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Death in the intestinal epithelium – Basic biology and implications for inflammatory bowel disease

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Abstract

Every four to five days, intestinal epithelial cells (IEC) are terminated as they reach the end of their life. This process ensures that the epithelium is comprised of the fittest cells that maintain an impermeable barrier to luminal contents and the gut microbiota, as well as the most metabolically able cells that conduct functions in nutrient absorption, digestion, and secretion of antimicrobial peptides. IEC are terminated by apical extrusion – or shedding – from the intestinal epithelial monolayer into the gut lumen. Whether death by apoptosis signals extrusion or death follows expulsion by younger IEC has been a matter of debate. Seemingly a minor detail, IEC death before or after apical extrusion bears weight on the potential contribution of apoptotic IEC to intestinal homeostasis as a consequence of their recognition by intestinal lamina propria phagocytes. In inflammatory bowel disease (IBD), excessive death is observed in the ileal and colonic epithelium. The precise mode of IEC death in IBD is not defined. A highly inflammatory milieu within the intestinal lamina propria, rich in the pro-inflammatory cytokine TNF-α, increases IEC shedding and compromises barrier integrity fueling more inflammation. A milestone in the treatment of IBD, anti-TNF-α therapy, may promote mucosal healing by reversing increased and inflammation-associated IEC death. Understanding the biology and consequences of cell death in the intestinal epithelium is critical to the design of new avenues for IBD therapy.

Graphical abstract

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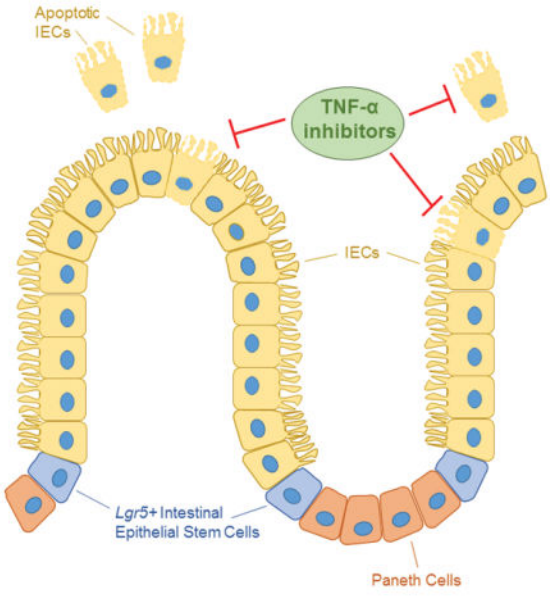

High levels of apoptosis are detected in the intestinal epithelium of inflammatory bowel disease (IBD) patients. This increased level of epithelial intestinal cell (IEC) death disrupts barrier integrity and leads to inflammation, but whether cell death is a symptom or cause of IBD is unknown. Although TNF-α inhibitors help restore barrier function in some patients, additional research on the mechanism of IEC death and how it goes awry in IBD is needed.

Keywords

apoptosis; intestinal epithelial cell; Tumor necrosis factor; inflammatory bowel disease; intestinal tolerance

The intestinal epithelium

The intestinal epithelium consists of a single layer of intestinal epithelial cells (IEC) shaped into invaginations that form the crypts of Lieberkühn and luminal protrusions that form the characteristic villi of the small intestine. *Lgr5*$^{+}$ stem cells reside at the base of the intestinal crypts [1]. These stem cells divide to generate precursors of secretory cells and enterocytes that proliferate and differentiate as they move upwards away from the crypt and towards the villus tip in the small intestine or luminal face of the crypt in the large intestine [1, 2]. Precursors differentiate into various types of specialized cells. Absorptive enterocytes, marked by alkaline phosphatase intestinal (*Alpi*) gene expression, are specialized in metabolic and digestive functions. Rare Tuft cells are taste-chemosensory epithelial cells that also serve as sentinels of type 2 immunity in response to parasites [3], and specialized microfold (M) cells cover lymphoid aggregates in the ileum called Peyer's patches and transport luminal antigens to lymphoid cells [2]. Additional specialized lineages of secretory IEC maintain the digestive or barrier functions of the epithelium. These lineages include entero-endocrine cells that secrete hormone regulators of digestive function, goblet cells that secrete mucus (MUC2) into the lumen, and Paneth cells at the crypt bottom that secrete

antimicrobial proteins such as the C-type lectin regenerating islet-derived protein IIIγ (REGIIIγ), α-defensins, cathelicidins and lysozyme [4–8]. Besides stem cells, Paneth cells are excluded from the upward migration during their life cycle [9]. The collective action of mucus and antimicrobial proteins establishes a physical and biochemical barrier against the luminal microbiota, precluding their adhesion to the epithelial surface and their translocation into the lamina propria where immune cells reside.

