Allergy in Wiskott-Aldrich syndrome

Wiskott-Aldrich Syndrome (WAS) is a severe primary immunodeficiency that results from defects in *WAS*. In the *Journal of Clinical Investigation*, Fiebiger and colleagues shed light on the mechanistic basis of the atopy often seen in patients with WAS. These patients have elevated serum concentrations of IgE and food allergy. *Was*$^{-/-}$ mice show a similar manifestation of food allergy that is independent of the microbiota but is dependent on the adaptive immune system and the presence of food antigens. The absence of *Was* specifically in regulatory T cells (T_{reg} cells) leads to (if anything) more-severe allergy and a strong type 2 immune-response signature, whereas allergic manifestations are not triggered by *Was* deficiency in dendritic cells or B cells. *Was*$^{-/-}$ T_{reg} cells fail to suppress the T_H2 subset of helper T cells and instead themselves acquire a T_H2 cell–like phenotype. These data suggest that much of the allergic phenotype of patients with WAS results from defective T_{reg} cell function. ***ZF***

***J. Clin. Invest.* (19 Sept 2016) doi:10.1172/JCI85129**

Compartmentalized selection

The butyrophilin-like (Btnl) molecule Skint, which is expressed specifically by thymic epithelial cells and keratinocytes, is required for the selection of mouse $V_\gamma5^+$ dendritic epidermal T cells. In *Cell*, Hayday and colleagues show that Btnl1 expressed by mouse enterocytes selectively promotes the maturation of intestinal $V_\gamma7^+$ γδ T cells. The mouse gut supports the maturation and proliferation of CD122^{hi} $V_\gamma7^+$ intraepithelial lymphocytes (IELs), a process that is independent of the thymus and the microbiota. *Btnl1*, *Btnl4* and *Btnl6* are expressed in the mouse small intestine. *Btnl1*$^{-/-}$ mice, but not *Btnl4*$^{-/-}$ mice, have highly selective loss of $V_\gamma7^+$ IELs, whereas thymic $V_\gamma7^+$ T cells are not affected, and co-expression of Btnl1 and Btnl6 on gut epithelial cells *in vitro* specifically activates the $V_\gamma7^+$ IELs. Human Btnl3 and Btnl8, which show enrichment on human epithelial cells in the gut, induce selective and T cell antigen receptor–dependent responses in $V_\gamma4^+$ T cells, which dominate the γδ T cell compartment in human gut samples. *IV*

Cell (22 September 2016) doi:10.1016/j.cell.2016.08.030

Hypoxic germinal centers

Cell-intrinsic and cell-extrinsic metabolic programs have emerged as modulators of T cell biology. In *Nature*, Boothby and colleagues show in mice that germinal center (GC) light zones are hypoxic and that low oxygen tension alters B cell function by promoting a higher glycolytic rate, which increases B cell apoptosis, diminishes proliferation and impairs immunoglobulin class switching to the pro-inflammatory IgG2c isotype. Expression of the hypoxia-induced transcription factor HIF is higher in GC B cells than in other spleen B cells. Hypoxia or experimental stabilization of HIF in mice deficient in the tumor suppressor pVHL results in a reduction in high-affinity IgG1 and total IgG2c antibody responses, whereas IgA responses are not affected. This effect is due to lower expression of the cytidine deaminase AID in IgG2c-switching conditions but not in IgA-switching conditions. The induction of HIF inhibits the activity of the metabolic checkpoint complex mTORC1, and partial inhibition of mTORC1 has similar effects on antibody switching. ***IV***

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

Caloric restriction and type 2 immunity

Caloric restriction is a universally efficient method for increasing healthy lifespan and enhancing metabolic function. In *Cell Metabolism*, Trajkovski and colleagues investigate the mechanism by which caloric restriction improves metabolic parameters in both normal mice and obesity-prone mice. They find that caloric restriction promotes the browning of white adipose tissue (WAT) and improves thermogenesis. Browning is known to be associated with type 2 immunity and especially the presence of M2 macrophages, group 2 innate lymphoid cells and eosinophils and, accordingly, they find that caloric restriction increases the abundance of all these cell types in WAT. The beneficial effects of caloric restriction on metabolic parameters are dependent on type 2 signalling, specifically pathways dependent on either the signal transducer STAT6 or the cytokine receptor IL-4Rα. These data link the beneficial effects of caloric restriction with the immunological pathways known to influence the browning of WAT. *ZF*

Cell Metab. (13 September 2016) doi:10.1016/j.cmet.2016.07.023

Negative control of T_{FH} cells

Migratory dendritic cells (DCs) deliver antigen to draining lymph nodes for the priming of naive T cells, including follicular helper T cells (T_{FH} cells). In *eLife*, Kumamoto *et al.* describe a subset of migratory DCs that express the transmembrane protein CD301b and negatively regulate the priming of T_{FH} cells, which diminishes their ability to provide help to germinal center B cells. CD301b$^+$ DCs are found in the skin and submucosa of barrier tissues. CD301b$^+$ DCs have abundant expression of PD-L1 and PD-L2, ligands for the inhibitory receptor PD-1 that is expressed on T_{FH} cells. Conditional deletion of CD301b$^+$ DCs in mice increases the frequency of antigen-specific T_{FH} cells and B cells. Transient loss of CD301b$^+$ cells enhances antibody responses to protein immunogens; however, increased generation of autoantibodies also occurs. These findings suggest that CD301b$^+$ DCs act early in the immune response to limit humoral immunity. ***LAD***

***eLife* (22 September 2016) doi:10:7554/eLife.17979.001**

Bile acids block NLRP3

Chronic activation of the inflammasome leads to the development of autoinflammatory diseases; therefore, inflammasome formation needs to be tightly controlled. In *Immunity*, Guo *et al.* report that bile acids (BAs) negatively regulate the activation of NLRP3 inflammasomes. BAs signal via the transmembrane receptor TGR5 (encoded by *Gpbar*) to activate adenylate cyclase, which leads to activation of the kinase PKA. Furthermore, they show that PKA directly phosphorylates mouse NLRP3 at Ser291 (Ser295 of human NLRP3), which enhances the ubiquitination of NLRP3. These BA-induced post-translational modifications of NLRP3 diminish its ability to form 'specks' with the other inflammasome components ASC and pro-caspase-1 and decrease the production of mature IL-1β. Notably, disease-related single-nucleotide polymorphisms have been associated with human *GPBAR1*. Moreover, agonists of TGR5 suppress the activation of NLRP3 in preclinical mouse models, suggestive of potential therapeutic intervention for some autoinflammatory diseases. *LAD*

Immunity (27 September 2016) doi:10.1016/j.immuni.2016.09.008