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Regulation of the gut microbiome by inflammasomes

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Abstract

Inflammasomes are multiprotein complexes whose primary function is to activate caspase-1, which allows the cleavage of pro-IL-1β and pro-IL-18 to their mature forms. The production of these cytokines has been shown to be critical for host defense as well as the maintenance of intestinal homeostasis and protection against pathologic intestinal inflammation. More recently, there has been growing evidence that inflammasomes are also capable of regulating the composition of the gut microbiota in mice models, which has significant implications for intestinal health and disease. Specifically, the absence of inflammasome components has been associated with pathologic alterations in the gut microbiota, or dysbiosis, that can result in increased susceptibility to colitis and tumorigenesis. In this review, evidence that inflammasome signaling is important for promoting a healthful microbiome and potential mechanisms by which inflammasomes modulate the gut microbiome will be presented. A better understanding of the function of inflammasomes in microbiome regulation may lead to the development of effective strategies for the prevention and treatment of diseases driven by dysbiosis.

Keywords

inflammasomes; IL-18; microbiome; colitis

I. Introduction

Alterations in the gut microbiota that are associated with the pathogenesis of multiple diseases, including inflammatory bowel disease, colorectal cancer, and metabolic disorders, have often been collectively termed dysbiosis. However, factors that contribute to the development of dysbiosis remain to be fully understood. There is increasing evidence that host immunity plays a significant role in shaping of the gut microbiome. In particular, innate immune receptors that participate in inflammasome assembly and activation have been implicated in regulating the composition of the gut microbiota, and deficiencies in these receptors have been associated with perturbations in the gut microbiome that are associated with susceptibility to systemic and intestinal diseases in mice models. In this review, the

function of inflammasomes and the consequences of inflammasome deficiency as it pertains to perturbations in the microbiome and disease susceptibility will be discussed.

II. Inflammasomes: regulators of IL-1β and IL-18 production

A hallmark of canonical inflammasome signaling is the activation of caspase-1, whose primary function is to cleave biologically inactive pro-IL-1β and pro-IL-18 to their mature, active forms[1]. Caspase-1 activation also leads to a specific form of macrophage cell death that usually occurs during infection, known as pyroptosis, which enables the release of intracellular cytokines important for host defense[2]. Inflammasomes are multiprotein complexes typically consisting of a pattern recognition receptor (PRR) belonging to either the Nod-like receptor (NLR) or the absent in melanoma (AIM)-2 like receptors (ALR) family[3]. A common feature of these receptors that participate in inflammasome assembly is the presence of a pyrin (PYD) domain, which is capable of interacting with the pyrin domain of the inflammasome adaptor protein ASC upon receptor activation. ASC also contains a caspase recruitment domain (CARD), and thus, recruitment of ASC allows the binding of the CARD-domain containing procaspase-1 through homotypic protein interactions. As certain NLRs also contain CARD domains, procaspase-1 may directly be recruited through interactions with these NLRs without the requirement for ASC. Thusfar, there have been 5 bona fide inflammasomes identified as evidenced by formation of inflammasome complexes and/or caspase-1 activation upon recognition of ligand, which includes both microbial-derived pattern-associated molecular patterns (PAMPs) or endogenous tissue injury-related damage-associated molecular patterns (DAMPs). These are the NLR containing, NLRP1, NLRP3, and NLRC4 inflammasomes, the ALR containing AIM2 inflammasome, and the pyrin inflammasome[1, 4–10]. The upstream signals for these inflammasomes are relatively well-defined and can be both microbial- and/or host-derived. For example, the lethal toxin of *Bacillus anthracis* and flagellin are PAMPs that activate the NLRP1 and NLRC4 inflammasomes, respectively[4, 11]. The AIM2 inflammasome recognizes cytosolic double-stranded DNA released by either pathogens or fecal microbiota[6–8, 12], but can also sense host DNA aberrantly located in the cytosol[13]. Although cyclic GMP-AMP synthase (cGAS) is also an intracellular DNA sensor, its function is distinct from that of AIM2 in that it induces Type I IFNs, which in turn, potentiates the activity of AIM2[14–16]. The NLRP3 inflammasome is unique in that it responds to a diverse array of stimuli, both microbial and non-microbial, such as bacterial pore-forming toxins, particulate matter, oxidized mitochondrial DNA, and extracellular ATP[17–22]. Collectively, these various stimuli can be linked to cellular injury and changes in homeostasis, and therefore, it is likely that NLRP3 senses a common downstream signal such as changes in cytosolic potassium ion concentration[21]. Whether inflammasomes such as AIM2 or NLRP3 respond differently to endogenous versus microbial activators remains to be determined.

