structure leads to the formation of an autophagosome, which differs from the conventional phagosome by the presence of a double delimiting membrane and intralumenal cytosolic content, and from other membranes in having few intramembrane proteins. Both of these features allow easy detection of autophagosomes by electron microscopy. The subsequent fusion between an autophagosome and lysosomes (maturation) results in a degradative compartment termed the autolysosome [12,23,24]. Experiments in yeast demonstrated that multimeric complexes formed by three autophagy gene (ATG) products, specifically ATG5, ATG12, and ATG16, were essential for the formation of the autophagosome [25]. Despite the high level of conservation of the autophagy apparatus from yeast to human there are significant differences. One of these differences is that mammalian ATG16L1 proteins possess seven WD repeats at their C-terminus (Figure 1A), which are completely absent in the yeast ATG16 gene product. Thus once ATG16L1 was identified as a CD susceptibility gene it was important to begin establishing its role in human autophagy and potential role in CD pathogenesis. Since WD repeats are most often associated with protein-protein or protein-membrane interactions, it is thought that those of ATG16L1 potentially reflect (i) a more complex regulation of mammalian versus yeast autophagy and (ii) a key role played by ATG16L1 in the autophagic clearance of pathogens, fulfilling a function absent in yeast. In an experimental system we knocked down the expression of the human ATG16L1 gene and demonstrated that it is essential for the formation of autophagosomes in response to serum starvation or bacterial infection confirming the role of the human ATG16L1 in autophagy in addition to implicating this process for the first time in the pathogenesis of CD [5].

As noted above, the IRGM gene has also been recently identified to play a role in the development of Crohn's disease and also shown to be involved in autophagy. In contrast, however, to the extensive amount of work that has been accomplished in identifying and characterizing the complex network of ATG gene products and the molecular mechanisms by which they accomplish a wide variety of autophagy-related functions, there is much less known about the role of the IRGM related autophagic pathways. This situation is further complicated by the fact that there is much less conservation of the IRG related autophagy machinery, and therefore much more difficult to drawn in information obtained from models systems (e.g. yeast, mice) which has been a key feature of the ATG pathways. For example, thus far only two human IRG genes have been found; IRGC and IRGM whereas in mice the IRGM gene belongs to a large family of 23 IRG genes (as identified in the C57BL6 strain of mice), 21 of which appear to encode proteins [26,27]. In addition, most of the mouse genes contain interferon stimulated response elements or gamma activated sequence sites in their promoters that mediate transcriptional activation by interferons [10]. The human IRGM protein, on the other hand, lacks the clear IFN regulatory elements and other essential sequence domains seen in the mouse [27]. Functions of the human proteins may therefore vary considerably from those of mouse proteins. It would appear, however, that it is likely that the broad family of IRG proteins in mice and man are important in protecting against invasion of the ancient systems of the endocytic and intracellular trafficking machinery by pathogens. This is supported by recent studies that have provided evidence that some IRG proteins may direct ER or Golgi localization of other IRG proteins and that IRG proteins re-localize during infection to vacuoles or phagosomes that contain latex beads, bacteria or protozoa [10,27-30]. More specifically, the human IRGM gene product has been demonstrated to stimulate the early stages of autophagy induced by interferon gamma [11].

Autophagy and gut immunity

Autophagy is an evolutionarily conserved process with many common signaling regulators and essential components found in both plant and animal immunity mechanisms [31,32]. Given its long evolutionary history, it is perhaps not surprising that autophagy interfaces with other

conserved anti-pathogen responses such as those of the innate immune system. Since innate immunity is thought to be amongst the most ancient forms of pathogen defense, it is likely that autophagy and innate immunity co-evolved and may share signaling components. Manipulation of evolutionarily conserved host cellular pathways, such as microbe induced autophagy, form an essential mechanism used by bacteria to promote pathogenicity. Furthermore, triggers of innate immunity (e.g. TLR/NLR ligands) have been implicated in promoting autophagy-induced clearance of microbes (Figure 1B) [20,28]. There is also evidence that TLR9 and NLR ligands may tag microbial proteins for enhanced autophagic clearance [13,19]. Autophagy is not always anti-pathogenic however, there is also ample evidence that pathogens are able to subvert autophagy and generate a permissive niche within, or on, the autophagosome itself [33-35]. Thus there is likely a need to balance autophagy and other forms of anti-microbial immunity, such as apoptosis of infected cells or cytotoxic killing by natural killer cells.