Genetic fate mapping of alkaline phosphate intestinal $(Alpi)^+$ enterocyte progenitors using tamoxifen-inducible *Cre* recombinase knocked into the *Alpi* gene showed reporter activity first in the upper crypt followed by the villus domain, higher regions of the villus by day 2, the villus tip by day 3, and finally disappearance by days 4–5 implying shedding into the lumen [10]. This kinetic pattern reflects the 4–5 day life cycle of an IEC [2, 11]. Notably, these studies also revealed that enterocyte precursors could also serve as a reservoir of potential stem cells by dedifferentiating into $Lgr5^+$ stem cells under conditions of injury where rapid crypt regeneration is required [10].

Termination of an intestinal epithelial cell at the end of its life cycle

Besides renewal from stem cells in the crypts, turnover of IEC is also regulated by loss of senescent cells from the epithelial monolayer. In humans, approximately 10^{10} IEC are shed every day [12, 13]. The rapid nature of the process precludes its visualization unless special handling, slicing and fixation of intestinal tissues are applied [14]. IEC loss occurs predominantly at the villus tip in the small intestine or luminal surface of the colon, and has historically been viewed as passive shedding [11]. Apoptosis as a mechanism of shedding emerged with studies showing the presence of cells positive for terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) at the tips of the villi in rodent and human intestinal sections [15–17]. Earlier studies had reported a small level of spontaneous cell death in the crypts with morphology typical of apoptosis [18, 19], but the villus tips contained only rare apoptotic cells [20, 21]. Apoptosis is a form of non-inflammatory cell death that accounts for loss of large numbers of cells during development and tissue remodeling [22]. Other studies in human and guinea pig intestinal epithelium presented transmission and scanning electron microcopy evidence for apoptotic enterocytes in the act of being shed – and interestingly apoptotic IEC appeared surrounded, and in some cases phagocytosed, by subepithelial macrophages [17, 23, 24]. These early studies set the stage for debates to come decades later as to whether apoptosis precedes or follows IEC shedding. Cell death following IEC shedding can occur when live cells are extruded as a consequence of overcrowding due to proliferation and upward migration of new IECs along the crypt-villus axis [25]. Loss of cell-substratum adhesion in this case leads to anoikis [26]. In the human intestinal epithelium, 5.3% of villus sections were reported to contain a shedding cell, and the majority of these cells stained positively for activated caspase-3, a marker for apoptosis, as well as a caspase-cleaved product of cytokeratin 18 [14]. Shedding IEC here were not found to be associated with macrophages [14]. Because late stage apoptotic cells were observed only in the crypt, it was suggested that IEC are shed as soon as they become apoptotic [14]. In healthy subjects with no symptoms or endoscopic findings, colonic sections showed $TUNEL^+$ cells mainly at the surface and not crypt epithelium [27].

In vitro studies have elucidated the mechanisms of apoptotic cell extrusion from epithelial monolayers. These studies have shown that apoptotic cells produce the bioactive lipid sphingosine-1-phosphate (S1P), which signals neighboring cells through S1P2 receptor to form and activate Rho-associated kinase (ROCK)-mediated contraction of an actin/myosin ring at the interface between the apoptotic cell and neighboring cells, and leading to apoptotic cell extrusion while maintaining barrier function [25, 28, 29]. In fact, ROCK is cleaved and activated by caspase-3 during apoptosis in order to enable phosphorylation of myosin light chain (MLC), which is necessary for membrane blebbing in apoptotic cells [30, 31]. Over 50% of shedding events observed in the human small intestine were associated with phosphorylated MLC [14]. Also of note, actin/myosin contraction preceded pro-caspase activation or phosphatidylserine exposure [29], an eat-me signal on apoptotic cells [32], making it difficult to accurately assess whether a cell is ‘alive and well’ or already committed to apoptosis prior to extrusion. Finally, the downward contraction of actin and myosin IIA at the basolateral surface along with basolateral targeting of the RHO guanine nucleotide exchange factor 1 (p115RhoGEF) favors the predominant apical as opposed to basal direction of extrusion [33].