More recently, the NLR family member NLRP6 has been considered to be capable of forming an inflammasome based on data demonstrating colocalization of NLRP6 with ASC in a prototypical speckled pattern, and impaired IL-18 production and caspase-1 activation in the colons of NLRP6-deficient mice[23–26]. However, the precise signal leading to assembly of an “NLRP6 inflammasome” remains unknown, making it difficult to definitively prove that NLRP6 activation is directly linked to activation of caspase-1. Levy *et al.* reported that

IL-18 production within the colon is regulated by microbial metabolites, in particular, taurine, which was sufficient to induce caspase-1 activation and IL-18 production in the colons of GF mice fed taurine in the drinking water[26]. Interestingly the ability of taurine to induce IL-18 was dependent on NLRP6, suggesting that taurine may be an upstream activator of NLRP6[26].

NLRP12 is another member that is also believed to be capable of functioning as part of an inflammasome under certain conditions based on early data demonstrating caspase-1 activation in transfection experiments *in vitro* using caspase-1, ASC, and NLRP12 expression plasmids[27]. In addition, *Nlrp12*$^{-/-}$ bone marrow-derived macrophages exhibited decreased caspase-1 activation and impaired secretion of both IL-1β and IL-18 in response to the pathogen *Yersinia*[28]. It is important to note that the activities of NLRP12 and NLRP6 are not necessarily limited to IL-1β or IL-18 production, respectively. For example, both have been suggested to negatively regulate NFκB and MAPK activation in response to microbial ligands[29–31]. In addition, NLRP6 has been shown to bind viral RNA via the RNA helicase Dhx5 and is capable of regulating Type I/II IFN responses to mediate resistance to viral infection in a caspase-1-independent process[32].

III. Inflammasomes: regulators of intestinal homeostasis

As proinflammatory cytokines, IL-1β and IL-18 have important functions in host defense. For example, IL-18 promotes Th1 responses by inducing IFNγ production[33], and IL-1β induces neutrophil influx, activates both myeloid cells and lymphocytes, and promotes Th17 differentiation[34]. Although elevated levels of IL-1β and IL-18 have been observed in patients with inflammatory bowel disease (IBD), mouse models of chemically-induced colitis using dextran sulfate sodium (DSS) have suggested that inflammasomes are important for maintaining intestinal homeostasis and reducing susceptibility to DSS-induced morbidity and mortality. More specifically, mice deficient in NLRP1, NLRP3, NLRP6, NLRP12, AIM2, or ASC have greater weight loss, significantly greater induction of proinflammatory mediators and increased inflammation and epithelial damage within the colon[12, 24, 25, 30, 31, 35–39](Table I). Similarly, susceptibility to colitis associated tumorigenesis using the (azoxymethane) AOM/DSS model in which mice are administered the carcinogen AOM followed by multiple rounds of colitis-inducing DSS, was also increased[12, 25, 30, 31, 35, 36, 39, 40]. With the exception of NLRP12, which was shown to negatively regulate NFκB and MAPK signaling to limit colitis and tumorigenesis, a common mechanism by which NLRP3, NLRP6 and AIM2 reduces colitis susceptibility is through the production of IL-18, which is important for tissue repair, epithelial restitution and consequently resolution of inflammation[24, 25, 41, 42]. Although IL-1β levels were also observed to be low in *Nlrp1*$^{-/-}$ and *Nlrp3*$^{-/-}$ mice, IL-1β levels were markedly elevated in *Nlrp6*$^{-/-}$ and *AIM2*$^{-/-}$ mice, suggesting that IL-1β is not necessarily protective in this model and that the production of IL-1β and IL-18 are not coupled[25, 35, 38]. Importantly, administration of recombinant IL-18 into *caspase-1*$^{-/-}$, *Nlrp1*$^{-/-}$ or *Nlrp3*$^{-/-}$ mice ameliorated colitis[35, 37, 42]. Furthermore, *IL-18*$^{-/-}$ mice also developed more severe colitis after DSS treatment[41]. However, unlike mice fully deficient in IL-18, mice in which IL-18 is conditionally knocked out in either the epithelial or hematopoietic compartments resulted actually in protection against DSS-induced colitis, suggesting that concerted IL-18

