Neonatal non-responsiveness

The postnatal immune system shows certain functional impairment, yet priming during a short time window after birth can have lifelong effects on the immune system. In *Nature Communications*, Hornef and colleagues characterize the mucosal immune system of neonatal mice. Systematic analysis of leukocytes in the gut shows that myeloid populations are already stably present at birth, whereas thymus-derived T cells appear as a spike after 2 days. A subsequent spike in T cells then occurs around weaning. The presence of these T cells is independent of signaling via TLRs and TCRs and does not require the gut microbiota. Functional and transcriptomic analysis shows these neonatal T cells to be in a relatively inactive state. This unresponsiveness is maintained by both regulatory T cells (T_{reg} cells) and the sequestration of antigens from the neonate by maternal IgA ingested during breastfeeding. This study therefore sheds light on active mechanisms that mediate neonatal suppression of T cells. ***ZF***

Nat. Commun. **(21 July 2015) doi:10.1038/ncoms8725**

Engineered for success

Dengue virus (DENV) is an important mosquito-borne virus represented by four serotypes: DENV1–DENV4. In *Cell*, Sasisekharan and colleagues use a structure-guided approach to generate antibodies broadly cross-reactive to all four DENV serotypes. Humoral responses generally result in good protective memory to a given serotype but usually poor heterologous protection. Despite this, the humoral response can include broadly reactive neutralizing antibodies, but they are usually only a minor component of the repertoire. On the basis of the epitope-paratope binding of a previously described antibody to DENV, the authors redesign an antibody with enhanced affinity for and neturalizing effect on all four serotypes. This antibody, Ab513, is also protective against all four serotypes in multiple mouse models of DENV infection. This study demonstrates how rational design of antibodies could lead to effective passive immunotherapy against DENV and potentially other pathogenic viruses that otherwise elicit only weakly neutralizing responses. *ZF*

Cell (30 July 2015) doi:10.1016/j.cell.2015.06.057

Oral mucosa Langerhans cells

Skin epidermal Langerhans cells (LCs) originate from embryonic precursors that self-renew locally at steady state. In *Immunity*, Capucha *et al.* show that in contrast to that, a large percentage of LCs in the oral mucosa derive from circulating progenitors under steady-state conditions. LCs appear in the oral mucosa 1 week after birth. In contrast to skin LCs, which are radioresistant and remain of host origin in parabiotic mice, a large percentage of oral mucosa LCs are donor derived in bone marrow–chimeric mice (50%) or parabiotic mice (20%), and they proliferate faster than epidermal LCs do after depletion of dendritic cells (DCs). Similar to conventional DCs, oral LCs derive from common DC and pre-DC progenitors, which contribute mostly to $CD103^+CD11b^-$ LCs and less to $CD103^-CD11b^+$ LCs in the oral mucosa, whereas a fraction of the $CD11b^+$ oral LCs originate from monocytes. In addition to the more dynamic homeostasis, the transcriptomic signatures and function of oral mucosa LCs resemble those of skin LCs. ***IV***

Immunity **(28 July 2015) doi:10.1016/j.immuni.2015.06.017**

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$ROR\gamma t^+$ T_{reg} cells

Microbiota imbalances or depletion in early life can lead to greater susceptibility to allergy. In *Science*, Eberl and colleagues show that the microbiota balances type 2 responses through the local induction of T_{reg} cells that express the transcription factor RORγt. These $IL\text{-}17^-IL\text{-}10^+Foxp3^+ROR\gamma t^+$ T_{reg} cells are induced by oral antigen– and microbiota-derived short-chain fatty acids and are lost in germ-free or antibiotic-treated mice. Similar to T_H17 cells, they are induced by segmented filamentous bacteria and are dependent on IL-6 and IL-23, and similar to T_{reg} cells, they are dependent on retinoic acid. Mice with Foxp3-driven deletion of RORγt show greater susceptibility to type 2 response–mediated colitis and are more resistant to helminth infection, whereas they have normal T_H1 or T_H17 responses. Thus, microbiota-induced type 3 $ROR\gamma t^+$ T_{reg} cells and T_H17 cells regulate type 2 immunity, possibly through expression of the immunomodulatory receptor CTLA-4 by $ROR\gamma t^+$ T_{reg} cells and activation of DCs. *IV*

Science (9 July 2015) doi:10.1126/science.aac4263

Nociceptors in asthma

Asthma is a heterogenous inflammatory disease characterized by massive infiltration of neutrophils or eosinophils into the lungs after exposure to allergens or other noxious agents. In *Neuron*, Talbot *et al.* reveal a role for lung nociceptor neurons in amplifying type 2 (eosinophilic) allergic responses. Airway allergen challenge induces the release of IL-5, which is recognized by $Na_v1.8^+$ nociceptor neurons that express IL-5 receptors. These lung nociceptors respond to IL-5 by releasing the vasoactive peptide VIP. Type 2 innate lymphoid cells and T_H2 cells recognize this mediator via its receptor VPAC2, which elicits the release of IL-5, IL-13 and other type 2 mediators. This response leads to further recruitment of T_H2 cells, eosinophils and macrophages into the inflammed lungs and thereby drives a feed-forward amplication loop that exacebates type 2 eosinophilic asthma. Notably, inhibition or ablation of lung nociceptors does not alter T_H1 cell–mediated lung inflammation. Therapeutic strategies that can interfere with this amplification loop might therefore offer relief to some asthmatic people. ***LAD***

Neuron **87, 341–354 (2015)**

Neutrophil contributions to tumors

Chronic inflammation or tissue wounding is associated with tumor development. In *The EMBO Journal*, Antonio *et al.* use a transparent zebrafish model to show that neutrophils recruited to wound sites are rapidly 'distracted' to nearby pre-neoplastic cells. This interaction promotes the proliferation of these pre-neoplastic cells, a process that involves prostaglandin E_2. Morpholinos that retard neutrophil development diminish the wound-associated increase in the population expansion of pre-neoplastic cells, but those that target macrophage development do not. Similar correlations can be seen in human melanoma tumors with tissue ulceration and neutrophil infiltration, both of which are indicators of a poor prognosis. It remains unclear what chemoattractant factors recruit neutrophils to the pre-neoplastic cells and what other roles neutrophils serve that promote tumorigenesis. *LAD*

EMBO J. (1 July 2015) doi:10.15252/embj.201490147