Regulating Lung Pathology with Dll4

The Notch signaling pathway, which is initiated by the interaction of Notch receptors with ligands that include Delta-like ligand 4 (Dll4), is known to participate in the regulation of multiple stages of thymocyte development and CD4+ T cell differentiation. However, how Notch/Dll4 signaling affects regulatory T cell (Treg) differentiation and function remains unclear. In this issue, Ting et al. (p. 1492) aim to resolve this question in the context of respiratory virus infection in mice, first demonstrating that Dll4 expression was upregulated on dendritic cells (DCs) in the lung, particularly CD11b+ DCs, following infection with respiratory syncytial virus (RSV). Blockade of Notch signaling during RSV infection using anti-Dll4 Abs augmented RSV-induced lung pathology and resulted in expansion of effector CD4+ T cells and group 2 innate lymphoid cells in the lung, accompanied by increases in Th2 and Th17 cytokines in the mediastinal lymph nodes (mLN)s. Analysis of Tregs in mLN)s of RSV-infected mice following Dll4 neutralization revealed that Foxp3+ central Tregs were present in decreased numbers and expressed lower levels of CCR7. Relative to controls, these mice also had an increased proportion of lung Tregs with a Th17-like phenotype and reduced expression of Granzyme B, which has been shown to be key for limiting RSV-induced pathology. In vitro experiments demonstrated that exposure of naive T cells to Dll4 increased the TGF-β-dependent differentiation of inducible Tregs (iTregs) and maintained their CD62LhiCD44loFoxp3+ phenotype. Compared with cells cultured without Dll4, iTregs differentiated in the presence of Dll4 had enhanced suppressive function and decreased ability to differentiate toward a Th17 phenotype in an inflammatory environment. These data suggest that the Notch ligand Dll4 promotes Treg stability and function to protect against pathology during RSV infection, findings that may be applicable to future investigations aimed at promoting Treg activity.

Pigs Rearrange Rearrangement Patterns

According to the generally accepted paradigm of mammalian B cell development, IgH chain gene rearrangements occur before IgL chain gene rearrangements, and the IgH chain must pair with the surrogate L chain (SLC) before IgL rearrangement can take place, beginning with IgLk chain genes and only progressing to IgLk chain genes once the κ options are exhausted. However, Sinkora et al. (p. 1543) have now found that B cell development in swine does not follow this paradigm. In swine early B cell precursors, cell surface expression of IgLk, but not IgH (which would be expected to pair with the SLC), was observed, and further analysis revealed that IgL rearrangements were produced before IgH rearrangements. In very early precursors, IgLk rearrangements predominated, but this preference shifted to IgLk before IgH gene rearrangements began. Contrary to B cell precursors in humans and mice, in which IgLk rearrangement can only occur if IgLk rearrangement has ceased, swine B cell precursors contained transcripts of both κ and λ chains in the same cells and IgLk CDR3 diversity decreased as IgLk CDR3 diversity increased, resulting in B cell precursors expressing only IgLk chains. IgH gene rearrangement first began in the IgLk-expressing precursors, and selection of productive IgH rearrangements occurred via a developmental checkpoint that required the presence of stromal cells and presumably relied upon intact IgL chains rather than the SLC used in human and mouse B cell development. After this checkpoint, a second wave of IgLk rearrangements was observed that resulted in immature B cells that could bear BCRs with IgLk or IgLk chains. This study indicates that B cell development in swine, and potentially other mammals, proceeds in a different order than that taken as dogma, and may explain the variability observed in the ratios of IgLk to IgLk-chains in Abs expressed by different species.

Long-Sighted Results of Corneal HSV-1

A common manifestation of ocular HSV type 1 (HSV-1) infection is epithelial keratitis, in which viral replication destroys corneal epithelial cells, resulting in lesions. Although epithelial keratitis lesions generally resolve without permanent visual impairment, investigation of their long-term subclinical effects on corneal immune responses is warranted, as epithelial disease is often a first step toward severe herpes stromal keratitis (HSK). In this issue, Rowe et al. (p. 1706) investigate whether a transient episode of HSV-1 epithelial keratitis can cause long-term changes in the corneal microenvironment that may influence subsequent immune responses. Ocular infection of mice with the KOS HSV-1 strain resulted in epithelial keratitis of the corneas that did not progress to HSK. Examination of corneas from KOS HSV-1–infected mice lacking overt pathology following viral clearance revealed a leukocyte infiltrate composed primarily of CD4+ T cells and F4/80+ macrophages and elevated production of multiple chemokines even at 34 d postinfection, indicating persistent subclinical corneal inflammation. The elevated chemokine levels in KOS HSV-1–infected animals required
CD4+ T cells, as systemic depletion of CD4+ T cells during KOS HSV-1 infection significantly reduced chemokine production in the cornea. In a model of surgical trauma, KOS HSV-1–infected corneas with subclinical inflammation developed significantly more inflammation than uninfected controls following transplantation of healthy corneal grafts. Additionally, HSV-1–infected corneas, when infected with the antigenically unrelated pseudorabies virus (PRV), demonstrated significantly lower PRV titers when compared with either contralateral noninfected corneas of the same mice or corneas of uninfected mice. Resistance to PRV infection was CD4+ T cell dependent, as local and systemic depletion of CD4+ T cells, but not macrophages, eliminated the enhanced PRV clearance observed in corneas previously infected with KOS HSV-1. Taken together, these data demonstrate that, although it does not cause clinically detectable disease, subclinical KOS HSV-1 infection can result in long-term changes to the local immune microenvironment that may provide a degree of CD4+ T cell–dependent innate resistance to an antigenically unrelated pathogen, but may also increase local inflammation when exposed to nonspecific stimuli such as surgical trauma.