production by different cell types may affect disease outcomes. Indeed, bone marrow chimera experiments have yielded conflicting results regarding the relative importance of inflammasome signaling in the epithelial versus hematopoietic compartment. Non-hematopoietic cells are the predominant sources of IL-18 production and studies by Elinav *et al.*, have suggested that non-hematopoietic production of IL-18 is associated with protection against DSS-induced colitis[24, 25]. However, IL-18 production by inflammatory monocytes reduced DSSinduced mortality in *Nlrp6*$^{-/-}$ mice[43]. Conflicting results were also observed with bone marrow chimera experiments to determine the relative importance of NLRP3 signaling in epithelial versus hematopoietic cells with one study demonstrating the importance of intact NLRP3 signaling in bone marrow-derived cells to reduce colitis susceptibility, but non-hematopoietic cells in another[36, 37]. These inconsistencies highlight the complexity of inflammasome signaling and may also reflect differences in experimental setup as well as other contributory factors such as facility-dependent differences in the gut microbiota.

Despite the redundant activities of the different inflammasomes, it is also not clear why colitis susceptibility as a result of deficiency in any one inflammasome is not compensated by other functional inflammasomes. One possibility is that there are innate immune receptor-specific activities beyond IL-18 production that contribute to intestinal homeostasis. For example, NLRP6 also regulates goblet cell function through autophagy pathways as well as promotes Muc2 secretion in response to bacterial signals, both of which are important for maintaining an intact mucus layer that provides an effective barrier against bacterial-driven inflammation[44, 45]. As each of the inflammasomes respond to different upstream signals, the presence or absence of these signals and the magnitude of response may also dictate the relative contributions of the different inflammasomes during inflammation.

IV. Inflammasome deficiency is associated with disease-promoting dybiosis

Reduction in the severity of DSS-induced colitis with antibiotic treatment provided the first evidence that the gut microbiota contributes significantly to the phenotype of inflammasome-deficient mice[24, 35]. Additional evidence was provided by cohousing wildtype (WT) with inflammasome-deficient mice or crossfostering WT or inflammasome-deficient mice with mothers of the opposite genotype, which demonstrated the transmissibility of colitis through transfer of microbiota. In a seminal study by Elinav *et al.,* when WT mice were either cohoused for 4 weeks with *Asc*$^{-/-}$ mice or crossfostered at birth with *Asc*$^{-/-}$ mothers, they developed more severe colitis comparable to that of singly housed mice, which strongly suggested that *Asc*$^{-/-}$ mice harbored colitogenic bacteria that can be transferred into WT mice to increase colitis susceptibility. Cohousing WT with susceptible caspase-1-deficient mice revealed similar results, with cohoused WT mice developing more severe colitis than singly housed, non-cohoused WT mice. With additional cohousing experiments between WT and different NLR members associated with inflammasome activity, it was determined that only *Nlrp6*$^{-/-}$ mice was capable of transmitting increased colitis susceptibility to WT mice[24]. On the other hand, WT mice cohoused with AIM2-, NLRP12-, or NLRC4-deficient mice did not develop worse colitis symptoms than singly housed WT mice. Based on these experiments, it was concluded that inflammasome-deficient mice and specifically, NLRP6–deficient mice, harbored an altered microbiome

characterized by the enrichment of potentially colitogenic bacteria that can be transferred to WT mice upon cohousing or crossfostering. Indeed, conventionalized germfree (GF) *Nlrp6*$^{-/-}$ mice developed a microbiome that resembled that of specific-pathogen free (SPF) *Nlrp6*$^{-/-}$ mice and distinct from that of conventionalized GF WT[26].

