Autophagy and Autoimmunity

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Abstract

Autophagy is a highly conserved protein degradation pathway from yeasts to humans that is essential for removing protein aggregates and misfolded proteins in healthy cells. Recently, autophagy-related genes polymorphisms have been implicated in several autoimmune diseases including systemic lupus erythematosus, rheumatoid arthritis, psoriasis, and multiple sclerosis. Numerous studies reveal autophagy and autophagy-related proteins also participate in immune regulation. Conditional deletions of autophagy-related proteins in mice have rendered protection from experimental autoimmune encephalomyelitis, and TNF-mediated joint destruction in animal models of multiple sclerosis and experimental arthritis respectively. As autophagy is strongly implicated in immune functions such as removal of intracellular bacteria, inflammatory cytokine secretion, antigen presentation, and lymphocyte development, in this review we summarized current understanding of the roles of autophagy and autophagy proteins in autoimmune diseases.

1. Introduction

1.1 Autophagy pathways

Autophagy is the only known conserved protein degradation pathway other than the ubiquitin-proteasome system (UPS). There are three major types of autophagy: 1) macroautophagy (referred as autophagy in general), 2) chaperone-mediated autophagy (CMA), and 3) microautophagy (Fig. 1).

1.2 Macroautophagy

The most studied autophagy pathway is macroautophagy that is generally referred as autophagy. Because the autophagy pathway is highly conserved, studies in yeast genetics advance our knowledge tremendously in the molecular process of autophagy. This process
involves phagophore formation, autophagosome formation, and fusion of autophagosomes and lysosomes to form autolysosomes for protein degradation. Phagophore is an isolation membrane, which may derive from the endoplasmic reticulum (ER) or mitochondria. Phagophore can recruit and enclose cytoplasmic components selectively or non-selectively to form a double layer membrane vesicle called autophagosome. Autophagosome later fuses with the lysosome and forms the autolysosome where degradative enzymes break down cytoplasmic components.

Similar to UPS, ubiquitin also plays essential roles in regulating autophagy, including activating autophagy-related (ATG) proteins and labeling targeted cargos for degradation [1]. ATG7 is one of the ubiquitin-activating enzymes, also known as E1 enzymes that initialized the process [2]. E2 ATG10 is responsible for the conjugation of ATG5-ATG12 to ATG16, which then facilitate conjugation of phosphatidylethanolamine (PE) to LC3 together with E2 ATG3 [3]. PE-conjugated LC3, also known as LC3-II tightly bound to autophagosomal membranes, therefore, is used as autophagic marker protein [4–6].

Autophagy has been long considered to be a non-selective process. However, recent studies demonstrate that autophagy also regulates highly selective degradation processes such as clearing damaged mitochondria (mitophagy) and clearing ubiquitinated protein aggregates (aggrephagy) (Fig. 2) [7–10]. Deficient in mitophagy-related proteins such as PTEN-induced putative kinase 1 (PINK1), Parkin, optineurin (OPTN) and Nix leads to impaired clearance of damaged mitochondria [11, 12]. Deficient in other autophagy adaptor proteins such as sequestosome-1 (SQSTM1), neighbor of Brca1 gene (NBR1), WDFY3 or HDAC6 leads to impaired clearance of misfolded proteins and protein aggregates [13–15].

1.3 Chaperone-mediated autophagy

Chaperone-mediated autophagy (CMA) is another type of autophagy that does not involve the formation of autophagosomes [16]. CMA involves several steps including 1) substrate recognition and lysosomal targeting, 2) substrate binding and unfolding, 3) substrate translocation and substrate degradation [17]. Firstly, cargos containing short degradation signal sequence related to KFERQ are recruited by a chaperone complex including Heat shock-cognate protein of 70KDa (Hsc70) in the cytosol [18]. Secondly, Lysosome-associated membrane protein type 2A (LAMP-2A) on the lysosomes targets and binds to the chaperone complex, which brings the targeted proteins close to lysosomes. Thirdly, the interaction between LAMP-2A and chaperone complex further induces LAMP-2A oligomerization to facilitate translocation of targeted proteins from the cytosol into lysosomes for degradation [19]. Recently, modulation of deregulated CMA by a phosphopeptide has been shown significantly reduced autoimmune pathologies in patients and an animal autoimmune disease model [20], but further studies are required to elucidate CMA mechanisms in autoimmune diseases.