Extrusion of live IEC serves as another mechanism of regulating the size of the IEC population. Live IEC extrusion requires stretch activated ion channels that are activated by stress and presumably function upstream of SIP that acts on Rho to mediate extrusion. Extruded cells subsequently undergo anoikis [26], but as mentioned above apoptosis may have already begun prior to extrusion and may have signaled extrusion itself. The aged IEC (live or apoptotic) are shed from the intestinal epithelial monolayer into the lumen, and tight junction protein reorganization beneath the shedding cell ensures that lamellopodia from the neighboring cell come together in a process that was likened to a “zipper” being drawn up, thereby maintaining the epithelial barrier at the shedding site [34].

Basal extrusion is common in the embryonic epithelia of Drosophila unlike in vertebrates [35–37]. Cancer cells exploit basal extrusion to invade and metastasize [38]. Loss or mutation of the tumor suppressor adenomatous polyposis coli (APC) switches cells from apical to basal extrusion [39]. Oncogenic K-Ras enables cells to extrude basally by autophagy-mediated degradation of S1P and disruption of signaling required for apical extrusion [40]. Induction of IEC shedding with a high dose of TNF-α (to mimic pathological conditions) combined with live imaging of mice transgenic for enhanced green fluorescent protein-occludin and red fluorescent protein-1-ZO-1, revealed only apically-oriented IEC shedding that required active basolateral redistribution of these tight junction proteins [41]. Myosin motor activity and microtubules were required to initiate extrusion, and its completion required microfilament remodeling and the activities of ROCK, myosin light chain kinase (MLCK), and dynamin II [41]. The combined activity of these factors maintained epithelial barrier function [41]. Detectable caspase-3 cleavage was reported after tight junction and microtubule protein remodeling in shedding cells [41]. The initiation and progression of IEC extrusion required caspase activity, as it was sensitive to the pan-caspase inhibitor Q-VD-OPH, which did not prevent MLC phosphorylation. Detection of caspase-3 cleavage after microtubule reorganization may reflect S1P production as the first signal from apoptotic epithelial cells that initiates shedding, consistent with the finding discussed above [29]. Collectively, the evidence argues that IEC extrusion from the intestinal epithelium is

initiated by signals from cells that begin to undergo apoptosis – while the cells are still anchored – rather than the induction of apoptosis after the cells have been extruded (anoikis).

Evidence from mice deficient for the initiator caspase-8 specifically in IEC has been considered to challenge the concept that apoptosis is essential for intestinal epithelial turnover [42, 43]. Indeed, the inability of IEC to undergo apoptosis in these mice did not lead to obvious histological or morphometric abnormalities in the intestinal epithelium at steady state [42]. Notably, however, the mice developed spontaneous ileitis [42]. On the other hand, spontaneous colitis was observed with 100% penetrance upon IEC-specific deletion of the TNF receptor-associated adaptor FADD ($FADD^{IEC\text{-}KO}$ mice) [44], a protein required for death receptor induced apoptosis [45]. Here, 50% of $FADD^{IEC\text{-}KO}$ mice died before weaning while surviving mice suffered from intestinal disease [44]. Importantly, in both studies, when apoptosis was impaired either by deletion of caspase-8 or FADD, IEC still underwent cell death albeit through an alternate program of cell death [42, 44]. Instead of apoptosis, RIPK3 and CYLD dependent necroptosis, an inflammatory form of cell death [46], was mobilized and was responsible for triggering colitis in $FADD^{IEC\text{-}KO}$ mice [44]. These results show that apoptosis is indeed not essential for intestinal epithelial turnover *per se*; IEC destined to die will undergo cell death even when key mediators of the apoptotic program of cell death are absent. However, these results strongly suggest that in maintaining a normal size of the IEC population, IEC death specifically by apoptosis may additionally serve a critical role in preserving intestinal homeostasis. Therefore, blockade of apoptosis within senescent IEC switches their death to necroptosis, which by its inflammatory nature leads to the spontaneous development of intestinal disease (either colitis or ileitis upon IEC-specific deletion of FADD or caspase-8, respectively).