To identify potentially colitogenic bacteria that were increased in abundance in SPF *Nlrp6*$^{-/-}$ mice, 16S rRNA sequencing was performed on the fecal microbiota, and *Prevotella*, a member of the family *Prevotellaceae* as well as the phylum TM7 were identified to be significantly associated with *Nlrp6*$^{-/-}$, *Asc*$^{-/-}$, *caspase1*$^{-/-}$, *IL-18*$^{-/-}$ and cohoused WT mice that developed severe DSS-induced colitis. However, whether the accumulation of these bacterial populations are truly regulated by inflammasome activity or merely reflect colony-specific changes remain to be determined. Nonetheless, antibiotic treatment of *Nlrp6*$^{-/-}$ mice leading to reduction in the relative abundance of *Prevotellaceae* resulted in amelioration of colitis symptoms although this result suggests only a correlation and not a direct causal relationship between *Prevotellaceae* abundance and colitis susceptibility[24].

In addition to colitis, *Asc*$^{-/-}$, *caspase1*$^{-/-}$, *Nlrp3*$^{-/-}$, or *Nlrp6*$^{-/-}$ mice are also more susceptible to the development of non-alcoholic fatty liver disease (NAFLD) than WT mice when mice are fed a methionine-choline-deficient diet[46]. This phenotype was transmissible to WT mice upon cohousing, suggesting that the severity of NAFLD is, in part, dependent on the microbiome. Comparison of the microbiomes of WT mice that were singly-housed or cohoused with *Asc*$^{-/-}$ mice confirmed the increased abundance of *Prevotellaceae* in WT mice cohoused with *Asc*$^{-/-}$ mice although this was not maintained upon change in diet. Rather, there was a significant expansion in bacterial members belonging to the family *Porphyromonadaceae* in WT mice cohoused with *Asc*$^{-/-}$ mice compared to singly housed WT mice after placement on a methioninecholine- deficient diet to induce NAFLD. These experiments suggest only a correlation between abundance of *Porphyromonodaceae* and therefore, additional experiments involving GF monoassociation studies will be helpful to determine a causal relationship between *Prevotellaceae* and *Porphyomondaceae* and the severity of colitis and NAFLD, respectively.

Elinav *et al.* previously reported that cohousing WT mice with *Aim2*$^{-/-}$ or *Nlrp12*$^{-/-}$ mice did not result in exacerbated DSS-induced colitis[24]. However, Hu *et al.* demonstrated amelioration of DSS-induced colitis in *Aim2*$^{-/-}$ mice after cohousing with WT mice, suggesting that WT mice may harbor protective bacteria populations that can be transferred to *Aim2*$^{-/-}$ mice although the possibility that the cohousing that was performed in this study was insufficient to permit transfer of potentially colitogenic bacteria found in *Aim2*$^{-/-}$ mice[38]. Regardless, GF mice colonized with the microbiota of *Aim2*$^{-/-}$ mice developed more severe colitis than GF WT mice colonized with WT microibota suggesting that the microbiome associated with AIM2-deficiency can confer increased colitis susceptibility. Similarly, in a separate study by Man *et al.*, AIM2 deficiency was associated with increased susceptibility to colitis-associated tumorigenesis, which decreased after cohousing with WT mice[47]. Based on a survey of the abundance of various bacterial populations by qPCR, Hu *et al.* did not observe an enrichment of *Prevotellaceae* or TM7 in *Aim2*$^{-/-}$ mice unlike in *Nlrp6*$^{-/-}$ mice. However, there were significantly increased levels of bacteria belonging to the family *Enterobacteriaceae* and, in particular, *E. coli*. In the study by Man *et al.*, a more

