Regulation by proteoglycans

Tumor environments are often associated with immunosuppressive factors, such as interleukin 10 (IL-10) and transforming growth factor-β1 (TGF-β1), that limit antitumor immune responses. In *Science Signaling*, Merline *et al.* show that soluble decorin, a matrix proteoglycan, promotes antitumor immunity by blocking TGF-β1 signaling and limiting IL-10 release. Macrophages express soluble decorin after stimulation with lipopolysaccharide. Decorin binds to Toll-like receptors 2 and 4, leading to higher expression of *Pdcd4*, which encodes the translational repressor PDCD4 that can suppress IL-10 production. However, PDCD4 is under translational regulation by the microRNA miR-21, which is activated by TGF-β1 signaling. Decorin-mediated inhibition of TGF-β1 relieves the suppression of PDCD4 by miR-21 and thereby decreases the secretion of immunosuppressive IL-10. Mice that ectopically express decorin have enhanced proinflammatory antitumor responses. It remains unknown whether cancer patients can likewise benefit from decorin treatment. ***LAD***

Sci. Signal. **(15 November 2011) doi:10.1126/scisign.2001868**

Mining antiviral complexity

Making sense of how pathogens respond to the complex web of interacting receptors and signaling pathways is a major challenge. In *Cell*, Hacohen and colleagues use an integrated approach of transcriptomics, proteomics and perturbation to unpick the complexity of the antiviral response. By examining dendritic cells stimulated by Toll-like receptor agonists or live virus, they confirm the importance of many classic molecules and pathways involved in antiviral responses. However, they also show that the polo-like kinases (PLKs) PLK2 and PLK4 have mutually redundant, but together critical, activatory roles in the antiviral response. They use a small-molecule PLK inhibitor to confirm the importance of PLKs in antiviral immunity both *in vitro* and *in vivo*. So far, PLKs have been examined only in the context of the cell cycle, so their involvement in the antiviral response is wholly unexpected, and this demonstrates the utility of such an unbiased approach. *ZF*

Cell (11 November 2011) doi:10.1016/j.cell.2011.10.022

Traffic control

Endothelial cells in the high endothelial venules (HEVs) control the recruitment of lymphocytes to the lymph nodes through their characteristic high expression of L-selectin ligands. It is known that the maintenance of these features depends on the lymphoid tissue microenvironment and signaling via the lymphotoxin-β receptor. In *Nature*, Moussion and Girard show that dendritic cells have an essential role in maintaining the HEV phenotype and subsequently in controlling the entry of lymphocytes into the lymph node. *In vivo* depletion of dendritic cells leads to reversion from a mature to an immature neonatal HEV phenotype, alterations in the rolling velocity and firm adhesion of lymphocytes and loss of total cellularity in the lymph nodes. Control of the maintenance of HEV endothelial cells by dendritic cells depends on the lymphotoxin-β receptor and is mediated through lymphotoxin secretion by the dendritic cells. ***IV***

Nature **(13 November 2011) doi:10.1038/nature10540**

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

Autophagy switch

Beclin-1 is critical in the initiation of autophagy and interacts with many proteins that either inhibit or trigger autophagy. In *The EMBO Journal*, Kroemer and colleagues show that TAB1 and TAB2, two upstream activators of the TAK1–IKK–NF-κB signaling axis, constitutively interact with beclin-1 and function as inhibitors of autophagy. After autophagy is induced by any of several distinct activators, such as starvation or pharmacological triggers, TAB2 and TAB3 dissociate from beclin-1 and bind to the kinase TAK1, an association known to activate TAK1 and the IKK pathway. Thus, the dissociation of TAB2 and TAB3 from beclin-1 and their association with TAK1 represents a switch that activates autophagy by releasing beclin-1 from an inhibitory interaction and by activating the TAK1-IKK pathway, also known to stimulate autophagy. The mechanisms that trigger the dissociation of TAB2 and TAB3 from beclin-1 and allow its activation remain unclear. *IV*

EMBO J. (11 November 2011) doi:10.1038/emboj.2011.413

Platelets hold the fort

Platelets are known mainly for their clotting function, but because they are among the first cells to encounter blood-borne pathogens, they could potentially be important in defense. In support of that possibility, Weyrich and colleagues in *PLoS Pathogens* show that human platelets rapidly surround pathogenic *Staphylococcus aureus* and enforce their clustering. In addition to simply sequestering bacteria, platelets and their progenitors (megakaryocytes) also contain β-defensin 1, an important antimicrobial peptide more commonly expressed by epithelial cells. This peptide does not seem to be actively secreted by clustering platelets but instead is released after the membrane is made permeable by bacterial exotoxins. Platelet β-defensin 1 not only attacks *S. aureus* and impairs their growth directly but also induces the activation of neutrophils in the vicinity of platelet clusters. Platelets may therefore provide the very first line of defense against blood-borne bacteria, retarding their growth until more specialized cells of the immune system can join the fray. ***ZF***

PLoS Pathog. **(10 November 2011) doi:10.1371/journal.ppat.1002355**

Gut conversations

Microbial colonization influences gut homeostasis and immunocyte activity. In *Nature Medicine*, Matzinger and colleagues report a tripartite 'conversation' among commensal microbes, B cells and gut epithelium that profoundly affects host metabolic function. Mice that lack B cells or secretory immunoglobulins have less absorption and use of lipids. Gene-expression profiling shows higher expression of interferon-inducible genes and lower expression of those encoding molecules involved in fat metabolism, especially those regulated by the transcription factor GATA-4. Network analyses show that the interferon-inducible GTPase GBP6 connects these differently regulated gene subsets. Intriguingly, upregulation of the cytosolic DNA sensor ZBP1 (DAI) is likewise upregulated in gut epithelial cells in mice that lack B cells. Thus, gut tissues increase interferon-related responses to compensate for the lack of secretory immunoglobulins A and M, but this response leads to diminished functioning of metabolic pathways. *LAD*

Nat. Med. (20 November 2011) doi:10.1038/nm.2505