

# An innately dangerous balancing act: intestinal homeostasis, inflammation, and colitis-associated cancer

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**Inflammatory bowel disease (IBD) is characterized by dysregulated immune responses to the intestinal microbiota, and by chronic intestinal inflammation. Several recent studies demonstrate the importance of innate microbial recognition by immune and nonimmune cells in the gut. Paradoxically, either diminished or exacerbated innate immune signaling may trigger the breakdown of intestinal homeostasis, leading to IBD and colitis-associated cancer (CAC). This dichotomy may reflect divergent functional roles for immune sensing in intestinal epithelial cells and leukocytes, which may vary with distinct disease mechanisms.**

Much evidence supports the central contribution of the microbiota to intestinal health and disease. Although it plays beneficial roles in host development, metabolism, and defense, the relationship between the microbiota and host can break down, culminating in IBD. With few exceptions, murine models of intestinal inflammation are attenuated in germ-free animals (Strober et al., 2002). In humans, both antibiotic treatment and diversion of the fecal stream can similarly attenuate disease in some Crohn's disease (CD) patients (Rutgeerts et al., 1991; Perencevich and Burakoff, 2006). CD clinical symptoms also tend to develop in the terminal ileum and colon, the sites of the intestine with the highest bacterial load (Sartor, 2008).

Genetic association studies have linked pattern recognition receptors (PRRs) that mediate microbial sensing with the development of IBD. These include *NOD2* and *NLRP3* (Hugot et al., 2001; Ogura et al., 2001; Villani et al., 2009) as well as multiple *TLR*

genes (De Jager et al., 2007; Pierik et al., 2006; Török et al., 2004). However, the functional characterization of PRRs in IBD is just starting to be unraveled. Recent studies published in this journal (Salcedo et al. [this issue]; Allen et al., 2010) and elsewhere (Dupaul-Chicoine et al., 2010; Zaki et al., 2010) provide fresh insights into the regulation of intestinal inflammation and carcinogenesis by the signaling pathways triggered by these innate sensors. These studies also highlight the diverse functions of microbial sensing in intestinal homeostasis.

## Epithelial protection

One hallmark of IBD is disruption of the intestinal epithelium. Normally, maintenance of the intestinal epithelium involves a dynamic process in which intestinal stem cells (ISCs) located at the crypt base undergo differentiation, proliferation, and migration along the crypt-villus axis. At the end of this journey, intestinal epithelial cells (IECs) undergo apoptosis. These processes appear to be dysregulated in the inflamed mucosa of IBD patients, which exhibit hyperplasia, goblet cell depletion, and enhanced apoptosis. More severe damage may manifest as either total epithelial destruction and ulceration, or dysplasia and progressive tumorigenesis. Because IECs and intestinal leukocytes both express PRRs, downstream signaling has the potential

to affect epithelial homeostasis at several levels.

A landmark study using a mouse colitis model in which dextran sodium sulfate (DSS) acutely damages the intestinal epithelium demonstrated that *Myd88*<sup>-/-</sup> mice (deficient in Toll-like receptor [TLR], interleukin 1 receptor [IL-1R], and IL-18R signaling) develop significantly enhanced disease compared with wild-type mice (Rakoff-Nahoum et al., 2004). In this context, innate signals are clearly protective and promote epithelial integrity via several mechanisms. These include the induction of antiapoptotic and cytoprotective factors and the promotion of tight junction formation (Rakoff-Nahoum et al., 2004; Cario et al., 2007; Kim et al., 2009). Moreover, microbial sensing by PRRs drives the recruitment of stromal and myeloid cells to the ISC niche, thereby facilitating regeneration of the epithelium after injury (Pull et al., 2005; Brown et al., 2007). In addition to facilitating epithelial renewal, PRR activation may limit bacterial translocation by inducing the production of antimicrobial peptides, such as defensins and RegIIIγ, by IECs (Kobayashi et al., 2005; Brandl et al., 2007; Nenci et al., 2007). These functions are partially mediated by activation of NF-κB- and PI3-Akt-dependent pathways in IECs (for review see Cario, 2008). For example, mice whose IECs lack NEMO (NEMO<sup>IEC-KO</sup>), a component of the IκB kinase required for NF-κB activation, develop spontaneous intestinal inflammation (Nenci et al., 2007).