1.4 Microautophagy

Microautophagy involves direct lysosomal engulfment of cytoplasmic cargo without forming autophagosomes, which is essential for cell survival when cells are under stress such as nutrient starvation [21, 22]. Microautophagy can be divided into five sequential steps: 1)
microautophagic invagination and autophagic tubes, 2) vesicle formation, 3) vesicle expansion, 4) vesicle scission and 5) vesicle degradation [23]. In microautophagy, lipids are essential for maintaining invagination and forming autophagic tubes, which are distinct from other types of autophagy [24].

Recently, microautophagy has been shown to regulate synaptic protein turnover in neurons and thus defects in microautophagy may result in accumulation of dysfunctional proteins and cause neurodegenerative disorders [25]. Although studies in yeast and Drosophila models have advanced our knowledge of microautophagy, the physiological function of microautophagy in mammalian cells remains poorly understood.

2. Autophagy in the immune system

Autophagy plays four principle roles in the immune system including 1) removal of intracellular pathogens, 2) secretory pathway, 3) lymphocyte development, and 4) pro-inflammatory signaling [26, 27].

2.1 Autophagy for removal of intracellular pathogens

There are two routes to eliminate intracellular pathogens through the autophagy pathway. The first route is termed xenophagy [28] that involves the engulfment of intercellular pathogens in double-membrane autophagosomes. The second route is termed LC3-associated phagocytosis (LAP) and is characterized by the enclosing of pathogens in single-membrane phagosomes decorated with LC3 [29, 30]. Some pathogen removal via autophagy requires additional receptors such as toll-like receptors (TLRs) [31]. The vesicles containing intracellular pathogens then fuse with lysosomes to form autolysosomes or autophagolysosomes [32] for degradation and elimination of intercellular pathogens.

2.2 Autophagy in the secretory pathway

The process of phagocytosis and the secretory pathway share a lot of common functions including vesicle trafficking and membrane fusion. Therefore, it’s no surprise that the autophagy pathway/autophagy proteins that play roles in phagocytosis also participate in secretory pathways. For instance, mice deficient in autophagy-related protein 5 (ATG5\textsuperscript{fl/fl} LysM Cre\textsuperscript{+}) present high level of IL-1α secreted by macrophages \textit{in vitro} and \textit{in vivo}, which lead to excessive inflammatory responses [33]. Furthermore, inhibition of autophagy in antigen-presenting cells leads to elevated IL-1β secretion upon TLRs stimulation \textit{in vitro} and induction of autophagy along with LPS stimulation reduced IL-1β secretion \textit{in vivo} [34]. Inhibition of autophagy in antigen-presenting cells also leads to elevated IL-23 secretion as a consequential event of increased IL-1β level [35]. Recently, autophagic regulation of mitochondrial reactive oxygen species (ROS) has been shown to control the secretion of another pro-inflammatory cytokine, macrophage migration inhibitory factor (MIF) [36], which aligns with previous studies and suggest defects in autophagy leads to increased pro-inflammatory cytokines secretion.
2.3 Autophagy in lymphocyte development

Lymphocytes including T cells and B cells are important for adaptive immunity. Proper activation of lymphocytes is critical for lymphocyte development, and defective activation may result in autoimmunity. One major T cell activation signal is antigen presentation via the major histocompatibility complex (MHC) molecules I, II that reside on the cell surface to display antigens. MHC class I are found on all nucleated cells and MHC class II are found in antigen presenting cells (APCs) including macrophages, dendritic cells and B cells. To enable proper presentation of antigens, peptides derived from intracellular or extracellular proteins need to be digested or processed via degradation pathways including the ubiquitin-proteasome system and autophagy.

Autophagy can enhance MHC class I presentation of viral antigens in macrophages during infection [37] and also promote MHC class II presentation of viral antigens [38, 39]. Furthermore, other reports have elegantly demonstrated that autophagy is required for generation of major histocompatibility complex (MHC) class II antigen-specific CD4 (+) T cell responses in dendritic cells [40, 41]. Similarly, autophagy deficiency in thymic epithelial cells (TECs) causes altered MHC class II presentation of MHC peptide ligands and tissue-restricted antigens, which contributes to the generation of autoreactive CD4 (+) T cell repertoire [42].

