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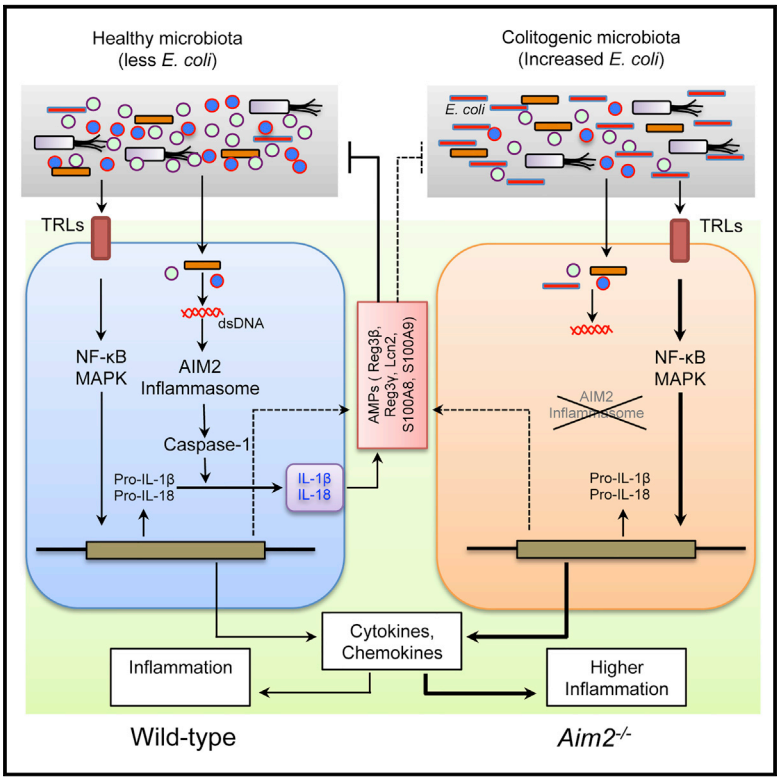
The DNA Sensor AIM2 Maintains Intestinal Homeostasis via Regulation of Epithelial Antimicrobial Host Defense

Graphical Abstract



Highlights

- AIM2 senses intestinal microbial DNA and activates the inflammasome
- The AIM2 inflammasome protects mice from experimental colitis
- The AIM2 inflammasome controls the growth of commensal *Escherichia coli*
- The inflammasome triggers antimicrobial peptide production by epithelial cells

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In Brief

AIM2 is a cytosolic DNA sensor. Hu et al. demonstrate that intestinal microbial DNA activates the AIM2 inflammasome. AIM2 activation leads to the production of IL-1β and IL-18, which participate in the regulation of intestinal microbiota such as *Escherichia coli* via induction of the antimicrobial peptides in intestinal epithelial cells.

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The DNA Sensor AIM2 Maintains Intestinal Homeostasis via Regulation of Epithelial Antimicrobial Host Defense

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SUMMARY

Microbial pattern molecules in the intestine play immunoregulatory roles via diverse pattern recognition receptors. However, the role of the cytosolic DNA sensor AIM2 in the maintenance of intestinal homeostasis is unknown. Here, we show that *Aim2*$^{-/-}$ mice are highly susceptible to dextran sodium sulfate-induced colitis that is associated with microbial dysbiosis as represented by higher colonic burden of commensal *Escherichia coli.* Colonization of germ-free mice with *Aim2*$^{-/-}$ mouse microbiota leads to higher colitis susceptibility. In-depth investigation of AIM2-mediated host defense responses reveals that caspase-1 activation and IL-1β and IL-18 production are compromised in *Aim2*$^{-/-}$ mouse colons, consistent with defective inflammasome function. Moreover, IL-18 infusion reduces *E. coli* burden as well as colitis susceptibility in *Aim2*$^{-/-}$ mice. Altered microbiota in inflammasome-defective mice correlate with reduced expression of several antimicrobial peptides in intestinal epithelial cells. Together, these findings implicate DNA sensing by AIM2 as a regulatory mechanism for maintaining intestinal homeostasis.

INTRODUCTION

The intestinal mucosal immune system of mammals evolved to coexist with densely populated microorganisms that reside in the intestinal lumen. The central physiological process for homeostatic immune response in the gut is the recognition of pathogen-associated molecular patterns (PAMPs) by host pattern recognition receptors (PRRs). There are several evolutionary conserved PRRs including Toll-like receptors (TLRs), NOD-like receptors (NLRs), RIG-I-like receptors (RLRs), C-type lectin-like receptors (CLRs), and HIN-200 family receptors. Defects in pathogen sensing systems lead to dysregulated immune responses in the intestine, resulting in the induction of intestinal inflammatory disorders such as inflammatory bowel disease (IBD) and colorectal cancer (Cho, 2008). Clinical and experimental studies have shown that dysfunctions in several TLRs (TLR2, TLR4, and TLR9) and NLRs (NOD2, NLRP3, NLRP6, and NLRP12) are associated with the pathogenesis of intestinal inflammation and tumorigenesis (Chen et al., 2008; Elinav et al., 2011; Hugot et al., 2001; Katakura et al., 2005; Maeda et al., 2005; Rakoff-Nahoum et al., 2004; Vijay-Kumar et al., 2007; Villani et al., 2009; Zaki et al., 2010a, 2011b). However, the precise mechanisms of the regulation of intestinal homeostasis by these pathogen sensors are not clearly defined, and the functions of the majority of PRRs in intestinal physiology have yet to be explored.

Absent in melanoma 2 (AIM2), a member of interferon-inducible gene HIN-200 family, has been implicated as a cytosolic sensor of DNA (Bürckstümmer et al., 2009; Fernandes-Alnemri et al., 2009; Hornung et al., 2009). Recent studies have underscored the importance of AIM2-mediated sensing of microbial DNA in host defense responses against bacterial and viral infections caused by *Listeria monocytogenes*, *Francisella tularensis*, *Streptococcus pneumoniae*, and murine cytomegalovirus (Fang et al., 2014; Fernandes-Alnemri et al., 2010; Jones et al., 2010; Kim et al., 2010; Park et al., 2014; Rathinam et al., 2010). Structurally, AIM2 contains an N-terminal pyrin domain (PYD) and a C-terminal oligonucleotide binding HIN domain. When cytosolic dsDNA binds to its HIN domain, AIM2 recruits apoptosis speck-like protein containing a caspase recruitment domain (ASC) and caspase-1 to form a molecular platform called the inflammasome. In addition to AIM2, at least three NLR family members—NLRP1, NLRP3, and NLRC4—are known to activate the inflammasome in biological systems (Lamkanfi and Dixit, 2009). Inflammasome-mediated activation of caspase-1 is required to cleave pro-IL-1β and pro-IL-18 into their active forms. Mounting evidence points to the critical roles caspase-1 and other inflammatory caspases play in regulating intestinal inflammation and tumorigenesis (Allen et al., 2010; Dupaul-Chicoine et al., 2010; Elinav et al., 2011; Salcedo et al., 2010; Zaki et al., 2010a). We and others previously demonstrated that the NLRP3 inflammasome regulates intestinal inflammation and tumorigenesis in mice (Allen et al., 2010; Hirota et al., 2011; Zaki et al., 2010a, 2010b). Recent studies showed that the

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