Spicing up immunity

Capsaicin, the main active component of chili peppers, binds via the receptor for vallinoid 1, expressed by neurons as well as a variety of immunocytes. In *Mucosal Immunology*, Basu and colleagues use two different mouse models of type 1 diabetes to investigate whether this widely consumed compound modulates immune responses. The administration of capsaicin orally results in a lower incidence of both spontaneous and induced type 1 diabetes, but capsaicin administration via other routes does not. Immune responses are diminished in the pancreatic lymph nodes—considered part of the gut-associated lymphoid tissue—but are unaffected systemically. The protective effects depend on a gut macrophage population with enhanced expression of the immunomodulatory molecule IL-10. Furthermore, bone marrow chimeras combined with deletion of the receptor for vallinoid 1 demonstrate that the expression of this receptor on macrophages is essential for capsaicin's immunomodulatory effects. This study demonstrates mechanistically how a common food component can modulate autoimmune responsiveness. ***ZF***

***Mucosal Immunol.* 5, 76–86 (2012)**

Erythropoiesis regulator

The lncRNAs are long noncoding RNA transcripts without protein-encoding ability that function as regulatory factors for modulating gene expression. In *Genes & Development*, Lodish and colleagues identify the 2,531-nucleotide intergenic lncRNA lincRNA-EPS, which has potent anti-apoptotic activity and is specifically upregulated in terminally differentiating erythroid cells. Assays of RNA-mediated interference and ectopic expression prove that lincRNA-EPS serves an antiapoptotic role without affecting erythroid terminal differentiation. Mechanistically, this is done at least in part through repression of *Pycard*, which encodes the proapoptotic adaptor ASC that can activate caspases. The nuclear localization of lincRNA-EPS suggests that it regulates gene expression via the modulation of nuclear events, such as epigenetic modifications, transcription or mRNA splicing, but the exact mechanism remains unclear. *IV*

Genes Dev. (8 December 2011) doi:10.1101/gad.178780.111

Asymmetric division

T lymphocytes are known to obtain polarity cues from antigen-presenting cells and to undergo asymmetric division and diversification of daughter cell fates. In *Science*, Reiner and colleagues show that germinal center B cells asymmetrically segregate the transcription factor Bcl-6, the receptor for interleukin 21 (IL-21R) and the polarity protein PKC-ζ between daughter cells. These three proteins segregate together in all asymmetric divisions and seem to be inherited by the daughter cell that arises from the side of the B cell proximal to the follicular helper T cell. Asymmetrical segregation is enhanced by CD40 signaling and is impaired in the absence of the adhesion molecule ICAM-1. B cells undergoing homeostatic division in unimmunized mice show infrequent polarity. The fate of the daughter B cells that arise from asymmetric divisions during the germinal center reaction remains to be investigated further. ***IV***

***Science* (15 December 2011) doi:10.1126/science1213495**

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

T cell timing

The circadian rhythm is tuned by the expression of 'clock' genes, which encode molecules that can exert a strong influence on widespread physiological processes. In the *Journal of Immunology*, Cermakian and colleagues investigate how the circadian rhythm affects T cell functionality. Mice housed in total darkness to prevent light- and melatonin-dependent triggers show rhythmic expression of the circadian *Clock* gene in peripheral lymph nodes. T cells show a similar cyclical variation in proliferation, with their highest mitogenic potential late in the day or at night. These cyclical differences in T cell proliferation are lost, however, when *Clock* is deleted. As a possible explanation for these functional differences, there is also rhythmic expression of the key T cell signaling molecule Zap70. Studies of mice immunized at different times of the day demonstrate variability in the functional differentiation of T cells. This study therefore highlights the potentially far-reaching effects of circadian cycling on immune responsiveness. *ZF*

J. Immunol. **187**, 6291–6300 (2011)

Inhibiting ubiquitin sensing

Ubiquitin ligases and ubiquitin-sensing proteins have histidine and cysteine residues that coordinate the zinc atoms essential for their activity. In *Nature*, Zhang *et al.* identify the virulence factor NleE, produced by enteropathogenic *Escherichia coli*, that modifies zinc-binding cysteine residues in the TAB2 and TAB3 ubiquitin-binding adaptors in the kinase TAK1 complex. NleE uses S-adenosyl methionine to methylate these cysteines, which prevents further interactions via their thiol groups. After infection, NleE targets TAB2 and TAB3 to prevent their recognition of polyubiquitin chains and prevents downstream activation of the transcription factor NF-κB and the generation of antimicrobial responses. NleE activity is highly specific for TAB proteins, as it does not inhibit activity of the NF-κB modulator NEMO or components of LUBAC, the linear ubiquitin chain–assembly complex. Whether other similar cysteine methylases exist that regulate other ubiquitin-dependent signaling pathways is open to investigation. ***LAD***

***Nature* (11 December 2011) doi:10.1038/nature10690**

Sec22b in cross-presentation

The cross-presentation of exogenous peptides is necessary for priming efficient antiviral and antitumor immune responses. Specific dendritic cell subsets specialize in cross-presentation, but how this process allows antigen processing and loading of antigen onto major histocompatibility complex class I molecules remains unclear. In *Cell*, Cebrian *et al.* show that phagosomes in dendritic cells fuse with endoplasmic reticulum–Golgi transport vesicles via a fusogenic SNARE complex composed of Sec22b and syntaxin 4. Sec22b is located on the membranes of transport vesicles that move cargo between the endoplasmic reticulum and *cis*-Golgi compartments and can capture syntaxin 4 present on phagosomes, which allows mixing of membrane proteins, including peptide-loading machinery dependent on the transporter TAP. Cells that lack Sec22b fail to cross-present antigen to $CD8^+$ T cells, which demonstrates the requirement for endoplasmic reticulum–phagosome vesicle fusion in this antigen-presentation process. How this Sec22b-dependent intracellular trafficking is regulated is unknown. *LAD*

Cell **147**, 1355–1368 (2011)