comprehensive survey by 16S rRNA sequencing was performed on mice feces and demonstrated instead relatively increased abundances of *Akkermansia muciniphila* and *Anaeroplasma* species, but decreased abundances of *Prevotella, Anaerostipes*, and *Paraprevotella* species in single housed *Aim2*$^{-/-}$ mice compared to that of WT, which was reversed upon cohousing with WT mice, suggesting that the enrichment or depletion of these bacterial populations can modulate tumor susceptibility. This study did not identify *Enterobacteriaceae*, which may be related to facility-dependent differences in microbiota. However, this also raises questions on whether the observed differences in microbiota can be directly attributed to AIM2 deficiency as it is unclear whether the microbiome analysis was performed on *Aim2*$^{-/-}$ and WT littermates. Additional experiments looking at heterozygote matings and conventionalization of GF WT and *Aim2*$^{-/-}$ mice will help resolve this issue.

Although less well-characterized, the microbiomes of NLRP1 or NLRP3-deficient mice have also been suggested to be different from that of WT mice. Terminal restriction fragment polymorphism analysis of the fecal microbiota of WT mice derived from littermates of *Nlrp3*$^{-/-}$ mice showed significant differences in the microbiome composition compared to that of WT mice[48]. Specifically, they identified several bacterial genera that were differentially abundance between the two genotypes, including the enrichment of *Enterobacteriaceae* in *Nlrp3*$^{-/-}$ mice. However, which of these differentially abundance bacterial populations are responsible for the disease phenotype remains unknown. There is also data suggesting that NLRP1-deficient mice have increased susceptibility to colitis, which is improved with antibiotics and can be transferred to WT mice upon cohousing, but it remains to be determined as well whether NLRP1 truly regulates the gut microbiota.

How bacterial populations that accumulate in the gut of inflammasome-deficient mice promote disease remains to be fully elucidated, but may be related to their ability to upregulate the production of proinflammatory mediators such as CCL5, IL-6 and TNF-α. Elinav *et al.* reported that their naive *Nlrp6*$^{-/-}$ mice exhibited low, subclinical levels of intestinal inflammation associated with elevated levels of CCL5, a chemokine that induces the recruitment of immune cells[24]. The increased production of CCL5 in *Nlrp6*$^{-/-}$ mice was attributed to host responses to colitogenic bacteria residing in *Nlrp6*$^{-/-}$ mice since CCL5 levels were upregulated in WT mice upon cohousing with *Nlrp6*$^{-/-}$ mice. Despite the increased relative abundance of *Prevotellaceae* in *CCL5*$^{-/-}$ mice upon cohousing with *Nlrp6*$^{-/-}$ mice, cohoused *CCL5*$^{-/-}$ mice were resistant to exacerbated DSS-induced colitis, suggesting that CCL5 contributes to worsening of DSS-induced colitis upon transfer of colitogenic bacteria. Similarly, increased susceptibility to colitis-associated tumors in WT mice cohoused with *Nlrp6*$^{-/-}$ mice was abrogated in cohoused *CCL5*$^{-/-}$ mice[49]. In addition to CCL5, the production of IL-6 by the epithelium also contributed to increased colitis-associated tumorigenesis[49]. In the case of NAFLD, susceptibility to liver inflammation and steatosis was mediated by TLR signaling pathways since Myd88/TRIF-doubly deficient mice cohoused with *Asc*$^{-/-}$ mice had decreased severity of liver disease compared to WT mice cohoused with *Asc*$^{-/-}$ mice. Although live bacteria were not observed in the liver, levels of TLR4 and TLR9 agonists were significantly increased in the portal circulation of WT mice cohoused with *Asc*$^{-/-}$ mice and fed the methionine-choline-deficient diet, suggesting that PAMPs from proinflammatory bacteria enriched in the gut of *Asc*$^{-/-}$ mice can contribute to systemic disease[46]. It is also important to note that the colitogenic effects