The relative contribution of autophagy to this host defense balance may be tissue or organ dependant. Indeed, there are certain features of the gut mucosa and its resident immune cells that may increase the reliance upon autophagy for both homeostasis and immune defense. Chief amongst these is the relatively refractory nature of the gut immune compartment, despite constant exposure to high bacterial and antigen load. Many innate immune cells from the intestinal mucosal compartment lack high-level expression of TLRs and other pathogen-detecting molecules, or are otherwise refractory to antigen exposure. To compensate for such lack, it is plausible that innate immune cells rely mainly upon detection/destruction of pathogens following phagocytosis and internalization. Thus these cells must be able to induce a variety of programs to destroy internalized pathogens before they, themselves are incapacitated. The use of the autophagic apparatus might therefore be favored under these circumstances. Induction of autophagy in response to pathogens is thought to be specific, but the sensors driving the process are yet to be identified. This predisposition to autophagic control of pathogenic microbes may be regulated by compartment-specific modulators of the autophagic apparatus, as have been observed in recent studies[36]. TLR signaling is already known to be required for intestinal homeostasis, recovery from injury and response to pathogenic challenge, and most recently a direct link between TLR signaling, autophagy and phagocytosis has been demonstrated [37-39].

The lack of hair-trigger pattern detection in the gut is also likely to affect adaptive immunity. Antigen presentation of pathogen-derived components is likely to be dependant upon autophagosome-HLA crosstalk, rather than the conventional lysosomal pathways. A number of studies have demonstrated that autophagy pathways efficiently transfer cytosolic antigens to late endosomal or lysosomal compartments, where they can be loaded onto HLA class II molecules. This cross-presentation process will promote HLA class II presentation of cytosolic antigen in cells with high levels of autophagy. Thus one can envision that, via autophagy, the antigen portfolio presented upon HLA class II may differ in intestinal epithelial cells, lamina propria APCs and B cells in the intestinal mucosa when compared to mucosal surfaces not exposed to a dense microbial load. This potential bias towards HLA class II presentation of cytosolic antigen may also contribute to the enhanced effectiveness of mucosal vaccination against enteric pathogens versus parenteral antigen exposure [40,41].

Furthermore, ATG genes are essential for T cell development, survival and proliferation [42, 43]. Programmed cell death plays a critical role in effector T cell contraction post immune response. Recent studies have demonstrated that a large number of Th2 cells undergo autophagy. In contrast, none of the naive CD4 T cells undergo autophagy. Signaling pathways in mature immune cells appear hypersensitive to reactive oxygen species (ROS) signals and the unfolded protein response (UPR) in the absence of autophagy[44]. In addition to TCR signaling, growth factor withdrawal can gradually induce autophagy in Th2 cells. Autophagy

is also induced by IFNγ, a hallmark Th1 cytokine, and inhibited by IL-13. Together these findings suggest that autophagy contributes to both immune activation and suppression mechanisms in the intestinal mucosa (Figure 1C).

Future Perspectives

It is clear from the genetic studies of CD and the functional studies of the ATG16L1 and IRGM gene products that autophagic processes play a key role in pathogenesis of CD. The early studies would suggest that common variation in these two genes, identified by multiple GWAS, are likely to have a major impact on how an individual's innate immune system interacts with their own gut flora. Elucidation of the specific mechanisms by which the genetic variants in IRGM and ATG16L1 contribute to protection or susceptibility to CD and how they fit in a model of disease which incorporates the knowledge about the other genetic and non genetic risk factors (Figure 2) remain as significant challenges that need to be addressed in order for these discoveries to have a significant impact on clinical practice.

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ABREVIATIONS

CD
: Crohn's disease

IBD
: inflammatory bowel diseases

GWAS
: genome-wide association study

SNP
: single nucleotide polymorphism

ATG
: autophagy-related gene

HLA
: human leukocyte antigen

WD domain
: protein domain consisting of a GH peptide motif, a variable spacer region, followed by the WD peptide motif – thought to mediate protein-protein interactions