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Recent studies also support a role for NOD-like receptor (NLR)-mediated inflammasome activation in maintaining epithelial integrity (Allen et al., 2010; Dupaul-Chicoine et al., 2010; Zaki et al., 2010). *Nlrp3*<sup>-/-</sup>, *Pycard*<sup>-/-</sup>, and *Casp-1*<sup>-/-</sup> mice, which lack the inflammasome signaling components Nlrp3, Asc, and caspase-1, respectively, all exhibit enhanced DSS-induced colitis compared with wild-type controls (Allen et al., 2010; Dupaul-Chicoine et al., 2010; Zaki et al., 2010). These findings are consistent with a protective role for NLR signaling in this model, analogous to that of MyD88 signaling. Indeed, because microbial stimuli and host danger signals, such as uric acid, extracellular ATP, and reactive oxygen species, synergize to activate the inflammasome (Franchi et al., 2009), acute epithelial damage in the microbe-rich gut may create a potent niche for such regulation. However, the question of whether inflammasome activation in epithelial or hematopoietic cells confers this protection has produced mixed findings (Allen et al., 2010; Dupaul-Chicoine et al., 2010; Zaki et al., 2010).

A major effector function of inflammasome-mediated activation of caspase-1 is the processing of pro-IL-1 $\beta$  and pro-IL-18 into their active forms. Tellingly, *Il1r*<sup>-/-</sup>, *Il18r*<sup>-/-</sup>, and *Il18*<sup>-/-</sup> mice exhibit enhanced DSS-induced colitis compared with wild-type controls (Takagi et al., 2003; Lebeis et al., 2009; Salcedo et al., 2010), and recombinant IL-18 can attenuate disease (Dupaul-Chicoine et al., 2010; Zaki et al., 2010), supporting a role for inflammasome-derived mediators in epithelial repair. Crucially, because MyD88 is a signaling adaptor shared by IL-1R, IL-18R, and TLRs, its indirect activation by NLRs and/or direct activation by TLRs may be a key event in the restoration of epithelial function. Nonetheless, the role of IL-1 and IL-18 in intestinal inflammation remains contentious, given that earlier studies support a pathogenic role of these cytokines (for review see Siegmund, 2002).

A comparable and perhaps more physiological model where TLR or

IL-1R family signals limit colitis is that induced by the attaching and effacing bacterium *Citrobacter rodentium*. Indeed, increased numbers of mucosally associated adherent-invasive *Escherichia coli* have been reported in CD and UC patients (Rolhion and Darfeuille-Michaud, 2007). Infected *Myd88*<sup>-/-</sup> mice exhibit delayed neutrophil recruitment and enhanced bacterial outgrowth in the intestinal mucosa with pronounced ulceration, bleeding, and mortality (Lebeis et al., 2007; Gibson et al., 2008a). In this context, dysregulated epithelial restitution and repair is compounded by pathogen outgrowth and further immune activation. However, some PRRs may contribute more to immune pathology than to protective immunity. For example, *Tlr4*<sup>-/-</sup> mice develop protective immunity to *C. rodentium*, but develop less severe intestinal pathology than infected wild-type mice (Khan et al., 2006). This pathogenic role of TLR4 contrasts with that of TLR2 and IL-1R, which both limit *C. rodentium*-induced inflammation (Gibson et al., 2008b; Lebeis et al., 2009).

