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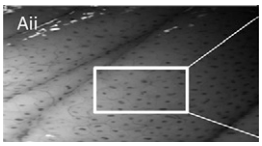
BCR-Based Bird B Cell Selection



Avian B cell development involves colonization of the bursa by B cell precursors, expression of surface Ig (sIg) molecules, cell proliferation and Ig diversification, and subsequent migration to the periphery. In two papers in this issue, Davani et al. sought to elucidate the role of the BCR in positive and negative selection by inoculating day 3 chicken embryos with chicken embryo fibroblasts transfected with BCR constructs generated by fusing the C region of chicken sIgM (Tμ) to an Ag-binding portion of the lamprey variable lymphocyte receptor (VLR) diversity region specific for either the self Ag hen egg lysozyme (HEL) (VLR^{HEL}Tμ), or the foreign Ag PE (VLR^{PE}Tμ).

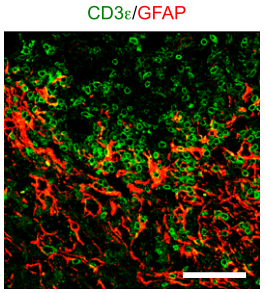
Davani et al. (p. 3207) first evaluated the role of BCR signaling during negative selection of self-reactive B cells. High levels of endogenous HEL led to the deletion of VLR^{HEL}Tμ-expressing B cells, while inoculation of embryos with soluble PE at day 13e, when splenic B cell precursors are prebursal, led to deletion of VLR^{PE}Tμ-expressing B cells, suggesting bursa-independent negative selection following BCR ligation. Furthermore, the authors expressed in chicken embryos a chimeric Ig receptor using the extracellular and transmembrane region of murine CD8α fused to the cytoplasmic domain of chicken Igα (mCD8α:chIgα) or a signaling defective mutant (mCD8α:$chIgα^{F1F2F3}$) alone or in combination with TL/mβ2m, a ligand for mCD8α expressed as a heterodimer with β2-microglobulin. Colonization of the bursa with B cells expressing mCD8α:chIgα, but not mCD8α:$chIgα^{F1F2F3}$, was significantly reduced in the presence of TL/mβ2m, suggesting that negative selection of mCD8α:chIgα-expressing B cells required BCR signaling.

In examining the role of BCR signaling during positive B cell selection, Davani et al. (p. 3218) showed that expression of VLR^{PE}Tμ in precursor B cells was sufficient for the early stages of bursal cell development; however, splenic VLR^{PE}Tμ–expressing B cells underwent reduced gene conversion relative to age-matched bursal B cells. At later stages of development, two populations of bursal emigrant B cells develop in the periphery: $LT2^+$ B cells, which are short-lived, and $LT2^-$ B cells, which are long-lived. Intrabursal application of PE increased the frequency of $LT2^+VLR^{PE}$Tμ- but not sIg-expressing B cells and the persistence of $LT2^-VLR^{PE}$Tμ-expressing B cells in PBLs, suggesting that Ag exposure drives B cell emigration from the bursa and maintains peripheral Ag-specific B cell populations. Taken together, these two studies demonstrate a clear role for Ag-mediated ligation of the BCR in positive and negative selection of precursor B cells in birds.

