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Insight into Ly49B Promiscuity

The Ly49 family comprises immunomodulatory receptors that bind MHC class I (MHC I) and are primarily found on NK cell surfaces. Ly49B has been reported to bind MHC I but is expressed on myeloid cells and exhibits substantial sequence divergence from other family members. To determine the requirements for murine Ly49B interactions with MHC I, Mickiewicz et al. (p. 1558) used sequence analysis techniques and site-directed mutagenesis of C57BL/6 (Ly49B^C57) and BALB/c (Ly49B^BALB) isoforms of this molecule. They found that the Ly49B NK receptor domain (NKD), which contains the MHC I–binding interface in most Ly49 molecules, shared only 26% sequence identity with other Ly49 family member NKDs and exhibited particular divergence in residues known to bind MHC I in other Ly49 family members. Rat YB2/0 cells transfected with constructs encoding Ly49B^BALB, but not Ly49B^C57, molecules displayed promiscuous binding to MHC I multimers in vitro. Binding was not affected by mutation of predicted N-linked glycosylation sites or by removal of the unique C-terminal 20-aa extension found in Ly49B, although adding an HA tag to the C terminus of Ly49B abolished binding, suggesting that this region may play a significant role in Ly49B–MHC I interactions. Amino acid substitutions between Ly49B^BALB and Ly49B^C57 revealed that Trp^166, Asn^167, and Cys^251 were integral to MHC I–Ly49B binding events. These data shed light on the structural requirements for Ly49B binding to MHC I molecules and highlight the evolutionary importance of conserved amino acids in these interactions.

DUSP14 Dampens T Cell Activation

T cell activation requires MAPK phosphorylation downstream of the TCR, which is negatively controlled by the activity of MAPK phosphatases. Dual-specificity phosphatase 14 (DUSP14) has been identified as a MAPK phosphatase that might act as a negative regulator of T cell activation. To determine the function of DUSP14 in T cells in vivo, Yang et al. (p. 1547) generated DUSP14-deficient (DUSP14-KO) mice. These mice demonstrated normal lymphocyte development but increased T cell activation, proliferation, and cytokine production following TCR stimulation, relative to wild-type (WT) mice. In vitro analysis supported a role for DUSP14 in the negative regulation of T cell activation through a direct interaction with TGF-β–activated kinase 1 (TAK1)-binding protein 1 (TAB1) during TCR signaling, resulting in dephosphorylation of TAB1 at Ser^438. Activation of DUSP14-KO T cells resulted in increased levels of phosphorylation of TAB1 and several downstream molecules, including TAK1, IKK, JNK, and ERK. Immunization of DUSP14-KO mice with a T cell–dependent Ag resulted in significantly increased Ag-specific T cell proliferation and cytokine production, as well as Ag-specific Ab production, compared with immunized WT mice. DUSP14-KO mice were also more susceptible than WT mice to the induction of experimental autoimmune encephalomyelitis, and the DUSP14-KO T cells showed enhanced differentiation to the Th1 and Th17 lineages in vitro. Taken together, these data define a molecular mechanism by which DUSP14 dampens T cell activation.

Vitiligo Poorly Primes Naive CD8s

Vitiligo is a CD8^+ T cell–mediated, melanocyte-specific autoimmune disease known to promote long-term memory T cell responses to melanoma. However, little is known about the mechanism by which vitiligo maintains anti-melanoma CD8^+ T cell memory. Byrne et al. (p. 1433) used a model of melanoma-induced autoimmune vitiligo to explore the possibility that ongoing melanocyte destruction may continually prime effector cells from the naive T cell pool. They found that adoptive transfer of naive melanocyte/melanoma–specific CD8^+ T cells (pmel) into vitiligo-affected, but not control, mice caused a large proportion of pmel cells to proliferate in an Ag-specific manner and express high levels of some activation markers. However, progressive vitiligo did not effectively prime naive pmel cells as they failed to produce IFN-γ. Adult mice subjected to sequential thymectomy and vitiligo-induction exhibited no discernible difference in vitiligo progression or anti-melanoma immunity compared with thymus-intact vitiligo mice, indicating that these processes do not require continual thymic output of naive T cells and that they are likely maintained by a long-lived memory T cell population primed early during disease initiation. However, depletion of the regulatory T cell–containing CD4^+ T cell population during progressive vitiligo rescued pmel cell priming. These data suggest that vitiligo maintains a poorly immunogenic environment and that self-reactive CD8^+ T cells are subject to complex regulatory mechanisms during progression of autoimmune diseases.

