The Inflammasome: Critical Roles in Intestinal Homeostasis

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Intestinal Homeostasis vs Inflammation

Cytokines, Chemokines, Inflammatory mediators

Healthy intestine

Inflammatory bowel disease

Homeostasis

Inflammation
Pathogen recognition receptors and inflammatory signaling pathways

- Toll-like receptors (TLRs) senses pathogen associated molecular patterns at cells surface and endosomal compartment.
- Nod-like receptors (NLRs) are cytosolic sensors for pathogen and danger associated molecular patterns.
Major inflammasome pathways

*Pro IL-1β*
*Pro IL-18*

**NLRP1b inflammasome**

**NLRP3 inflammasome**

**NLRC4 inflammasome**

**AIM2 inflammasome**

**DAMPs:**
- MSU, PPD,
- Silica, alum,
- Asbestos, amyloid-β

**PAMPs:**
- LPS, peptidoglycan,
- Viral and bacterial
- RNA, DNA

*Flagellin*

*dsDNA*

*Cytosolic dsDNA*

**Active caspase-1**

*Pro IL-1β*
*Pro IL-18*
The NLRp3 inflammasome protects mice from dextran sodium sulfate (DSS)-induced colitis

Zaki MH, Immunity, 2010
Multiple inflammasome pathways maintain intestinal homeostasis

**Figure**: 
- **Diagram**: Shows the interaction between NLRP3, ASC, and Caspase-1 leading to pro IL-1β & IL-18, resulting in IL-1β, IL-18.
- **Graph 1**: Shows body weight (%) over days after DSS with lines for WT, Nlrp3-/-, and Casp1-/-.
- **Graph 2**: Displays IL-18 (pg/mg) in colon with data points for WT, Nlrp3-/-, and Casp1-/-, indicating statistical significance with asterisks.
Absent in Melanoma 2 (AIM2)

- AIM2 is a member of interferon inducible gene HIN-200 family.
- AIM2 contains an N-terminal Pyrin domain and a C-terminal HIN-200 oligonucleotide binding domain.
- AIM2 is a cytosolic sensor for dsDNA.
- Interaction of AIM2 with DNA leads to the inflammasome activation.
- Several bacteria and virus including *Listeria monocytogenes*, *Francisella Tulerensis*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, murine cytomegalovirus and vaccinia virus can activate AIM2 inflammasome.
Aim2-deficient mice are susceptible to DSS-induced colitis

Body weight change (%)

Diarrhea score

Bleeding score

Colon length (cm)
Colitis susceptibility of AIM2-deficient mice is associated with increased inflammation
AIM2 is involved in the activation of the inflammasome
How does AIM2 protect mice from colitis?

**Cytokines and Chemokines**

**Bacterial count (Log10 cfu/g of tissue)**

- **Colon tissue:**
  - WT: 4
  - Aim2⁻/⁻: 8
- **Stool:**
  - WT: 4
  - Aim2⁻/⁻: 8

**Inflammation**
Gut microbiota plays an essential role in Aim2-dependent colitis susceptibility

WT and Aim2<sup>-/-</sup> mice were treated with antibiotics (ampicillin, neomycin, metronidazole, vancomycin) for 3 weeks before colitis induction.
AIM2 regulates the growth of *E. coli*
Microbiota in *Aim2*−/− mice are colitogenic

Littermate study

Body weight change (%) vs. Days after DSS administration.
E. coli is responsible for higher colitis pathogenesis in Aim2<sup>−/−</sup> mice

Germ-free (GF) mice were co-housed with either conventionally raised wild-type or Aim2<sup>−/−</sup> mice.
How does AIM2 control the growth of *E. coli*?
AIM2 regulates production of anti-microbial peptides

$\beta$-defensin

Reg3b

Reg3g

Lipocalin 2

S100A8

S100A9
The inflammasome downstream cytokines induces expression of anti-microbial peptides in intestinal epithelial cells

Primary intestinal epithelial cells were treated with either IL-1β (10 ng/ml) or IL-18 (10 ng/ml).
IL-18 treatment reduces colonic burden of *E. coli* and rescue *Aim2*−/− mice from DSS-induced colitis.
Conclusion

E. coli

Microbiota

Antimicrobial host defense

IL-1R

Pro-IL-1β, Pro-IL-18

Antimicrobial peptides

Cytokines, Chemokines

Lcn2, Reg3β, Reg3γ, S100A8, S100A9

dsDNA

AIM2 Inflammasome

Pro-IL-1β, Pro-IL-18

IL-1β IL-18

Proliferation

Inflammation
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