Death of intestinal epithelial cells in inflammatory bowel disease

Intestinal epithelial damage is characteristic of inflammatory bowel disease (IBD) [43, 47–52]. IBD is a chronic inflammation of the intestinal tract and comprises Crohn's disease (CD) and ulcerative colitis (UC) [53–57]. Its pathogenesis involves complex interactions among genetic susceptibility factors, the gut microbiota, and the mucosal immune compartment [53, 58–63]. Intestinal damage in IBD manifests in a notable increase in programmed cell death of IEC [27, 43, 48, 51, 64–66]. High levels of cell death are reported in the epithelium of both patients with UC or CD [27, 43, 49, 64, 65, 67, 68].

Increased apoptosis has been reported in the epithelium of patients with ulcerative colitis (UC) [27, 68]. Apoptotic indices, representing the ratio of $TUNEL^{+}$ IEC to total IEC, were significantly higher in UC patients compared to healthy controls but not compared to intestinal sections from patients with infectious colitis [27]. $TUNEL^{+}$ IEC were frequently distributed at the surface rather than crypt epithelium [27]. Patients with active UC who ultimately require surgery had higher apoptotic indices and CD68 staining, which marks macrophages, than UC patients who were receiving medication [27]. More epithelial cells with markers of apoptosis – including TUNEL positivity, Fas (CD95) and Fas ligand expression as well as DNA laddering and morphological features of apoptosis by electron microscopy – were found in involved and adjacent uninvolved areas of untreated patients

with active UC than in the crypts of the normal colon [68]. Increased numbers of TUNEL$^+$ IEC have also been reported in inflamed compared to uninflamed areas of ileal and colonic biopsy specimens from CD patients [64]. Electron microscopy on rectal biopsies of patients with CD and UC compared with normal controls showed morphology characterized as patchy necrosis in four out of seven of the CD patients [65]. RIPK3, associated with necroptosis, is notably expressed at high levels in the terminal ileum of patients with CD [42]. IEC necroptosis is thought to underlie the microerosions and epithelial gaps observed in mice and humans by *in vivo* imaging [69, 70].

An association between apoptosis and IBD has also been found in epithelial cell proteome studies in both IBD patients and IBD mouse models [71, 72]. A combination of 2-dimensional SDS-PAGE, MALDI-TOF mass spectrometry and Western blots was used to analyze protein expression profiles of primary IEC isolated from inflamed *versus* uninflamed areas of ileal or colonic tissues from patients with CD and UC, as well as patients with colorectal carcinoma (the latter served as healthy controls) [72]. Proteomic profiles revealed 21 proteins with at least 2-fold changes compared to control samples. Of these, 9 proteins achieved statistical significance of which Rho-GDP dissociation inhibitor α was common to both UC and CD samples [72]. Increased expression of this protein was associated with IEC damage. When comparing inflamed *versus* uninflamed IEC samples, 40 proteins with significantly altered expression levels were identified of which programmed cell death protein 8 (also known as apoptosis inducing factor AIF – a mitochondrial pro-apoptotic factor [73]) and Annexin A2 (a possible therapeutic target for refractory UC [73]) were notable and showed the highest fold changes [72]. There were also significant changes in proteins with functions in signal transduction, stress response, and energy metabolism especially changes in glycolysis and Tricarboxylic acid (TCA) cycle [72]. A similar approach was used on IEC isolated from *Il10*$^{-/-}$ mice that had been monocolonized with the colitogenic *Enterococcus faecalis* [71]. *Il10*$^{-/-}$ mice are susceptible to chronic intestinal inflammation [74]. 76 target proteins were identified that had to do with endoplasmic reticulum stress, energy metabolism and apoptosis [71]. Combined, these studies paint a stressed and dying picture of IEC in IBD and under conditions of chronic inflammation.

The exact nature and role of IEC death in the pathogenesis of IBD has not been clarified to date. Whether it is causative or secondary to the chronic inflammation is not known. The consequences of IEC death in IBD patients would be predicted to be two-fold. First, IEC death would disrupt barrier integrity leading to alterations in the quality and quantity of epithelium-derived factors and anti-microbial peptides, as well as translocation of the commensal microbiota into the intestinal lamina propria. Second, it leads to inflammation, and increased levels of inflammatory cytokines such as tumor-necrosis factor-α (TNF-α) [60].