B Cell Ab Restrains Autoimmunity

B cell–targeted therapies have become a popular and efficacious means of treating many autoimmune diseases. Here, Hardy et al. (p. 1641) describe a mAb targeting CD79b, the transducer subunit of the BCR complex, as a therapeutic alternative to B cell–depleting Abs such as CD20. Using a model of collagen-induced arthritis (CIA), they found that pretreating mice with anti-CD79b mAb temporarily depleted peripheral blood B cells and resulted in delayed onset and reduced severity of disease compared with
isotype control–treated mice. In contrast to mice treated with anti-CD20, CD79b-mediated protection against autoimmunity was not dependent on B cell–depleting/Fc-dependent mechanisms, as treating CIA mice with CD79b mAbs engineered to eliminate Fc and complement receptor engagement was efficacious. B cells recovered from wild-type mice treated with anti-CD79b, but not isotype control, exhibited characteristics typical of anergic B cells, including reduced intracellular Ca^{2+} flux and Ag-specific serum levels and reduced cell surface expression of IgM, IgD, and CD79b markers. These data demonstrate that anti-CD79b mAb tempers autoimmunity, likely by inducing B cell anergy, suggesting that this mAb presents a potential therapeutic alternative to treating autoimmune disease with B cell–depleting therapies.

Nuclear Factor Keeps Colitis at Bay

Genome-wide association studies of ulcerative colitis and Crohn’s disease patients have identified the gene encoding the transcription factor nuclear factor IL-3-regulated (Nfil3), which is inducible by IL-10 and represses IL-12p40 cytokine production, as a susceptibility gene for the development of inflammatory intestinal diseases. Kobayashi et al. (p. 1918) set out to determine if NFIL3 plays a role in the development of colitis using Nfil3-deficient (Nfil3^{−/−}) mice. Compared with wild-type (WT) mice, Nfil3^{−/−} mice spontaneously developed Th1/Th17-mediated colitis and exhibited colon pathology and increased production of inflammatory cytokines (including IL-12p40) by intestinal macrophages. Nfil3 and Il10 double deficiency in mice severely exacerbated disease compared with Nfil3^{−/−} mice, suggesting that, despite IL-10’s ability to induce Nfil3, these two factors regulate mucosal homeostasis by independent means. Rag1^{−/−} Nfil3^{−/−} mice did not develop disease; however, adoptive transfer of WT CD4^{+} T cells into these mice rescued colitis development, indicating a requirement for Nfil3 deficiency in accessory cells but not lymphocytes. Colitis induction in Nfil3^{−/−} mice was IL-12p40- and microbiota-dependent, as eliminating either of these factors abrogated disease. Together, these data suggest a central role for Nfil3 in maintaining homeostasis between immune cells and the microbiota in the intestine and identify this transcription factor as a potential therapeutic target for the treatment of inflammatory intestinal diseases.

Resisting Complement in Leukemia

Addition of the anti-CD20 mAb rituximab to other chemotherapeutic agents has proven therapeutic, but noncurative, in chronic lymphocytic leukemia (CLL). A search for more effective anti-CD20 mAbs for CLL treatment has led to exploration of ofatumumab (OFA), which activates complement more efficiently than rituximab. Because a major impediment to effective CLL treatment is the development of resistance to these mAbs, Baig et al. (p. 1620) sought to identify mechanisms of resistance by analyzing CLL cells collected from patients before and after OFA administration. Treatment with OFA, together with pentostatin and cyclophosphamide, caused decreases in absolute lymphocyte counts, serum complement levels, and CD20 expression on surviving CLL cells, relative to levels prior to treatment. CLL cells collected after OFA treatment had much lower levels of activated complement C3 fragment deposition than cells not exposed to OFA, resulting in resistance to complement-dependent cytotoxicity. This resistance was linked to the reduction in CD20 expression observed following OFA treatment and resultant reduction in OFA binding, and was not related to levels of complement regulatory proteins. The rapid decrease in complement and CD20 expression seen in this study suggests that although the first dose of OFA effectively targets many CD20-expressing CLL cells, a second dose of OFA is likely to be ineffective and possibly even detrimental to CLL patients. Further work will be needed to determine whether a more optimal regimen of OFA therapy could be used to more effectively treat CLL.