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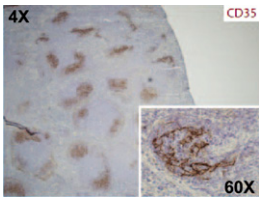
Complementing B Cell Development



Murine follicular dendritic cells (FDCs) capture Ag through complement receptors 1 (Cr1) and Cr2, which is necessary for the proper development of humoral immunity. Unique to mice, the Cr1 protein is encoded by an isoform of the *Cr2* gene. Cr1 and Cr2 expression on both B cells and FDCs is necessary for follicular transport of Ag, FDC immune complex retention, and secondary signal production during B cell activation. Donius et al. (p. 434) determined that in mice, FDCs predominantly express the Cr1 isoform, whereas B cells predominantly express Cr2. To examine the role of Cr1 in humoral immunity, they generated mice that maintained expression of Cr2 but were deficient in Cr1 (Cr1KO). These mice developed normal B1 and B2 populations and had normal naive serum Ab levels. However, levels of natural Abs such as anti-phosphorylcholine were significantly lower in Cr1KO mice than in wild-type mice. Cr1KO animals had defective responses to T-dependent Ags following immunization, although they could mount a response to T-independent Ags. Like animals deficient in both Cr1 and Cr2 or complement component 3 (C3), immunized Cr1KO animals lacked activated germinal center B cells. Interestingly, Cr1KO mice were comparable with wild-type animals when it came to their ability to withstand *Streptococcus pneumoniae* infection. This is of particular relevance because mice lacking either C3 or both Cr1 and Cr2 are susceptible to this pathogen. Thus, the authors have demonstrated that Cr1 expression by FDCs is necessary for germinal center B cell development and normal Ab production. In addition, they have introduced a new mouse model for exploring the intricacies of complement's influence on the immune system.

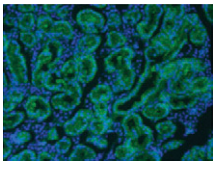
Dominating the T Cell Response

Immunodominance (ID) of pathogen-derived peptides and complex Ags creates a hierarchy of T cell responses based on the total number of naive Ag-specific $CD8^+$ T cells and the amount of peptide generated by APCs, both of which are influenced by proteasome composition. The three active proteasome subunits, β1, β2, and β5, can be replaced by "immuno" versions β1i, β2i, and β5i to create immunoproteasomes that are expressed and induced by cytokines in a variety of immune cells. "Mixed" proteasomes of both standard and immunoproteasome subunits are also commonly expressed and the subunit variations can greatly affect epitope presentation, thereby shaping the ID hierarchy. To explore the role of mixed proteasomes in $CD8^+$ T cell responses to influenza A virus (IAV), Zanker et al. (p. 52) analyzed $CD8^+$ T cell responses to 38 H-2^b–restricted peptides postinfection in $\beta1i^{-/-}$, $\beta5i/\beta2i^{-/-}$, and $\beta2i^{-/-}$ mice relative to wild-type mice. The specificity and magnitude of antiviral $CD8^+$ T cell primary and recall responses were significantly impacted by the absence of immunoproteasome subunits, and these differences varied between systemic and local $CD8^+$ T cell populations. Cultures of polyspecific $CD8^+$ T cells with IAV-infected immunoproteasome-competent or subunit-deficient bone marrow dendritic cells demonstrated that immunoproteasome subunits were required for optimal peptide generation and Ag processing efficiency. In this study, the authors demonstrate that specific proteasome subunits influence the ID to IAV by altering the specificity and efficiency of peptide generation and that these alterations lead to diversification of the antiviral repertoire and support a broad $CD8^+$ T cell response.

DCs Divided over *Leishmania*

Bystander and infected dendritic cells (DCs) have distinct immunomodulatory roles during *Leishmania* infection, with bystander DCs providing protective immunity and infected DCs promoting disease progression. To clarify the dichotomous roles played by DCs, Resende et al. (p. 262) examined the phenotypic profile of bone marrow–derived dendritic cells (BMDCs) and their ability to polarize and activate $CD4^+$ T cells after *L. infantum* infection. Relative to infected BMDCs, bystander BMDCs had higher expression of costimulatory and MHC class II molecules, produced *Il12p40* and *Il6* transcripts preferentially, and activated T cells more efficiently. Infected BMDCs produced *Il10* and *Tnfα* transcripts and, although they were unable to induce $CD4^+$ T cell activation, polarized $CD4^+$ T cells toward a T-bet^+IFN-γ^+IL-10^+ double-producing (DP) phenotype. The absence of IL-10 from infected BMDCs restored $CD4^+$ T cell activation to levels similar to those observed with bystander BMDCs, and blocking IL-12p70 increased IFN-γ levels and prevented the emergence of DP $CD4^+$ T cells. Adoptive transfer of bystander DC–primed $CD4^+$ T cells into infected BALB/c mice reduced liver and spleen parasite burden, whereas the transfer of DP T cells impaired the immune response and increased parasite burden. These results highlight a dichotomy in DC populations during *Leishmania* infection and suggest a mechanism by which T-bet^+IFN-γ^+IL-10^+ T cells promote parasite persistence during infection.