B cells can differentiate into plasma cells that are responsible for generating autoantibodies and are critical for autoimmunity. It was previously shown that ATG5 is required for B cell survival during development and for the maintenance of B cell subset (B-1a) in the periphery [43] and plasma cells require autophagy for sustainable immunoglobulin production [44]. In fact, autophagy-deficient plasma cells secrete more antibodies accompanied with higher apoptosis rate compared to wild type plasma cells in vitro, suggesting that autophagy is specifically required for plasma cell homeostasis and long-lived humoral immunity. [44]. Defective or overactive autophagy modulates B cell development and function and therefore contributes to autoimmunity.

2.4 Autophagy in pro-inflammatory signaling

Recent evidence supports crosstalk between autophagy/autophagy-related proteins in nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation. For instance, T cell receptor (TCR) mediated NF-κB activation is modulated by B-cell lymphoma/leukemia 10 (BCL10) in association with the autophagy adaptor p62/SQSTM1 [45]. In macrophages, SQSTM1/p62-dependent clearance of damaged mitochondria modulates NLRP3-inflammasome activation; ablation of SQSTM1/p62 leads to increased activation of inflammasome and overproduction of IL-1β [46]. Although this mechanism limits excessive IL-1β dependent inflammation, other studies have shown that autophagy enhances NF-κB activity in specific tissue macrophages by sequestering A20 to boost antifungal immunity [47]. This evidence suggests that autophagy can modulate survival and pro-inflammatory signaling via many pathways including NF-κB activation in many cell types. Since autophagy plays multiple roles in the immune system, disturbances in autophagic activity are likely to affect the development of autoimmunity. In fact, a plethora of evidence from
genome-wide association studies and basic research highlight the autophagy roles in autoimmune diseases and are summarized in (Table 1.).

### 3. Autophagy/Autophagy-related proteins in autoimmune diseases

#### 3.1 Multiple sclerosis

Multiple sclerosis (MS) is a common autoimmune disease that caused inflammation and demyelination in the human central nervous system [58]. Since autophagy plays multiple roles in the immune system, extensive studies have investigated the role of autophagy in multiple sclerosis. A link between autophagy and multiple sclerosis is provided by the observed elevated autophagy-related protein, ATG5, expression in autoreactive T cells isolated from multiple sclerosis patients and mice with experimental autoimmune encephalomyelitis (EAE), [59]. The study further demonstrates that autophagy promotes T cell survival by degradation of apoptosis proteins in EAE model, and inhibition of autophagy in CD4 T cells using Beclin-1 conditional knockout mice (Beclin-1^fl/fl CD4 Cre^+) leads to protective phenotypes in EAE model [48]. In myeloid cells, disrupted antigen presentation in dendritic cells is observed in ATG7 conditional knockout mice (ATG7^fl/fl CD11c Cre^+) that again lead to reduced disease severity in EAE model [49]. Moreover, autophagy deficiency in neutrophils also reduced disease severity in EAE model due to defective degranulation [50]. Taken together, inhibition of autophagy leads to ameliorated disease severity in EAE model by regulating survival and activation of autoreactive T cells and reduced inflammatory cytokine secretion from neutrophils. The implication of autophagy in MS remains to be elucidated.

#### 3.2 Systemic Lupus Erythematosus

Systemic Lupus Erythematosus (SLE) is an autoimmune disease that is characterized by acute and chronic inflammation of various tissues of the body including skin, joints, heart, kidneys and/or nervous system [60]. Several cellular and immune system components are disturbed in SLE, such as clearance of apoptotic cells, abnormal B and T cell signaling, autoantibody secretion and deregulated cytokine secretion. The cause of the SLE is currently unknown, but both genetic and environmental factors contribute to disease development [61]. Genome-wide association studies link autophagy-related gene 5 (ATG5) with SLE in both Chinese [62] and European [63] populations suggesting that defects in the autophagy pathway may contribute to SLE pathogenesis. A follow-up study suggested that ATG5 single nucleotide polymorphism (SNP) rs573775 implicated a role of the mutation with aberrant IL-10 cytokine secretion and higher risk for SLE [64]. Deregulation of autophagy has also been observed in T cells derived from SLE patients and confirmed in animal models of the disease [65], [66]. Moreover, activation of autophagy in B cell differentiation is observed in a lupus mouse model (NZB/W) and SLE patients. Inhibition of autophagy by inhibitors or transgenic mice partly inhibits plasma cells differentiation that suggests autophagy may regulate the survival rate of autoreactive B Cells and plasma cell differentiation in SLE [51].