Mobilizing against Graft-versus-Host Disease

Graft-versus-host disease (GVHD), which leads to organ failure, is a common complication following allogeneic stem cell transplantation. The use of recombinant human G-CSF-mobilized stem cell grafts has fostered a significant improvement in hematopoietic reconstitution and disease-free survival, presumably through the effects of G-CSF on the generation of IL-10-producing regulatory T cells (Tregs). To examine how T cell function is modulated by G-CSF, MacDonald et al. (p. 3180) generated chimeric mice with either wild-type (WT) or G-CSFR–deficient ($G\text{-}CSFR^{-/-}$) hematopoietic or non-hematopoietic compartments. GVHD mortality was enhanced in WT recipients engrafted with donor WT T cells mixed with T cells from $G\text{-}CSFR^{-/-}$ hematopoietic chimeras, indicating that the effects of G-CSF were mediated through hematopoietic cells. This effect was T cell signaling–dependent and specific to G-CSF. Further experiments with WT, $G\text{-}CSFR^{-/-}$, IL-10–deficient and mixed chimeras demonstrated that IL-10 production by non-hematopoietic cells, but not T cell-derived IL-10, was required for GVHD attenuation. G-CSF, but not control saline treatment, led to a significant increase in the absolute numbers of $CD4^+$ Tregs, and microarray expression analysis of these Treg populations revealed distinct expression profiles, specifically in genes known to be involved in Treg survival. These data demonstrate that G-CSF stem cell mobilization attenuates GVHD by promoting Treg expansion and function and support the use of this mobilization protocol during allogeneic stem cell transplantation.

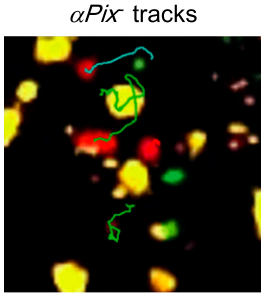
$CD8^+$ T Cells in the CNS Spotlight



The majority of studies of the pathogenesis of multiple sclerosis (MS) and its mouse model, experimental autoimmune encephalomyelitis (EAE), have focused on the roles of $CD4^+$ T cells. However, evidence increasingly indicates that $CD8^+$ T cells can also play both pathogenic and immunoregulatory roles in these diseases. In C57BL/6 mice, Sasaki et al. (p. 3029) identified $CD8^+$ T cells reactive to myelin Ags and to the astrocyte-expressed molecule glial fibrillary acidic protein (GFAP), and then proceeded to develop TCR transgenic mice bearing $CD8^+$ T cells specific for the $GFAP_{264\text{-}272}$ peptide (BG1 mice). These BG1 mice developed spontaneous CNS autoimmunity that generally followed an atypical pattern of relapsing-remitting disease and was greatly exacerbated in BG1 mice on a $Rag^{-/-}$ background, due at least in part to the absence of B cells in the $Rag^{-/-}$ mice. Disease was associated with the infiltration of GFAP-specific $CD8^+$ T cells resembling tissue-resident memory

T cells into the gray matter and white matter of the CNS. In contrast, when disease was actively induced by a vaccinia virus expressing GFAP, severe, acute CNS autoimmunity developed rapidly and was associated with BG1 $CD8^+$ T cells with short-term effector and effector-memory phenotypes in the CNS, mainly in the meninges and vascular/perivascular space. This mouse model of $CD8^+$ T cell-mediated atypical EAE reveals interesting differences in disease patterns based on whether disease is triggered endogenously or exogenously and will be useful for the future dissection of the autoimmune components that combine to cause human MS.

A PIX-ture of Thymocyte Motility

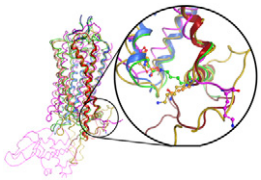


Maturation of thymocytes involves their migration through different compartments of the thymus via molecular mechanisms that are not well defined. Korthals et al. (p. 3228) assessed thymocyte development in mice deficient in α p21-activated kinase-interactive exchange factor (αPIX), which, as part of a large oligomeric complex, activates Rac and Cdc42 GTPases and has been implicated in cytoskeletal dynamics. Relative to wild-type (WT) thymocytes, αPix^- thymocytes migrated with greatly increased velocity and decreased arrest intervals on a 2-dimensional surface, and these differences were associated with increased cytoskeletal dynamics in the αPix^- cells. In vivo, positive selection was impaired in αPix^- mice due to a cell-intrinsic defect in αPix^- thymocytes, whereas negative selection and TCR signaling in αPix^- thymocytes remained unharmed. The augmented motility of αPix^- thymocytes observed in vitro was also seen in the intact thymus, as 2-photon microscopy revealed that αPix^- cortical thymocytes migrated significantly faster than their WT counterparts, covering larger distances and stopping less frequently and for shorter durations. αPix^- thymocytes were also shown to be impaired in the formation of stable contacts with stromal cells and were resistant to TCR-induced stop signals. Taken together, these data suggest that αPIX plays an important role in thymic positive selection by controlling thymocyte migration and supporting arrest to allow scanning of cortical thymic epithelial cells.

