Microbial DNA Regulates Intestinal Homeostasis via the AIM2 Inflammasome

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Background: The surveillance of microbial patterns by diverse pattern recognition receptors plays a central role in the regulation of intestinal homeostasis. Microbial DNA is a major pattern molecule that can be sensed by TLR9, AIM2 and cGAS. The cytosolic DNA sensor AIM2 has recently emerged as a critical regulator of innate immunity against microbial infections via formation of the inflammasome, a molecular platform for caspase-1 activation. However, the role of AIM2 in sensing microbial DNA in the intestine and maintaining intestinal homeostasis is unknown.

Methods: To understand the role of AIM2 in intestinal homeostasis, we induced colitis in Aim2-/− and wild-type (WT) mice by feeding them with 3% DSS for 5 days. Colitis susceptibility was monitored by measuring body-weight loss and clinical scores. Colons collected at different days after DSS administration was examined histopathologically. Epithelial barrier permeability and proliferation of epithelial cells were measured. Finally, activation of the inflammasome and production of pro-inflammatory cytokines in the colons at different days after colitis induction were analyzed by Western blotting and ELISA.

Results: Our results show that Aim2-/− mice are highly susceptible to DSS-induced colitis. Increased colitis susceptibility in Aim2-/− mice is associated with increased inflammation, colonic invasion of commensal bacteria and increased permeability of intestinal epithelial barrier as compared to those of WT mice. Interestingly, the proliferation of intestinal epithelial cells is reduced in Aim2-/− mouse colon during DSS-induced colitis. Further investigation reveals that AIM2-mediated protection against colonic inflammation and epithelial injury is linked to its function as an activator of the inflammasome since caspase-1 activation and IL-1β and IL-18 production were remarkably attenuated in the absence of AIM2. To confirm that bacterial DNA present in the colonic lumen can activate the AIM2 inflammasome, we transfected DNA isolated from mouse feces into WT or Aim2-/− macrophages. While fecal DNA activates caspase-1 in WT macrophages, no such cleavage of caspase-1 is detected in Aim2-/− macrophages.

Conclusions: Together, these findings implicate DNA sensing by AIM2 as a regulatory mechanism for maintaining intestinal homeostasis.