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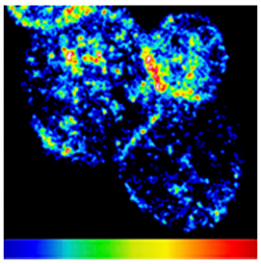
Bridging the NK Cell Synapse Gap



Gap junctions (GJs), which are channels composed of connexin subunits, mediate direct cell–cell communication and participate in myriad important immunological processes. Connexin 43 (Cx43), the main GJ protein found in immune cells, has recently been shown to accumulate and allow GJ-mediated intercellular communication (GJIC) at immunological synapses between dendritic cells (DCs) and $CD4^+$ T cells. Tittarelli et al. (p. 1313) have now assessed whether GJs are involved in immunological synapses between human NK cells and either DCs or tumor cell targets. Indeed, Cx43 accumulated at the interface between mature DCs and resting NK cells and mediated bidirectional GJIC between these cells. Blockade of GJ formation strongly inhibited activation of NK cells by DCs, as measured by NK cell expression of CD69 and CD25 and secretion of IFN-γ. Cx43 also accumulated at interfaces between NK cells and myelogenous leukemia or melanoma cell targets and mediated intercellular communication, including NK cell–mediated tumor cell lysis. Cx43-mediated GJIC did not affect NK cell degranulation but did control NK cell cytotoxicity by contributing to granzyme B activity and Ca^{2+} influx into tumor cells. Cx43-containing GJs are therefore important for the activity of NK cell synapses, both in the context of cellular activation and antitumor cytotoxicity.

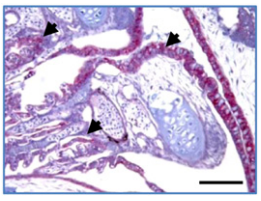
Lyn-king Autoimmunity to B Cells

The Src family tyrosine kinase Lyn inhibits signaling downstream of the BCR in a non-redundant manner and also mediates inhibitory signaling in myeloid cells. Mice lacking Lyn develop a lupus-like inflammatory autoimmune disease characterized by hyperactive autoantibody-producing B cells and myeloproliferation. To tease apart the relative contributions of Lyn deficiency to autoimmunity in different cell types, Lamagna et al. (p. 919) generated conditional knockout mice specifically lacking Lyn expression in B cells (B-$lyn^{-/-}$). Phenotypically, B-$lyn^{-/-}$ mice were very similar to conventional $lyn^{-/-}$ mice, including having reduced numbers of mature peripheral B cells, increased numbers of B1a and plasma cells, and enhanced levels of BCR signaling, relative to wild-type mice. Specific deletion of *lyn* in B cells was also sufficient to induce myeloid cell expansion and the production of high levels of autoantibodies comparable to those in $lyn^{-/-}$ mice. B-$lyn^{-/-}$ and $lyn^{-/-}$ mice also showed similar levels of immune complex–mediated glomerulonephritis. Deletion of MyD88 in the B cells of B-$lyn^{-/-}$ mice did not affect alterations in B cell homeostasis, but did reverse the splenomegaly and myeloid cell expansion observed in MyD88-sufficient B-$lyn^{-/-}$ mice. Interestingly, B-$lyn^{-/-}$ $myd88^{-/-}$ mice did not develop autoimmunity, due to a failure of class switching to pathogenic IgG autoantibodies. The identification of a key role for B cell–specific Lyn signaling in protection from autoimmunity may be applicable to the understanding of human lupus, which has been linked to alterations in *LYN* expression.

Enhancing Pro–B Cell Activity

Similar to gene regulation strategies in developing lymphocytes, the gene assembly and expression of mouse Ag receptor (AgR) genes are controlled by a collection of *cis*-acting regulatory elements, including promoters and enhancers. Previous studies have defined a variety of "superenhancers" for the *Ig* and *Tcr* loci; however, the identification of the *cis*-elements that regulate AgR assembly and expression is far from complete. To identify novel enhancers within the *Ig* loci, Predeus et al. (p. 1064) analyzed chromatin features of seven AgR loci (*Igh, Igk, Igl, Tcra/d, Tcrb* and *Tcrg*) in pro–B cells. AgR-specific chromatin patterns in pro–B cells were evaluated using the ChromHMM algorithm and divided into chromatin states to identify regulatory elements. Chromatin states that were the most enriched for activation features were localized to the *Ig* loci, especially *Igh*. Focusing on a chromatin state that encompassed most of the known AgR enhancers, the authors selected three chromatin regions corresponding to L chain loci to analyze for the presence of novel enhancers. They identified a novel *Igk cis*-element with enhancer activity in pro–B cells, but not in pro–T or plasma cell lines, and additional pro–B and plasma cell–specific enhancers in the *Igl* locus, and also characterized a previously identified superenhancer in the *Igh* locus. In this study, the authors identify novel enhancers in the *Ig* loci specific for precursor B lymphocytes that are likely to contribute to the composition of the Ig repertoire.

