

## Drivers of metastasis

Neutrophils are important in inflammation, but their contribution to tumorigenesis has remained unclear. In *Nature*, Wculek and Malanchi show that neutrophils are the main drivers of metastatic invasion of the lungs in a mouse model of breast cancer. CD11b<sup>+</sup>Ly6G<sup>+</sup> neutrophils are present at low frequencies in the primary tumors, but they accumulate in the pre-metastatic lung before infiltration by cancer cells, and their numbers increase in the metastatic lung. Genetic, conditional or antibody-mediated depletion of neutrophils at the pre-metastatic stage diminishes metastatic progression with no effect on the primary tumors. Pre-metastatic lung neutrophils isolated *ex vivo* and neutrophil-derived leukotriene mediators enhance the metastatic initiation potential of cancer cells, possibly by providing a proliferative advantage to highly tumorigenic cells. Genetic or pharmacological deletion of leukotrienes diminishes spontaneous lung metastasis in mice. *IV Nature* (9 December 2015) doi:10.1038/nature16140

## CCR7 polysialylation

Leukocytes use the chemokine receptor CCR7 to traffic from interstitial tissues into lymphatics and draining lymph nodes, in response to the chemokines CCL19 and CCL21. In *Science*, Kiermaier *et al.* reveal that polysialylation of CCR7 regulates dendritic cell (DC) trafficking. Mice lacking the polysialyltransferase ST8Sia IV fail to post-translationally modify CCR7 and have diminished lymph node cellularity. ST8Sia IV-deficient DCs fail to migrate in response to CCL21; however, their migration to CCL19 remains unaltered. Accordingly, CCL21 exists in an auto-inhibited conformation. This autoinhibition is relieved by interaction with polysialyl carbohydrate chains of CCR7, which allows ST8Sia IV-sufficient DCs to respond to CCL21. Further investigation is warranted to understand why such regulatory mechanisms arose to 'fine-tune' DC migration and how this modification is altered during infection or other disease states. *LAD Science* (10 December 2015) doi:10.1126/science.aad0512

## Coinfection enhances inflammation

Helminth infections tend to be endemic in regions with a high incidence of pulmonary tuberculosis and have a modulatory effect on immune responses to *Mycobacteria tuberculosis*. In the *Journal of Clinical Investigation*, Khader and colleagues assess mice coinfecting with the helminth *Schistosoma mansoni* and *M. tuberculosis*. Preinfection with *S. mansoni* or vaccination with *S. mansoni* egg antigen reversibly impairs *M. tuberculosis*-specific type 1 helper T cell responses, and lung inflammation. Furthermore, latent *M. tuberculosis* is reactivated by vaccination with *S. mansoni* egg antigen. The exacerbated lung inflammation is strongly dependent on the presence of arginase-1-positive macrophages. Finally, using outbred mice with a spectrum of *M. tuberculosis*-dependent pulmonary inflammation, the authors show that the expression of arginase-1 is proportional to disease severity even in the absence of helminth coinfection. These results thus shed light on how helminths can enhance the severity of tuberculosis. *ZF J. Clin. Invest.* 125, 4699–4713 (2015)

## Sensing cholesterol dynamics

Perturbations in lipid metabolism are observed in viral and microbial infections, while type 1 interferon signaling is known to downregulate cellular cholesterol synthesis and increase uptake of lipids from extracellular sources. In *Cell*, Bensinger and colleagues confirm that viral infection and type 1 interferon signaling induce a metabolic shift from *de novo* synthesis to import and also show that limiting the cholesterol-biosynthetic pathway induces spontaneous type 1 interferon responses and enhances antiviral immunity. Deletion of the endoplasmic reticulum chaperone SCAP or the transcription factor SREBP2, which decrease cholesterol synthesis, induces viral resistance and a type 1 interferon response in bone marrow-derived macrophages and mouse embryonic fibroblasts. The type 1 interferon response in these cells is dependent on the cGAS-STING-TBK1-IRF3 pathway and is 'rescued' by the addition of exogenous cholesterol, which suggests that the amount of cholesterol in a cell can modulate the sensitivity of STING to its ligands. *IV Cell* (10 December 2015) doi:10.1016/j.cell.2015.11.045

## RANK recruiting

The blood-brain barrier restricts the entry of leukocytes into central nervous system tissues. This border consists of an endothelial layer and a glial cell layer, separated by cerebrospinal fluid. In *Immunity*, Guerrini *et al.* report that the entry of T cells into the central nervous system parenchyma requires interaction between the cytokine receptor RANK, expressed on astrocytes, and its ligand RANKL, expressed on activated T cells. RANK signaling induces astrocyte expression of the inflammatory chemokine CCL20. Mice lacking expression of RANKL on T cells or expression of RANK by astrocytes fail to develop experimental autoimmune encephalomyelitis, due to diminished production of CCL20 and vastly lower numbers of T cells that accumulate at the glial border. Similarly, pharmacological inhibition of RANKL blocks astrocyte expression of CCL20 and diminished cellular infiltration. Thus, signaling via the RANK-RANKL axis contributes to cellular migration through the blood-brain barrier and presents a potential therapeutic target for blocking such breaches. *LAD Immunity* (15 December 2015) doi:10.1016/j.immuni.2015.10.017

## Evading hyaluronan danger

Hyaluronan (HA) is a major extracellular matrix component that, when broken down, acts as a damage-associated molecular pattern sensed by Toll-like receptor 2 (TLR2) and TLR4. In *Cell Host and Microbe*, Liu and colleagues demonstrate that hyaluronidases produced by certain Gram-positive bacteria serve an immunoevasive function. Group B *Streptococcus* (GBS) hyaluronidase digests HA into disaccharides that are much smaller than those produced by host hyaluronidases. Unlike host-generated HA fragments, these HA disaccharides are not stimulatory and block signaling via TLR2 and TLR4. GBS with mutant hyaluronidase trigger greater inflammation and show diminished infectivity *in vivo*. In contrast to the HA fragments produced by Gram-positive pathogens, those produced by the free-living bacteria *Streptomyces hyalurolyticus* are still stimulatory, which probably reflects differing evolutionary pressures. Hyaluronidases derived from certain Gram-positive pathogens therefore aid evasion of the immune system and bacterial spreading *in vivo*. *ZF Cell Host Microbe* 18, 694–704 (2015)

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