APC
: antigen-presenting cell

ROS
: reactive oxygen species

TCR
: T cell receptor

UPR
: unfolded protein response

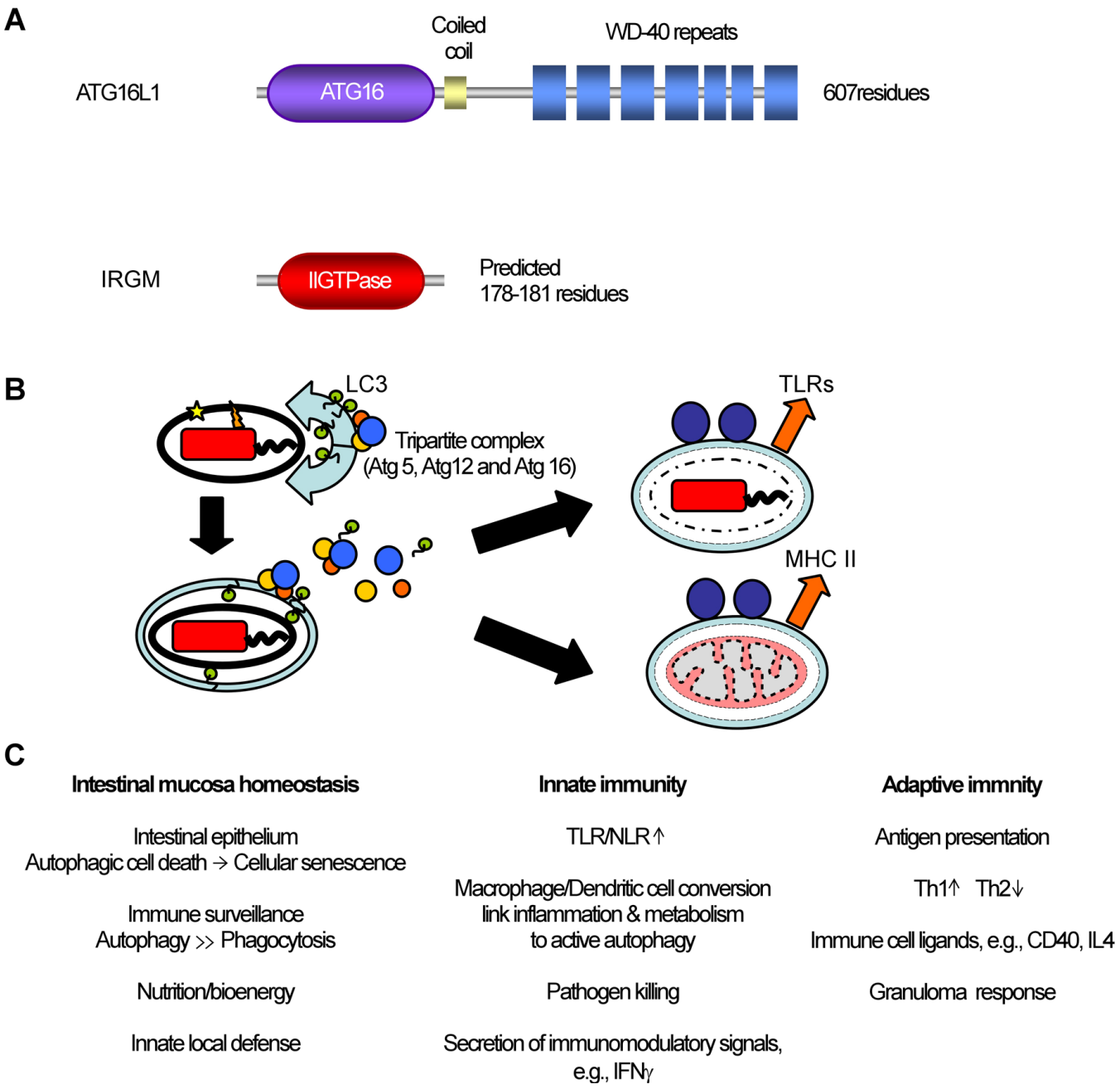

Figure 1. Structure and proposed function of two genes implicated in autophagic processes and susceptibility to Crohn's disease

(A) Domain structure of the ATG16L1 and IRGM proteins. Human ATG16L1 has an N-terminal interaction domain, postulated to be essential for interaction with other autophagy proteins such as ATG5 and ATG12, a coiled-coil domain thought to mediate homodimeric interactions and seven WD repeats. Although proteins with WD repeats demonstrate a very high degree of functional diversity, the structures formed by these repeats are believed to create stable platforms that can coordinate the formation of reversible multi-protein complexes. In contrast, IRGM has just a single identified domain, belonging to the Interferon-Inducible GTPase family. (B) Proposed mechanism for autophagy of intracellular pathogens and subsequent immune events. Responding to uncharacterized signals upon the bacteria-

containing vacuole (or the bacterium itself if free in the cytoplasm), the autophagy apparatus initiates an encapsulation process. The double membrane characteristic of autophagy envelops the pathogen, driven by the core autophagic machinery, including the ATG5,12 and 16 complex. Completion of the autophagic vacuole results in dissolution of the ATG complex from the vacuole and the autophagosome is fused with lysosomes (large blue circles) and degrade its contents. Vacuolar contents can then be loaded onto HLA class II molecules or possibly trafficked to compartments where TLR recognition may occur. (C) Potential consequences of autophagy for mucosal homeostasis and immunity. Autophagy is likely to play important roles in both mucosal barrier maintenance and innate and adaptive immunity. As yet, the effects of known human mutations upon these functions is unknown, but the implication of autophagy-related SNPs in CD is likely to reflect subtle alterations in the balance of autophagy versus other immune and homeostatic gut processes.