Increased systemic and intestinal tissue levels of TNF-α in IBD patients [60, 75] along with IBD risk alleles associated with TNF signaling (*RELA, NFKB1, TNFAIP3*) that have been identified through genome wide association studies (GWAS), point to a critical role for TNF-α in IBD [76]. Deletion of the TNF-α AU-rich elements (ARE) in mice results in increased steady state levels of TNF-α mRNA and chronic overproduction of TNF-α [77]. TNF*ΔARE* mice develop chronic inflammatory arthritis, but also inflammatory changes

resembling human CD with alterations localized primarily to the terminal ileum and on occasion the proximal colon [77]. The impact of TNF-α on the intestinal epithelial response is complex and depends on its levels and poorly understood secondary signals. TNF-α has many roles in supporting survival and inflammation [78]. TNF-α enhances expression of the polymeric immunoglobulin receptor (pIgR) that transports secretory IgA across IEC [79]. Homeostatic patterns of bacterial secretory IgA coating are altered with the emergence of highly secretory IgA coated bacteria, which marks the most colitogenic species [80].

TNF-α can also induce extrinsic caspase-8 and executioner caspase-3 dependent apoptosis as well as RIPK3-dependent necroptosis under conditions where the activities of caspase-8 or TNFAIP3 (A20, a ubiquitin editing enzyme) are impaired [42, 81–85]. To date, no involvement has been reported for necroptosis related genes as IBD susceptibility loci. However, these proteins could be post-transcriptionally regulated. IEC shedding can also be induced by TNF-α [60, 75, 78, 86]. Unlike homeostatic IEC shedding where barrier integrity is maintained by rapid basolateral tight-junction protein redistribution and zipper-like replacement by neighboring cells [34, 41], TNF-α-induced shedding has been reported to be accompanied by necroptosis where multiple adjacent IEC lose contact [70, 75]. Collectively, increased IEC death and loss of barrier integrity would drive further inflammation, more damage to the intestinal epithelium and perhaps even dysbiosis, making it difficult to distinguish cause from effect.

Potential impact of anti-TNF-α therapy on death of intestinal epithelial cells

TNF-α levels in IBD patients directly correlate with clinical manifestations and disease severity. Antibodies targeting TNF-α represent the most successful clinical treatment for IBD to date inducing intestinal healing and improving long-term patient outcomes [87–94]. In SAMP1/YitFc mice, an animal model of spontaneous CD-like ileitis, anti-TNF-α normalizes the increased inflammatory IEC death in these mice [95]. Anti-TNF-α has also been reported to downregulate IEC death and restore the epithelium barrier in a subset of CD patients undergoing anti-TNF-α therapy [96, 97]. In the clinic, a subgroup of patients does not respond to anti-TNF-α therapy within 4–12 weeks after initiation of therapy [98–100]. These patients show little or no changes of clinical symptoms and no macroscopic mucosal healing upon anti-TNF-α therapy but are potentially exposed to side effects of this type of therapy, such as infections, reactivation of tuberculosis, allergic reactions, skin or demyelinating disorders, and lupus-like autoimmunity [101]. Anti-TNF-α therapy may fail due to TNF-α-independent gut inflammation, insufficient dosing [102], or development of anti-drug antibodies in 37–61% of patients that ultimately lead to suboptimal serum levels of the biotherapeutic [103, 104]. The precise mechanisms of action of anti-TNF-α in IBD are not well defined. Apoptosis of lamina propria T cells that mediate intestinal inflammation is proposed to be the main mechanism [105–109] blocking the interaction between membrane-bound TNF-α on macrophages and TNF-α receptor TNFR2 on T cells. Besides T cells, IEC express both TNF-α receptors, TNFR1 and TNFR2, and can also serve as a target of TNF-α. The anti-TNF-α benefits that have been reported in some responder patients include fistula closure in CD [90, 110] and mucosal healing in both CD and UC [89, 111]. Mucosal healing

has emerged as a new therapeutic goal and an important correlate of long periods of clinical remission [87–94]. In that respect, how anti-TNF-α therapy impacts IEC death and healing of the intestinal epithelium has not been studied extensively. In patients undergoing anti-TNF-α therapy, a significant decrease in the levels of IEC apoptosis has been noted suggesting that TNF neutralization may rescue IEC from premature death [64, 96]. Gaining a better understanding of the mechanisms for how anti-TNF-α therapy works and why it fails is essential.