of bacteria that are capable of promoting inflammatory cytokine production may only be realized in the context of a breached epithelial barrier together with defective repair mechanisms as inflammasome-deficient mice do not develop frank spontaneous colitis. In addition, inflammatory cytokines including TNFα and IL-6, which can be induced by bacterial stimulation of PRRs, are still important for epithelial repair and homeostasis[50, 51], but are detrimental when produced beyond a certain threshold in the context of chronic, sustained inflammation. Altogether, these results suggest that deficiencies in inflammasome signaling result in perturbations in the gut microbiota that lead to the accumulation of bacteria capable of exacerbating pro-inflammatory responses in the appropriate context that predispose to inflammation-related diseases including colitis, tumorigenesis, and metabolic syndrome.

V. Mechanisms of inflammasome regulation of the microbiota: the IL-18/AMP axis

The mechanism by which inflammasome signaling influences the composition of the gut microbiota remains unclear. However, a common theme that has emerged is a predominant role for IL-18 in modulating the microbiome (Figure 1). The increased susceptibility of colitis in *Asc*$^{-/-}$, *Nlrp6*$^{-/-}$, *Nlrp1*$^{-/-}$, *Nlrp3*$^{-/-}$, *Aim2*$^{-/-}$ or *caspase-1*$^{-/-}$ mice that consistently exhibit decreased levels of IL-18 as opposed to IL-1β. *IL-18*$^{-/-}$ mice also have increased severity to DSS-induced colitis and colitis-associated tumorigenesis compared to WT mice[41]. Elinav *et al.* also determined that WT mice cohoused with *IL-18*$^{-/-}$ mice, but not *IL-1*β$^{-/-}$ or *IL-1R*$^{-/-}$ mice developed increased sensitivity to DSS colitis, suggesting that similar to deficiencies in other inflammasome components, IL-18-deficiency results in alterations in the gut microbiota that can be transmitted to WT mice and affect colitis severity[24].

Besides inducing Th1 responses through the upregulation of IFNγ, IL-18 also upregulates the production of anti-microbial peptides (AMPs), which mediate bacterial clearance[26]. AMPs are expressed by the epithelium consistent with high expression levels of IL-18[24, 25]. Decreased levels of specific AMPs have been observed in *Asc*$^{-/-}$, *caspase-1*$^{-/-}$, *AIM2*$^{-/-}$ or *Nlrp6*$^{-/-}$ mice compared to WT mice, and administration of recombinant IL-18 restored levels of specific AMPs[2638]. Notably, *Nlrp6*$^{-/-}$, *Asc*$^{-/-}$ or *IL-18*$^{-/-}$ mice had decreased levels of the AMPS, Ang1, Ang4, Relnβ, and Itln1, while *Aim2*$^{-/-}$ had decreased production of Reg3γ and Reg3β, and β-defensin2[12, 26, 38]. In addition, colon crypt secretions obtained from *Nlrp3*$^{-/-}$ mice *ex vivo* had decreased bactericidal activity against *E. coli in vitro* compared to that from WT mice[48]. That AMP production may contribute to the abundance of certain bacterial populations in inflammasome-deficient mice was further suggested by experiments in which the injection of Ang4 into *Asc*$^{-/-}$ mice resulted in changes in overall diversity and community structure of the gut microbiome although the resultant microbiome remained significantly different from WT mice[26]. In addition, injection of IL-18 into *Aim2*$^{-/-}$ mice reduced the relative abundance of *E. coli,* which was significantly increased in *Aim2*$^{-/-}$ mice compared to WT mice. Although AMPs can exhibit species-selective bacteriocidal activity[52], it is not clear whether impaired AMPs entirely explains changes in abundance of specific bacterial populations, and it possible that IL-18 regulates other

processes than the microbiome. Also of note, the fecal microbiome of *IL-18*$^{-/-}$ mice was different from that of *Asc*$^{-/-}$ or *Nlrp6*$^{-/-}$ mice suggesting that additional mechanisms independent of IL-18 may contribute to microbiome changes in *Asc*$^{-/-}$ or *Nlrp6*$^{-/-}$ mice. For example, regulation of mucus secretion by NLRP6 may theoretically affect the abundance of bacteria that can utilize mucin oligosaccharides for nutrition.