Increased methylation patterns of histone deacetylase-6 (HDAC6), an ubiquitin-binding deacetylase critical for aggrephagy and mitophagy [67], compare to healthy controls are also observed in SLE patients [68]. Further animal studies reveal increased HDAC6 expression in
T cells and B cells derived from NZB/W mice [69], and inhibition of HDAC6 reduces lupus pathogenesis in NZB/W mice, which suggest a potential role of HDAC6-dependent selective autophagy in SLE pathogenesis. Therapeutic treatments inhibiting autophagy pathway or autophagy-related proteins may improve SLE clinical outcomes by reducing autoreactive lymphocytes differentiation and their associated functions.

3.3 Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease that exhibits various clinical manifestations including synovial inflammation and bone loss. Immune cells such as T_h17 cells, B cells, macrophages, neutrophils, mast cells and fibroblast-like synoviocytes are critical for inducing and maintaining synovial inflammation in RA pathology [70, 71]. This chronic inflammation leads to secretion of a plethora of pro-inflammatory cytokines and RANKL, which are primarily responsible for the activation of osteoclasts and the subsequent bone destruction. Autophagy has been associated with RA fibroblast-like synoviocytes (RA-FLS) survival, which is a major source of pro-inflammatory cytokines and RANKL. Specifically in in vitro experiments RA-FLS treated with a proteasome inhibitor (MG-132) prevented cell death whereas in contrast, treatment with an endoplasmic reticulum (ER) stress inducer, (thapsigargin) led to the formation of ubiquitinated protein aggregates and cell death via a mechanism involving autophagy proteins SQSTM1 and WDFY3 [72]. Other reports have shown that inhibition of autophagy-related protein HDAC6 using Tubastitin A reduces the inflammatory cytokine secretion from macrophages and FLS, and ameliorated arthritis disease severity in collagen antibody-induced arthritis (CAIA) and collagen-induced arthritis (CIA) in mouse models [73, 74]. Collectively, these data demonstrate a prominent role of autophagy in synovial inflammation both in vitro and in vivo.

Autophagy also modulates osteoclast-mediated bone destruction in rheumatoid arthritis. Increased expressions of autophagy-related protein Beclin1 and ATG7 are observed in osteoclasts of rheumatoid arthritis patients and inhibition of autophagy using ATG7^{fl/fl} LysM Cre^+ transgenic mice show reduced bone destruction in TNF-mediated arthritis [52]. The protective effect in TNF-mediated bone destruction resulted from the inhibition of autophagy may be in part due to impaired secretion of inflammatory cytokines IL-1 and IL-6 that affects osteoclastogenesis [52]. In addition, autophagy regulates the osteoclast ruffled border formation, (specialized organelle that facilitates bone resorption) which is evidenced by reduced bone resorption in both in vitro and in vivo assays in ATG5 deficient mice (ATG5^{fl/fl} LysM Cre^+) [53]. Furthermore, mutations in autophagy-related protein SQSTM1 impair osteoclast differentiation and are associated with Paget’s disease of bone [75]. Disrupted RANKL-induced osteoclastogenesis is observed in SQSTM1 deficient mice where SQSTM1 forms complex with TNF receptor associated factor 6 (TRAF6) and leads to NF-κB activation [76]. Deletion of SQSTM1 ubiquitin-binding domain (UBD) leads to increased osteoclast differentiation and function suggesting that SQSTM1 may regulate osteoclastogenesis via multiple pathways [77]. Interaction of autophagy-related proteins SQSTM1 and WDFY3 has been observed in human osteoclasts [78], and we recently showed that WDFY3 deficient mice (WDFY3^{fl/fl} LysM Cre^+) show enhanced osteoclastogenesis and RANKL-mediated bone resorption in vitro and in vivo assays via
TRAF6 dependent activation of NF-κB [79]. Another autophagy-related protein, optineurin (OPTN) also negatively regulates osteoclastogenesis by modulating NF-κB and IFN-β signaling [80]. Furthermore, inhibition of autophagy using chloroquine prevents TRAF3 degradation and inhibits osteoclast differentiation in vitro and in vivo [81]. In summary, autophagy influences RA pathologies in two major ways; synovial inflammation and bone destruction. As inhibition of autophagy may ameliorate RA disease pathologies by modulating inflammation and bone destruction at synovial joints a detailed understanding of autophagy mechanisms in RA are needed to develop effective treatments.

