Apoptotic turnoff

Apoptosis is an immunologically silent process, but the mechanisms underlying this have yet to be fully defined. In *eLife*, Nagata and colleagues find an important role for adenosine monophosphate (AMP) in mediating the anti-inflammatory effects of apoptotic cells on macrophages. Caspases triggered during the induction of apoptosis cleave and activate the plasma membrane channel pannexin-1, which allows its release of AMP. This is then converted extracellularly to adenosine, possibly through the action of the ectonuclease CD73 expressed on macrophages. The adenosine then triggers the macrophage purinergic receptor A2a to elicit an anti-inflammatory program characterized by the expression of thrombospondin and the Nr4a family of nuclear receptors. Accordingly, administration of AMP *in vivo* lessens inflammation in a zymosan-induced model of peritonitis and in a pannexin-1- and A2a-dependent manner. Therefore, AMP release is another mechanism by which apoptotic cells are able to 'calm' macrophages. ***ZF***

eLife **(25 March 2014) doi:10.7554/eLife.02172**

T cell specificity

Segmented filamentous bacteria (SFB) in the microbiota are sufficient to induce T_H17 cells in the lamina propria of the small intestine. In *Nature*, Yang *et al.* show that the T cell antigen receptor (TCR) repertoire of intestinal T_H17 cells is distinct from that of other intestinal $CD4^+$ T cell subsets and recognizes antigens encoded by SFB. Lamina propria T_H17 cells show enrichment for $V_\beta14^+$ TCRs, and dominant CDR3 sequences shared by mice show enrichment in either T_H17 cells or non-T_H17 cells. TCRs cloned from T_H17 cells respond to SFB-encoded antigens. Naive T cells from mice with transgenic expression of SFB-specific TCRs migrate to the small intestine and become either T_H17 cells in SFB-colonized hosts or T_H1 cells if the specific antigen is engineered to be expressed by *Listeria monocytogenes*. These results indicate that the bacterial context in which cognate antigen is delivered dictates the fate of the antigen-specific T cell. *IV*

Nature (13 April 2014) doi:10.1038/nature13279

Microbiota-induced priming

How specific components of the microbiota, such as *Clostridium* and SFB, modulate the homeostasis of regulatory T cells and the T_H17 subset of helper T cells remains unknown. In *Immunity*, Ivanov and colleagues show that SFB induce T_H17 cells in a manner dependent on SFB-derived antigens and that intestinal $CD11c^+$ dendritic cells (DCs) are necessary and sufficient for this process. The induction of T_H17 cells by SFB in the lamina propria requires the expression of major histocompatibility complex class II. An SFB-conditioned intestinal environment does not induce IL-17 expression in non–SFB-specific transgenic T cells. Lamina propria T_H17 cells from SFB-colonized mice, but not those from SFB-negative mice, respond strongly and specifically to SFB-derived antigens, whereas non-T_H17 cells do not. The response is diverse and polyclonal. Peyer's patches or mesenteric lymph nodes are not required for the induction of T_H17 cells by SFB, which suggests that DCs prime the $CD4^+$ T cells locally in the lamina propria. ***IV***

Immunity **40, 594–607 (2014)**

Written by Laurie A. Dempsey, Zoltan Fehervari & Ioana Visan

Interferon targets

Type I interferons have critical antiviral functions, but their main cellular targets are unclear. In *PLOS Pathogens*, Diamond and colleagues use conditional deletion of the receptor for type I interferons (IFNAR) to determine the key cells that require signaling via type I interferons to mediate resistance to infection with West Nile Virus (WNV). As expected, germline deletion of IFNAR leads to rapid death after WNV infection but, unexpectedly, conditional deletion of IFNAR specifically in dendritic cells, granulocytes, macrophages or monocytes results in an equally severe pathology. The morbidity of WNV-infected mice with germline or conditional deletion of IFNAR is due to sepsis and includes elevated viral loads and cytokine production by IFNAR-deficient cells. The signaling adaptor MAVS is at the vertex of several key antiviral recognition pathways, and deletion of MAVS in conjunction with deletion of IFNAR largely normalizes cytokine production but leaves WNV loads high. The action of type I interferons in myeloid cells, therefore, is essential in controlling the permissiveness and pathology of WNV. *ZF*

PLoS Pathog. (17 April 2014) doi:10.1371/journal.ppat.1004086

New PD-L2 partner

PD-L2 functions as a ligand for the inhibitory receptor PD-1; however, several studies have hinted at additional binding partners. In the *Journal of Experimental Medicine*, Xiao *et al.* show that PD-L2 also binds to the repulsive guidance molecule RGMb to mediate immunotolerance in the lung. RGMb is a glycosylphosphatidylinositol-anchored membrane protein that is known to associate via signaling receptors such as bone morphogenetic proteins and neogenin. RGMb is expressed on macrophages in the lungs and peritoneal tissues, whereas PD-L2 is expressed on dendritic cells. Blocking the RGMb–PD-L2 interaction impairs the development of respiratory tolerance, but blocking the PD-1–PD-L2 interaction does not. The molecular details of the RGMb–PD-L2 signaling complex remains to be delineated, as neither protein directly triggers downstream signaling pathways. Nevertheless, these findings provide insight into tissue-specific immunotolerance mechanisms that are mediated by PD-L2 independently of PD-1. ***LAD***

J. Exp. Med. **(21 April 2014) doi:10.1084/jem.20130790**

Recognizing bacteria

The NLRs are a family of pattern-recognition receptors that sense intracellular pathogens. NLRs have leucine-rich repeat (LRR) regions and nucleotide-binding domains that regulate the formation and function of inflammasomes. In *Molecular Cell*, Vance and colleagues reveal the molecular basis of ligand recognition by a class of NLRs that associate with NLRC4 to form inflammasomes. Analysis of a library of chimeric NLRs with swapped NAIP2, NAIP5 and NAIP6 domains reveals that α-helical domains located adjacent to the nucleotide-binding domains are responsible for specific ligand recognition, contrary to expectation that flexible LRR regions mediate such recognition. Comparative genetic analysis suggests this α-helical region has undergone positive selection to diversify. Although the LRR regions might contribute to the recognition of ligand by other NLRs, this domain seems to mediate only autoinhibition to prevent spurious inflammasome activation by NAIPs. *LAD*

Mol. Cell **54**, 17–29 (10 April 2014)