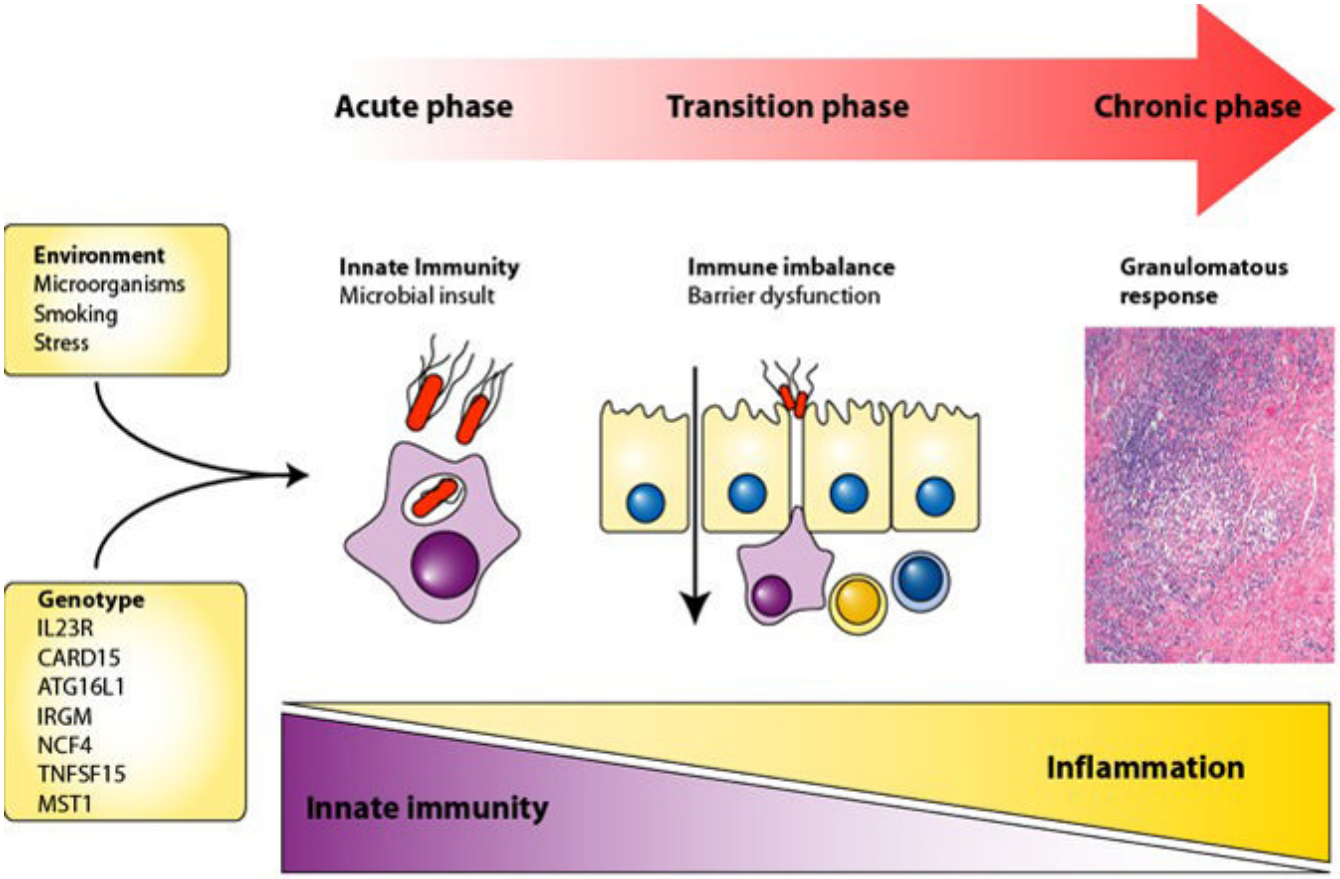

Figure 2. Genetic variation in the autophagic machinery contributes to the development of chronic inflammation in the gut

Crohn's disease is a complex genetic disorder whereby genetic and non-genetic risk factors contribute to disease susceptibility. Genetic variation in the ATG16L1 and IRGM genes identified in the recent GWA studies, in combination with genetic variation at other genes identified in these and previous studies, likely result in an inappropriate response to the intestinal microbial flora and eventually to a chronic granulomatous inflammatory state.