FcγRIIB: Master Modulatory Molecule

Alterations in the activity and regulation of the inhibitory Fcγ receptor, FcγRIIB, have been associated with increases in autoimmune disease susceptibility and progression in both mouse and human systems. To clarify how this broadly expressed receptor may control tolerance, Li et al. (p. 3021) analyzed mouse strains conditionally deficient in FcγRIIB expression in specific cell types. Mice were generated on the C57BL/6 background that were completely FcγRIIB-deficient ($Fc\gamma RIIB^{-/-}$) or specifically lacked FcγRIIB in all B cells, in germinal center (GC) and post-GC B cells, in dendritic cells (DCs) and some monocytes, or in monocytes and macrophages. Using these mice, the authors found that FcγRIIB expression in B cells controlled both primary and secondary IgG responses to a model Ag, and expression in DCs regulated T cell responses. Mice specifically lacking FcγRIIB in GC and post-GC B cells, but not in DCs or myeloid cells, spontaneously produced antinuclear autoantibodies at a level comparable to $Fc\gamma RIIB^{-/-}$ mice. In a model of collagen-induced arthritis that is normally non-permissive in C57BL/6 mice, FcγRIIB expression in B cells or DCs was important to maintain tolerance, whereas in a permissive model of collagen-induced arthritis, FcγRIIB expression in GC and post-GC B cells was key for controlling autoimmunity. Finally, FcγRIIB deficiency in myeloid effector cells recapitulated the exacerbated arthritis observed in $Fc\gamma RIIB^{-/-}$ mice in a passive autoantibody transfer model of disease. Thus, FcγRIIB expression on different cell types, and at different stages of differentiation, may control peripheral tolerance through a variety of mechanisms.

CCR4's Dual Personality



The chemokine receptor CCR4 is the sole known receptor for the chemokines CCL22 and CCL17 and is preferentially expressed by Th2 cells, regulatory T cells (Tregs), and mast cells. Combined with data from both mouse models and patients, this expression pattern suggests that CCR4 might be a useful therapeutic target for allergic disease. In this issue, Viney et al. (p. 3419) sought to identify a molecular basis for a reported dominance of CCL22 over CCL17 in CCR4 activation, which might have implications for targeting CCR4 function on specific cell types. CCL17 and CCL22 demonstrated similar potency and maximal effects in inducing calcium flux and chemotaxis in human CCR4–expressing cells, but CCL22 dominantly caused CCR4 endocytosis. CCL22 treatment also desensitized cells to CCL17, but CCL17 treatment did not affect responses to CCL22. These data, together with results from radioligand binding assays, suggested that CCR4 exists in at least two distinct conformations and that CCL22 and CCL17 are conformationally selective ligands. Although a CCR4-specific Ab blocked the majority of binding by both CCL17 and CCL22, a subset of CCR4 that remained unblocked mediated chemotaxis in response to CCL22 but not CCL17. Mutation of a conserved lysine in the C-terminal region of CCR4 did not affect binding by either ligand but completely abolished chemotaxis in response to CCL17 while allowing chemotaxis in response to CCL22. These data provide a structural explanation for CCR4 ligand hierarchies and suggest the possibility of targeting CCR4 activity in a ligand-specific manner to, for example, selectively inhibit allergic Th2 responses without affecting Treg activity.