### 3.4 Psoriasis/Psoriatic arthritis

Psoriasis is a chronic skin autoimmune disease where the skin undergoes abnormally excessive proliferation of keratinocytes, which also contribute to skin inflammation with increased secretion of pro-inflammatory cytokines. [82]. About 6–42% of psoriasis patients also have psoriatic arthritis [83]. Increased epidermal expression of the autophagy-related protein, SQSTM1, has been observed in psoriatic skin [54]. Autophagy negatively regulates TLR2/6 mediated NF-κB activation, SQSTM1 expression, and cytokine secretion in human keratinocytes that are critical to skin inflammation as observed in psoriasis/psoriatic arthritis [54]. Indeed other studies have shown that mutation of psoriasis risk gene API53 that leads to impaired autophagy, and accumulation of SQSTM1, results in up-regulation of IL-36 in keratinocytes and causes skin inflammation [84]. Furthermore, increased expression of autophagy-related protein ATG16L1 is observed in dendritic cells derived from psoriatic arthritis patients compared to healthy controls that suggests autophagy involvement in psoriatic arthritis pathogenesis [85]. Inhibition of autophagy by chloroquine may aggravate psoriasis by increased IL-23 secretion from myeloid cells, which also leads to an induction of Th17 cells [55]. Taken together, inhibition of autophagy results in exacerbating skin inflammation in psoriasis and psoriatic arthritis. Modulation of autophagy may be a therapeutic approach for psoriasis/psoriatic arthritis, which merits further studies.

### 3.5 Inflammatory bowel diseases

Crohn’s disease and ulcerative colitis are the two common forms of inflammatory bowel disease (IBD) that are characterized as autoimmune diseases [86]. A human genome-wide association study identified autophagy-related genes ATG16L1 and immunity related GTPase M (IRGM) for Crohn’s disease and implicated autophagy in disease pathogenesis [87]. Deletion polymorphism upstream of IRGM alters IRGM expression, leads to defect autophagy and associates with Crohn’s disease [88]. Deletion of autophagy-related proteins such as ATG16L1 and ATG5 leads to disrupted exocytosis of antimicrobial peptides of Paneth cells, which are essential for mucosal immunity [56]. Furthermore, deletion of ATG16L1 also leads to increased IL-1β production in macrophages that may also contribute to Crohn’s disease pathogenesis [57]. ATG16L1 interacts with nucleotide-binding oligomerization domain-containing protein 2 (NOD2) to degrade intracellular bacteria via autophagy pathway which is also deregulated in Crohn’s disease [89]. In summary, modulation of autophagy/autophagy-related proteins contributes to inflammatory bowel diseases. Restoring the functional autophagy-related proteins may be a great therapeutic approach for treating inflammatory bowel diseases in the future.
4. Conclusions

