Know your enemy

How the immune system discriminates between commensals and pathogens remains a hotly debated topic. In Cell Host & Microbe. Naglik and colleagues offer an answer to this question by looking at responses to Candida albicans, which is present ubiquitously at host epithelial surfaces. This dimorphic fungus is composed of a commensal yeast stage and an invasive and potentially harmful hyphal stage. The yeast form triggers signaling by the transcription factor NF-KB and transient mitogen-activating protein kinase signaling in epithelial cells via fungal cell wall components. However, the hyphal form triggers a qualitatively different response characterized by the phosphatase MKP1 and abundant inflammatory cytokine production. The extent of MKP1 activation also directly correlates with the dose of infection. Notably, the nonpathogenic fungus Saccharomyces cerevisiae does not trigger MKP1 activation. Presumably a unique motif associated with hyphae is responsible for the triggering of pathogen-specific responses, but its identity and that of the host receptor remain unclear. ZF

Cell Host Microbe 8, 225-235 (2010)

DC developmental pathways

How the cytokine Flt3L controls dendritic cell (DC) development via the common DC progenitor pathway, which generates plasmacytoid DCs and CD8⁺ and CD103⁺ conventional DCs, is poorly understood. In Immunity, Reizis and colleagues show that signaling via the Flt3L receptor Flt3 in DCs induces activation of the nutrient and energy sensor mTOR. DC-specific deletion of PTEN, an inhibitor of phosphatidylinositol-3-OH kinase that affects downstream activation of mTOR, results in more CD8+ and CD103⁺ DCs in lymphoid organs and other tissues. This phenotype recapitulates Flt3L administration in vivo. Rapamycin counteracts the in vivo DC population expansion and also impairs in vitro DC development mediated by Flt3L but not that mediated by granulocyte-macrophage colony-stimulating factor. These results indicate that endogenous PTEN functions as a negative regulator of the phosphatidylinositol-3-OH kinase-mTOR pathway, with effects on DC homeostasis. IVImmunity 33, 597-606 (2010)

SUMO regulates T_{reg} cells

Expression of the transcription factor Foxp3 is essential for the generation and function of regulatory T cells (T $_{\rm reg}$ cells). In Science, Liu et al. report that the SUMO E3 ligase PIAS binds to the Foxp3 promoter and negatively regulates the generation of natural T_{reg} cells. PIAS-deficient mice have more thymic and peripheral Treg cells. The association of PIAS with the Foxp3 locus is more prominent in CD4+CD25- T cells than in CD4+CD25+ T cells, consistent with the expression of PIAS protein in these cells. Similarly, the presence of repressive methylation of CpG and histone 3 Lys9 methylation marks at the Foxp3 promoter correlates with PIAS expression. PIAS associates with the DNA methyltransferases DNMT3A and DNMT3B. Loss of PIAS expression leads to enhanced accessibility of the Foxp3 promoter and more binding of STAT5 to this regulatory locus. How the expression and activity of PIAS is regulated during thymic differentiation and in effector T cells versus T_{reg} cells needs further study. LAD Science 330, 521-525 (2010)

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A good start in life

The early embryonic development of many animals occurs outside the mother. A paper by Bosch and colleagues in the Proceedings of the National Academy of Sciences shows how such embryos survive this particularly vulnerable period of life. Hydra oocytes develop as a bud on the outside of the female polyp and lack a protective cuticle. The early embryo has not only small amounts of bacterial colonization but also a distinct composition of bacteria species. Bacterial colonization is controlled by periculin1a, an antimicrobial peptide (AMP) unique to Hydra. Only females express this AMP, and it is restricted to interstitial cells. These cells are engulfed by the oocyte, and periculin1a granules can be seen in the ooplasm. Later in embryogenesis and after cuticle development, the AMP expression pattern switches to expression of other periculin family members, which results in a shift in colonizing bacteria. Acquisition of maternal AMPs therefore pre-arms the embryo to face the challenges of life outside the mother. ZF

Proc. Natl. Acad. Sci. USA 107, 18067-18072 (2010)

Foxo1-TLR4 crosstalk

Adipose tissue macrophages elicit proinflammatory cytokines that underlie insulin-resistant diabetes, a major contributor to chronic inflammation associated with obesity. In the EMBO Journal, Fan et al. show that the transcription factor Foxo1 regulates the expression of Toll-like receptor 4 (TLR4) in macrophages and potentiates activation of the NF-kB and Jnk kinase pathways, which leads to more inducible nitric oxide synthase and other inflammatory mediators. Free fatty acids likewise signal via TLR4 and activate these downstream pathways. The administration of lipopolysaccharide to wild-type mice leads to a transient increase in blood glucose concentrations, whereas this effect is blunted in mice haplosufficient for Foxo1. Modulation of the expression or activity of Foxo1 coordinately alters TLR4 abundance in macrophages. Signaling via TLR4 and the insulin receptor activates the kinase Akt, which phosphorylates Foxo1 to promote its expulsion from the nucleus, establishing a negative feedback loop to limit TLR4-initiated inflammatory responses. In insulinresistant disease, this regulatory pathway is disrupted. Targeting Foxo1 may be beneficial in such scenarios. LAD EMBO J. (2 Nov 2010) doi:10.1038/emboj.2010.268

Pre-TCR assembly

In the absence of structural data, speculative models have been proposed to explain pre-TCR ligand-independent signaling and spontaneous dimerization on the cell surface. In Nature, Rossjohn and colleagues provide the crystal structure of the pre-TCR extracellular domain and propose a head-to-tail arrangement of the pre-TCR dimers. The constant-like immunoglobulin domain of the invariant α -chain (pT α) is sandwiched between the constant β -domain of the same pre-TCR and the variable β -domain of another pre-TCR. The resulting dimer sits flat, almost parallel to the membrane. Hydrophobic residues situated on both sides of the pT α domain and invariable residues present in conserved positions in all variable and joining β-domain segments allow this association. Mutations that affect pre-TCR head-to-tail dimerization result in defective surface expression. Thus, the pT α acts as a checkpoint for correct rearrangement and folding of both the variable and constant domains of the TCR β-chain. IVNature 467, 844-848 (2010)