VI. Conclusion

Significant advances have been made in understanding the influence of the immune system on the composition of the gut microbiota. Studies involving the natural colonization of GF WT and mutant mice have provided the strongest evidence that inflammasome signaling, in particular, through NLRP6, can dictate the composition of the gut microbiota with respect to certain bacterial populations. Additional studies looking at littermate mice and GF mice will help determine more rigorously whether other inflammasome components truly affect microbiome composition that include not only bacteria, but also viruses and fungi. Similarly, whether inflammasome deficiency results in changes in specific microbial populations that directly promote or cause disease also needs to be further clarified. Unlike AIM2 that has been shown to directly bind to cytosolic double-stranded DNA, there is no conclusive evidence as yet that inflammasome-associated PRRs interact directly with their activating microbial or endogenous molecules. A better understanding of the precise signals that activate each of the inflammasomes to regulate microbiome composition would be important for developing therapeutic strategies to prevent the development of dysbiosis and disease.

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Highlights

- Inflammasomes regulate the production of IL-1β and IL-18.
- Inflammasome deficiency results in increased susceptibility to colitis in mice.
- Impaired inflammasome activity and IL-18 production are associated with dysbiosis.
- IL-18-mediated antimicrobial peptide production may regulate the gut microbiome.

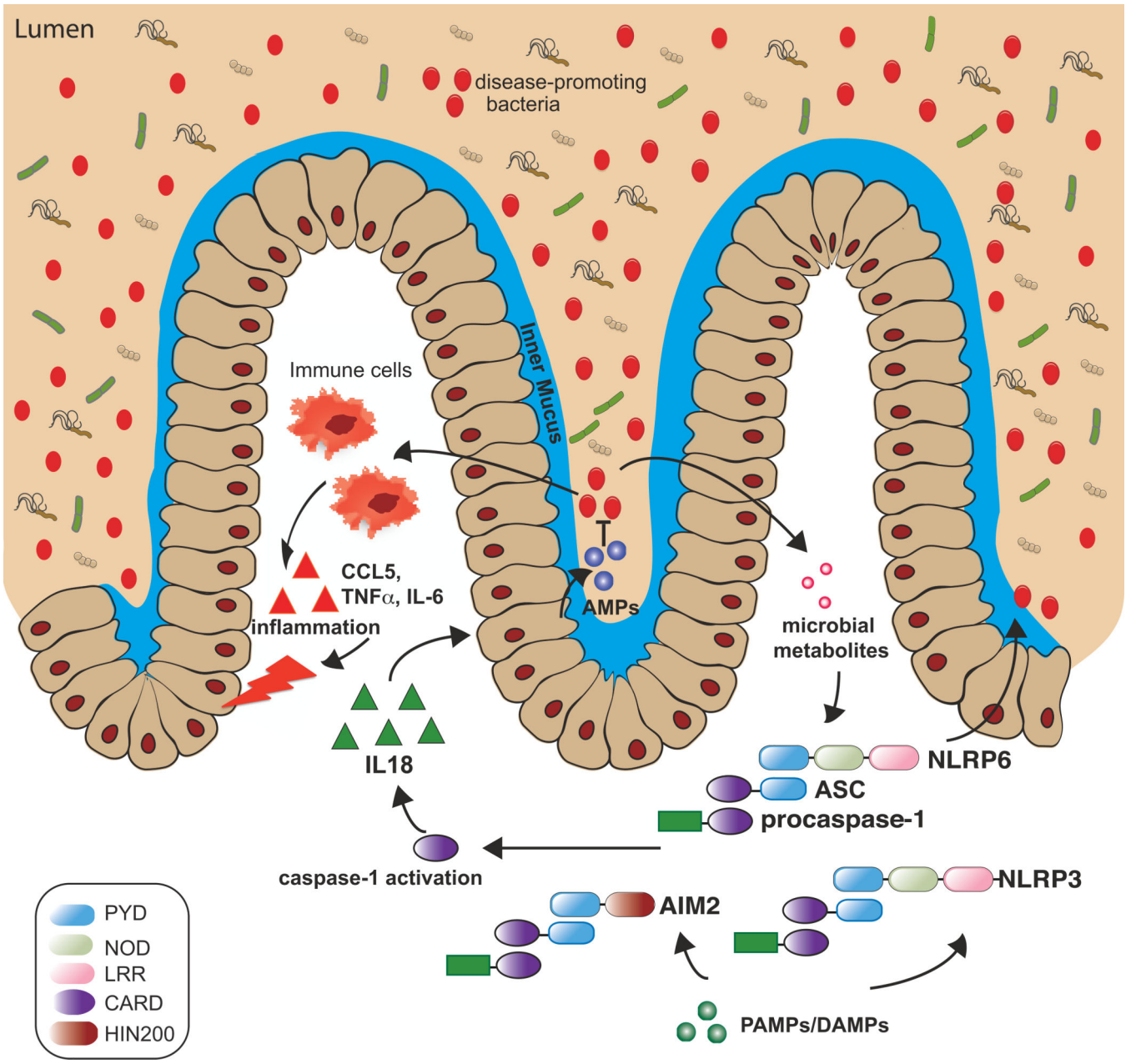

Figure 1. Inflammasome activity affects the composition of the microbiome in part via IL-18 signaling