Autophagy is a conserved cellular degradation pathway. Recent evidence ranging from genome-wide association studies to basic in vivo and in vitro research have linked the autophagy pathways and/or autophagy-related proteins to autoimmunity. Crosstalk between autophagy and immune system includes removal of intracellular pathogens, secretory pathway, lymphocytes development, and pro-inflammatory signaling. Using transgenic animals, to model human diseases, important roles of autophagy in autoimmunity have been uncovered. Although in certain studies presented in this review inhibition of autophagy ameliorates diseases including multiple sclerosis, systemic lupus erythematosus, and rheumatoid arthritis in other cases it seems to exacerbate diseases such as psoriasis, psoriatic arthritis and Crohn’s disease. Since the autophagy pathway and autophagy-related proteins are highly conserved in many cell types the variation between effectors and transducers in different cells/tissues (bone-osteoclasts, skin-keratinocytes etc.) affected in the autoimmune diseases discussed and crosstalk of multiple pathways may be the underlying cause for this effect. For instance, SQSTM1 can regulate NF-κB activation via forming a complex with TRAF6 but also can degrade NF-κB via selective autophagy. In such cases the availability of effectors and transducers within a given cell may dictate the outcome. Distinguishing the autophagy-related protein's roles in autophagy or other cellular mechanisms in autoimmune disease pathologies remains to be a challenge [90]. A detailed understanding of autophagy is paramount, for the development of treatments for autoimmune diseases in the near future.

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References


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Highlights

- Autophagy is a highly conserved protein degradation pathway essential for removing protein aggregates and misfolded proteins in healthy cells.
- Autophagy pathways are strongly implicated in immune functions such as removal of intracellular bacteria, inflammatory cytokine secretion, antigen presentation, and lymphocyte development.
- Autophagy-related genes polymorphisms have been implicated in several autoimmune diseases including systemic lupus erythematosus, rheumatoid arthritis, psoriasis, and multiple sclerosis.
1. Macroautophagy (autophagy)

In the process, protein aggregates and misfolded proteins are recruited by the phagophore and then enclosed in double-membrane vesicles named autophagosomes that later fuse with lysosomes for degradation.

2. Chaperone-mediated autophagy

In chaperone-mediated autophagy, proteins contain KFERQ degradation signal are recruited by chaperone and bind to LAMP-2A on lysosomes. Proteins then translocate from cytosol through LAMP-2A multimers into lysosomes for degradation.

3. Microautophagy

Directly engulfs cytoplasmic components for degradation.

**Figure 1. Illustration of the three types of autophagy**

1) Macroautophagy is generally referred to as autophagy. In the process, protein aggregates and misfolded proteins are recruited by the phagophore and then enclosed in double-membrane vesicles named autophagosomes that later fuse with lysosomes for degradation.

2) In chaperone-mediated autophagy, proteins contain KFERQ degradation signal are recruited by chaperone and bind to LAMP-2A on lysosomes. Proteins then translocate from cytosol through LAMP-2A multimers into lysosomes for degradation.

3) Microautophagy directly engulfs cytoplasmic components for degradation.
Figure 2. Illustration of ubiquitinated proteins undergoes two major degradation pathways
Ubiquitinated-labeled misfolded proteins or protein aggregates can be degraded via ubiquitin-proteasome system (UPS) and/or autophagy. UPS system cannot process large proteins or protein aggregates due to its limitation of size. In contrast, macroautophagy can enclose large proteins and aggregates in autophagosomes (0.5–1.5µm), which later fuse with lysosomes for degradation. Autophagy adaptor proteins such as SQSTM1 and WDFY3 can recruit ubiquitinated-labeled misfolded proteins or protein aggregates into phagophore and

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form autophagosomes. The autophagosomes then fuse with lysosomes that contain degradative enzymes and form autolysosomes and degrade proteins.
Table 1

Summary of effect of inhibiting autophagy in cellular pathways and outcomes of different autoimmune diseases.

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<tr>
<th>Inhibition of Autophagy</th>
<th>Outcomes</th>
<th>References</th>
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<tr>
<td>Multiple sclerosis</td>
<td>Reduce autoreactive T cells, disrupted antigen presentation, defect neutrophils degranulation</td>
<td>↓ disease severity</td>
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<tr>
<td>Systemic Lupus Erythematosus</td>
<td>Partly inhibits plasma cells differentiation</td>
<td>↓ disease severity</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>Reduced inflammatory cytokines secretion, reduced osteoclast function</td>
<td>↓ disease severity ↓ bone destruction</td>
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<td>Psoriasis/Psoriatic arthritis</td>
<td>Increased inflammatory cytokine secretion</td>
<td>↑ disease severity</td>
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<tr>
<td>Inflammatory bowel diseases</td>
<td>Disrupted exocytosis of antimicrobial peptides of Paneth cells, increased inflammatory cytokine</td>
<td>↑ disease severity</td>
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