### Chronic inflammation

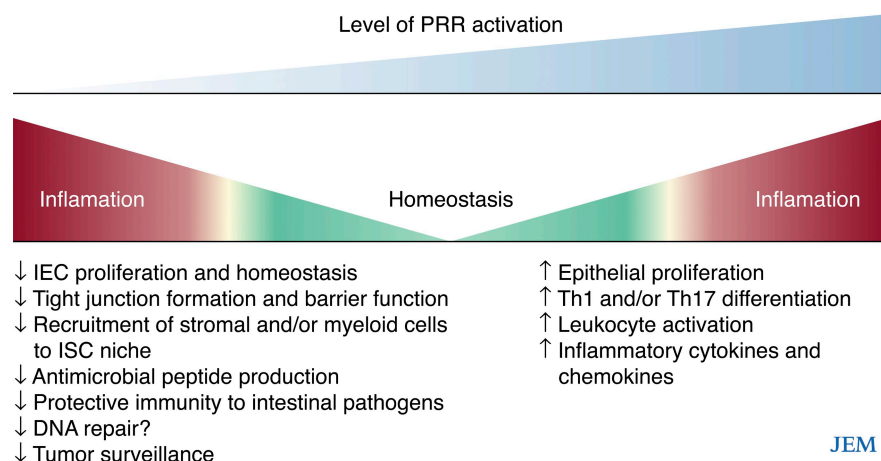
These broadly protective roles for gut TLR and inflammasome signals in acute intestinal inflammation contrast starkly with pathogenic roles played by these signals in the *Il10*<sup>-/-</sup> or *Helicobacter hepaticus*-induced chronic colitis models. MyD88 signaling promotes spontaneous colitis in both *Il10*<sup>-/-</sup> mice and *LysM*<sup>Stat3KO</sup> mice; the latter mice are rendered hyporesponsive to IL-10 by a myeloid cell-specific deletion of Stat3 (Kobayashi et al., 2003; Rakoff-Nahoum et al., 2006). Moreover, we have recently shown that colitis induced by *H. hepaticus* colonization of RAG<sup>-/-</sup> mice requires *MyD88* expression by hematopoietic cells (Asquith et al., 2010). Together, these findings suggest that a failure to regulate TLR/IL-1R family-dependent activation of myeloid cells in the presence of a triggering microbiota can precipitate chronic intestinal inflammation.

A key difference in these chronic colitis models is that damage to the epithelium is likely secondary to the

microbiota-driven inflammatory response mediated by tissue-resident leukocytes. This notion is supported by the spontaneous colitis that occurs in *Nemo*<sup>IEC-KO</sup> mice, in which tumor necrosis factor produced by MyD88-activated myeloid cells is thought to drive epithelial apoptosis (Nenci et al., 2007). In contrast, acute epithelial disruption by DSS or *C. rodentium* infection may be a primary pathophysiological mechanism, with gross disruption of the epithelium allowing MyD88-independent activation by the intestinal microbiota. In this acute disease setting, the epithelial repair functions of MyD88 play a protective role, promoting restoration of epithelial barrier function and a return to homeostasis. It will be of interest to extend studies of inflammasome function to chronic colitis models with distinct pathophysiological mechanisms.

### Tumorigenesis

Intestinal tumorigenesis is intimately linked to intestinal inflammation, and by extension to microbial sensing by PRRs. Intestinal tumors may originate from dysplastic epithelial or intestinal stem cells, and are infiltrated by several cell types, including lymphoid and myeloid cells (Terzic et al., 2010). Evidently, as in models of colitis, in models of CAC, PRR signals may modulate the neoplastic and infiltrating leukocyte populations distinctly, complicating the dissection of their role in CAC pathophysiology. Several previous studies have indicated that signals mediated by the TLR/IL-1R family promote intestinal tumorigenesis. For example, TLR4 is up-regulated in both human and mouse neoplastic lesions of the inflamed intestine and promotes CAC in mice treated with the chemical procarcinogen azoxymethane (AOM) followed by DSS (Fukata et al., 2007). In addition, the size and frequency of adenocarcinomas in *Apc*<sup>Min+/-</sup> mice, which express a mutant version of the tumor suppressor gene APC, are greater than in *Apc*<sup>Min+/-</sup> *MyD88*<sup>-/-</sup> mice (Rakoff-Nahoum and Medzhitov, 2007). Moreover, *Il10*<sup>-/-</sup> mice treated with AOM develop MyD88-dependent CAC (Uronis et al., 2009).



**Figure 1. Diminished or enhanced intestinal PRR signals may promote intestinal inflammation and tumorigenesis.** PRR signals are maintained at a critical threshold to maintain intestinal homeostasis. PRR signals may be required to restore barrier function after epithelial insult and for protective immunity against pathogens; impairment of these processes caused by insufficient PRR signaling may result in pathogen outgrowth and, indirectly, excessive subsequent inflammation (left). Excessive PRR-driven repair or inflammatory responses (right) may also threaten homeostasis, e.g., through dysregulated epithelial proliferation leading to tumorigenesis and overexuberant pathogenic inflammatory responses to the intestinal microbiota.