Implications of intestinal epithelial cell death for immune-mediated intestinal homeostasis

Despite the fact that apoptosis is a normal component of the physiology of the intestine, its impact on the immune mechanisms of gut homeostasis is poorly understood. Perhaps a major reason for this is the paradigm that IEC are merely shed into the gut lumen as part of natural intestinal epithelial turnover and with no consequence on immune homeostasis. However, as discussed here, IEC begin to signal their extrusion, for example by producing S1P, at very early stages of apoptosis and before many of the characteristic markers of apoptosis become detectable. Even if the majority of IEC are extruded live (and undergo apoptosis post shedding), and only a small fraction of IEC initiate apoptosis as a prelude to shedding, the sheer number of IEC in the order of 10^{10} that are shed daily makes this small fraction quite substantial. Intestinal homeostasis is maintained through innate and adaptive functions of intestinal lamina propria dendritic cells and macrophages [58], modulation by CD4 T helper 17 and regulatory T cell (T_{REG}) cytokines such as IL-17, IL-22, IL-10 and TGF-β [112–120], and innate lymphoid cells (ILC), particularly IL-22-producing ILC3, which maintain epithelial barrier integrity and mediate an early repair response to the damaged epithelium [121, 122]. How IEC apoptosis under healthy steady state conditions impacts gut homeostasis is an important question that has been little explored. Clearance of apoptotic cells by professional phagocytes is known to induce immune tolerance [123, 124]. While most studies have focused on intestinal phagocyte sampling of commensals and pathogens [125–130], only one study in rats has examined phagocyte sampling of apoptotic IEC [131]. Interestingly, disruption of apoptotic cell uptake in mice deficient for the phagocytic receptor BAI1 made these mice more susceptible to colitis and conversely, mice overexpressing BAI1 had attenuated disease [132]. Surprisingly, BAI1 mediated effects did not appear to be dependent on phagocytes such as macrophages, but rather BAI1 expression in colonic epithelial cells, which engulf apoptotic cells within the colon, was sufficient to dampen colitis [132]. A different study has shown that phosphatidylserine on apoptotic IEC, acting through the inhibitory receptor CD300, suppresses commensal driven IFN-β production by intestinal lamina propria $CD11c^{+}CD11b^{+}CX3CR1^{+}CD103^{-}$ dendritic cells, and consequently IFN-β dependent T_{REG} cell proliferation [133]. Here, $CD300a^{+}CD11c^{+}$ cells were found in proximity to apoptotic IEC [133]. Further investigations are a must in gaining a full understanding of the mechanisms by which apoptotic IEC contribute to intestinal tolerance and homeostasis. The knowledge we gain will provide additional much needed avenues for therapeutic intervention and prevention in IBD.

Acknowledgments

The studies cited in this review are not inclusive of the vast literature on cell death in the intestinal epithelium. Readers are encouraged to also refer to the review articles cited here and references therein in order to gain a full appreciation of different and additional aspects of the biology not discussed here. J.M.B. and her laboratory are supported by NIH grants DK072201, AI095245 and AI123284, the Burroughs Wellcome Fund, and a Leukemia and Lymphoma Society Scholar Award.

Abbreviations

IEC
intestinal epithelial cells

IBD
inflammatory bowel disease

TNFa (a in symbol as alpha)
Tumor necrosis factor alpha

M cells
microfold cells

MUC2
mucus 2

TUNEL
terminal deoxynucleotidyl transferase dUTP nick end labeling

S1P
sphingosine 1 phosphate

MLC
myosin light chain

ROCK
Rho-associated kinase

p115 RhoGEF
RHO guanine nucleotide exchange factor 1

APC
adenomatous polyposis coli

MLCK
myosin light chain kinase

FADD
Fas-associated via death domain

RIPK3
receptor interacting protein kinase 3

CYLD
Cylindromatosis (turban tumor syndrome)

CD
Crohn's disease

UC
ulcerative colitis

TCA cycle
Tricarboxylic acid (TCA) cycle

GWAS
genome wide association studies

ARE
AU-rich elements

pIgR
polymeric immunoglobulin receptor

TNFAIP3
Tumor necrosis factor, alpha-induced protein 3, also known as A20

TNFR2
TNF-a (symbol alpha) receptor 2

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