Activation of PRRs that participate in inflammasome assembly such as NLRP6, NLRP3, and AIM2 by their respective signals results in caspase-1 activation followed by production of mature, biologically active IL-18. IL-18, in turn, upregulates the production of antimicrobial peptide (AMP), which can affect the relative abundance of bacterial populations through its bacteriocidal activity. In the absence of inflammasome signaling, dysbiosis develops with the accumulation of disease-promoting bacteria (red dots) that can upregulate inflammatory responses such as the production of CCL5, IL-6 and TNFα that can cause inflammatory disease.

Table 1

Increased susceptibility to inflammation-related disorders in inflammasome-deficient mice is associated with changes in IL-1b, IL-18, and microbiome composition. NASH, non-alcoholic steatohepatitis; NAFLD, non-alcoholic fatty liver disease

Mice Strain	Phenotype	Phenotype Transmissible?	IL-1β levels	IL-18 levels	Microbiome Changes
Nlrp1$^{-/-}$	↑ DSS-induced colitis[35]	Yes	↓	↓	Not identified
	↑ colitis-associated tumors[35]				
Nlrp3$^{-/-}$	↑ DSS-induced colitis[36,37]	Yes	↓	↓	↑*Enterobacteriaceae*[48]
	↑ colitis-associated tumors[36,40]				
Nlrp6$^{-/-}$	↑ DSS-colitis[24,25]	Yes	↑	↓	↑*Prevotellaceae, Prevotella, TM7*[24]
	↑ colitis-associated tumors[25, 39,49]				
Nlrp12$^{-/-}$	↑ DSS-induced colitis[30,31]	Yes	↑	↓	Not identified
	↑ colitis-associated tumors[30,31]				
Aim2$^{-/-}$	↑ DSS-induced colitis[12,38]	Yes	↑	↓	↑ *Akkermansia, Anaeroplasma*[47]
					↑ *Enterobacteriaceae*[38]
	↑ colitis-associated tumors[47]				↑ *Prevotella, Bacteroides*[12]
					↓ *Prevotella, Anaerostipes, and Paraprevotella*[47]
Asc$^{-/-}$	↑ DSS-induced colitis	Yes	↓	↓	↑*Prevotellaceae, Prevotella,TM7*[24]
	↑ colitis-associated tumors				↑*Porphyromonadaceae*[46]

Mice Strain	Phenotype	Phenotype Transmissible?	IL-1β levels	IL-18 levels	Microbiome Changes
	↑NASH/NAFLD				
Caspase1$^{-/-}$	↑ DSS-induced colitis[42]	Not tested	↓	↓	Not identified
	↑ colitis-associated tumors[40]				