In contrast to the tumorigenic role of TLR4 signals in the DSS + AOM model, the Nlrp3 inflammasome and MyD88 signals prevent CAC in this setting. This paradox remains unresolved. However, whereas epithelial TLR4 signals promote tumorigenesis (Fukata et al., 2009), hematopoietic Nlrp3 activation may be required for protection (Allen et al., 2010). Thus, distinct compartmentalized roles may underscore these divergent functions. Alternatively, MyD88-independent TLR4 signaling through the adaptor TRIF may play a role, and merits further investigation.

When treated with DSS, *MyD88*<sup>-/-</sup> (Fukata et al., 2005; Rakoff-Nahoum et al., 2004), *Nlrp3*<sup>-/-</sup>, and *Casp-1*<sup>-/-</sup> mice exhibit enhanced epithelial apoptosis and diminished or comparable epithelial proliferation relative to DSS-treated wild-type mice (Zaki et al., 2010). Rather counterintuitively, *MyD88*<sup>-/-</sup>, *Nlrp3*<sup>-/-</sup>, and *Casp-1*<sup>-/-</sup> mice show enhanced tumorigenesis compared with wild-type mice if also treated with AOM (Allen et al., 2010; Salcedo et al., 2010). A possible explanation provided by Salcedo et al. (2010) is that *MyD88*<sup>-/-</sup> mice treated with AOM +

DSS exhibit down-regulation of multiple DNA repair genes and have a higher frequency of mutations in the oncoprotein  $\beta$ -catenin, specifically in the domain required to target the protein for degradation. This indicates that failed repair of DNA damage in *MyD88*<sup>-/-</sup> mice may render epithelial cells prone to deregulation of the cell cycle and tumor progression, despite their increased propensity for cell death. Nonetheless, untreated *MyD88*<sup>-/-</sup> mice exhibit “normal” expression of DNA repair genes (Salcedo et al., 2010), suggesting that this is a downstream effect of enhanced inflammation in these mice.

Excessive TLR/IL-1R-driven signaling can itself drive proinflammatory responses that fuel tumorigenesis, as shown by the MyD88-dependent development of CAC in *Il10*<sup>-/-</sup> mice treated with AOM (Uronis et al., 2009). Moreover, the removal of negative regulators of TLR/IL-1R family and inflammasome signaling, such as Tir8 or caspase-12, respectively, also leads to increased colitis and CAC in the DSS + AOM model (Dupaul-Chicoine et al., 2010; Garlanda et al., 2007). In addition to excessive production of inflammatory cytokines in these mice, hyperproliferative

epithelial repair responses may also drive tumorigenesis.

PRR signals may also modulate tumorigenesis independently of their pathogenic and protective roles in inflammation. This is exemplified by *Apc*<sup>Min+/-</sup> mice, which model familial adenomatous polyposis patients with mutations in the APC gene who develop intestinal polyps and colorectal cancer early in life. TLR-MyD88 signals promote tumorigenesis in these mice, partially through stabilization of oncoprotein c-Myc, which induces epithelial hyperproliferation and inhibits apoptosis (Lee et al., 2010). In this case, the presence of a genetic lesion such as APC mutations may divert the homeostatic function of PRR signaling toward tumorigenesis.

### Concluding remarks

Functional analyses of PRR pathways in intestinal homeostasis have revealed a complex picture with evidence for both protective and pathogenic roles. Optimally, PRR-signaling should be maintained at a homeostatic level at which tissue repair and host defense are preserved (Fig. 1). Beyond this middle ground, immune pathology can result from either impaired or exuberant PRR responses. A key challenge now is to translate these diverse functions of PRR in different animal models to determine which pathophysiological mechanisms underpin distinct forms of IBD and CAC. For example, ablation of PRR-driven leukocyte activation may limit pathogenesis in some settings, but may prove futile, and even exacerbate symptoms, if barrier dysfunction is the primary disease mechanism. Careful dissection of PRR-signaling networks in different cellular compartments and in acute and chronic models of intestinal inflammation is an important first step in designing rational therapeutic strategies designed to restore PRR-mediated intestinal homeostasis in IBD.

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