Fishing for New B Cell Populations



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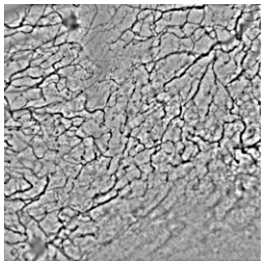
The homeostatic chemokine receptor CCR7 is known to regulate lymphocyte and dendritic cell migration to secondary lymphoid organs. A homolog of CCR7 has recently been identified in rainbow trout (*Oncorhynchus mykiss*), and in this issue, Castro et al. (p. 1257) analyzed the expression and potential function of this receptor. In rainbow trout, the largest population of $CCR7^+$ cells was found in a mucosal tissue, the gills, from an early developmental stage, and expression of this molecule increased as development progressed. The majority of $CCR7^+$ cells in the gills expressed IgD on the cell membrane ($_{mem}$IgD) but did not express IgM, CD8, or myeloid cell markers. These

$_{mem}IgM^{-}$ $_{mem}IgD^{+}$ $_{mem}CCR7^{+}$ cells were found to be a subpopulation of B cells that have not previously been identified in fish. Challenge with viral hemorrhagic septicemia virus (VHSV) resulted in a decrease in $CCR7^{+}$ cells in the gills and an associated increase in $CCR7^{+}$ cells in the head kidney, relative to mock-infected controls. Interestingly, $_{mem}IgD$ expression was not observed on $CCR7^{+}$ cells in the head kidney, indicating the need for additional research to determine the source and function of these cells. Taken together, these data identify a subpopulation of B cells expressing IgD and CCR7 that responds to viral infection and is involved in mucosal immunity in rainbow trout.

T Cell Transfer Targets Tumors



Immune suppression is a significant impediment to effective cancer immunotherapy. Although the adoptive transfer of tumor-specific T cells shows potential for tumor eradication, the presence of immunosuppressive tumor-associated macrophages and myeloid-derived suppressor cells in tumor-bearing mice and patients is thought to limit the efficacy of T cell–mediated therapies. Using in vivo imaging to evaluate T cell immunotherapy in the context of suppressive myeloid cells, Arina et al. (p. 1286) adoptively transferred splenocytes from mice immune to the UV-induced 8101 tumor into 8101-Cerulean tumor-bearing DsRed-*Rag*$^{-/-}$ mice 21 d post–tumor challenge. Analysis of the highly immunogenic 8101 tumor cell line confirmed that established 8101 tumors were accompanied by the generation of both systemic and local immunosuppressive myeloid cells comparable to other transplantable and autochthonous tumors. Maximum T cell infiltration, seen at day 11–12 post–T cell transfer, was accompanied by a significant and progressive destruction of both tumor vasculature and cancer cells. Interestingly, analysis of tumor infiltrates during T cell–mediated tumor destruction showed a tumor stroma rich in macrophages that retained their suppressive functions in vitro. 8101 tumors, typically rejected in immunocompetent mice, grew progressively in mice with UV-induced Pro4L tumors, indicating systemic immune suppression in these mice. Preimmunization against 8101 in Pro4L-bearing mice led to the rejection of 8101, indicating that tumor-associated immune suppressive myeloid cells suppress naive but not memory T cell responses. Together, these results indicate that adoptive transfer of immune T cells can overcome local and systemic immunosuppression driven by myeloid cells.

Brain B Cells Make MS Mischief

Multiple sclerosis (MS) and its mouse model, experimental autoimmune encephalomyelitis (EAE), are inflammatory demyelinating autoimmune diseases that have been most thoroughly studied in relation to pathogenic myelin-specific T cells. Alterations in the ratio of Th17/Th1 cells specific for myelin Ags such as myelin oligodendrocyte glycoprotein (MOG) affect the localization of CNS inflammation. However, the B cell–depleting anti-CD20 mAb Rituximab has therapeutic potential in MS, and studies in EAE have suggested that B cells may play a variety of roles throughout the course of disease. In this issue, Pierson et al. (p. 929) addressed the involvement of B cells in EAE during the earliest phase of T cell entry into the CNS. In a C3HeB/FeJ mouse model of EAE, which develops atypical disease associated with parenchymal brain inflammation, B cells were found to play important roles both in T cell priming during disease initiation and in the effector stage of disease. Interestingly, in naive mice, B cells comprised the majority of MHC II–expressing cells in the brain and spinal cord and were a major source of IL-12 p35 and TNF-α. Comparing the localization of adoptively transferred MOG-specific T cells in the CNS of wild type versus B cell–deficient mice revealed that the absence of B cells did not impair initial T cell infiltration into the CNS. However, B cells were necessary for the reactivation of these T cell infiltrates, allowing them to recruit a second wave of donor T cells from the periphery and subsequently cause the development of EAE. In vitro, both splenic and CNS-resident B cells acted as APCs that preferentially activated MOG-specific Th1 over Th17 cells, and B cell deficiency in vivo increased the Th17/Th1 ratio and altered the localization of CNS inflammation. CNS-resident B cells therefore appear to play an important role as APCs in the development of EAE, and thus potentially in MS.