Chronic Thymic Damage in GVHD



Allogeneic hematopoietic cell transplantation (HCT) is often associated with the initial development of acute graft-versus-host disease (aGVHD) followed by the onset of chronic graft-versus-host disease

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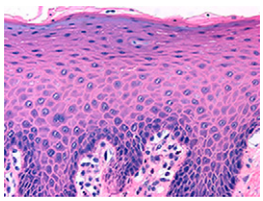
(cGVHD). Although GVHD is mediated by both $CD4^+$ and $CD8^+$ T cells, the exact roles played by these T cell subsets are unclear. To evaluate the function of donor $CD4^+$ and $CD8^+$ T cells in the development of aGVHD and cGVHD, Wu et al. (p. 488) transplanted T and B cell–depleted donor bone marrow (TBCD-BM) cells with or without titered donor C57BL/6 spleen cells into lethally irradiated allogeneic BALB/c recipients. Recipient mice receiving TBCD-BM recovered after HCT, whereas recipient mice also given a low dose of spleen cells developed clinical features of cGVHD. Transplantation of titered numbers of donor $CD4^+$ or $CD8^+$ T cells with TBCD-BM cells into recipient mice demonstrated that donor $CD8^+$ T cells were more potent than $CD4^+$ T cells in causing cGVHD and associated thymic damage, whereas donor $CD4^+$ T cells were more potent in causing aGVHD. Similar experiments in thymectomized mice further indicated that cGVHD caused by $CD8^+$ T cells resulted from thymic damage, whereas the absence of a thymus allowed $CD4^+$ T cells to induce cGVHD. $CD8^+$ T cell recipients also demonstrated a secondary phase of thymic damage resulting from de novo generation of donor-derived autoreactive $CD4^+$ T cells, but not $CD8^+$ T cells, and depletion of $CD4^+$ de novo T cells led to thymic recovery and prevention of GVHD. These data demonstrate a predominant role for donor $CD8^+$ T cells in the development of cGVHD through thymus-dependent mechanisms.

Understanding PNP



Paraneoplastic pemphigus (PNP) is one of the three major forms of the cutaneous autoimmune diseases classified as pemphigus. Like pemphigus foliaceus and pemphigus vulgaris, PNP is characterized by IgG autoantibodies that target desmoglein 3 (Dsg3). PNP pathology also includes IgG autoantibodies against plakins, and surprisingly induces lung-infiltrating T cells that cause fatal lung disease. To determine how T cell–mediated lung disease develops in a skin Ag–specific autoimmune disease, Hata et al. (p. 83) developed a mouse model of PNP. $Dsg3^{-/-}$ mice received wild-type ($Dsg3^{+/+}$) skin grafts and developed anti-Dsg3 IgG and Dsg3-specific T cells. Splenocytes from these animals were subsequently transferred into $Rag2^{-/-}$ mice, causing suprabasilar acantholysis and interface dermatitis, two histologic features indicative of PNP. These recipient mice (now termed PNP mice) exhibited bronchial inflammation and lung-infiltrating $CD4^+$ and $CD8^+$ T cells, and had a high rate of mortality. In addition, ectopic expression of Dsg3 was found in the PNP mouse lung, which mimics the pulmonary expression of Dsg3 caused by squamous metaplasia. The authors also found that the administration of naphthalene, which causes pulmonary injury, was sufficient to induce the expression of Dsg3 and other epidermal Ags in the lung, which in turn recruited Dsg3-specific $CD4^+$ T cells. Thus, the squamous metaplasia found in PNP or caused by pulmonary epithelial injury acts to direct a skin Ag–specific cell-mediated autoimmune response to the lungs.

Managing Mast Cells with MrgX2

Human β-defensins (hBDs) play a role in host defense, induce costimulatory molecule expression, act as chemoattractants, and can drive tumorigenesis. These human molecules can also cause vascular permeability and mast cell degranulation in rats. Subramanian et al. (p. 345) investigated whether hBDs had the same effect on human and mouse mast cells. Mouse mast cells, either peritoneal or bone marrow–derived, did not degranulate after exposure to hBDs. In addition, hBDs had no effect on mouse vascular permeability in vivo. However, both hBD2 and hBD3 caused degranulation and Ca^{2+} mobilization in human mast cells, with hBD3 as the more effective of the two. This Ca^{2+} mobilization could be inhibited with La^{3+} and 2-aminoethoxydiphenyl borate (2-APB) but not pertussis toxin (PTx), whereas hBD-mediated degranulation was inhibited by La^{3+}, 2-APB, and PTx. Human mast cells express the partially PTx-sensitive G-protein–coupled receptor Mas-related gene X2 (MrgX2), leading the authors to examine whether hBDs were acting through this molecule. Previous work from another laboratory showed that MrgX2 stimulated signaling through the Gαq and Gαi pathways. Silencing of MrgX2 led to an inhibition of hBD-mediated mast cell degranulation, although C3a-induced anaphylatoxin responses were still present. Ectopic expression of MrgX2 in cells that normally lack this G-protein–coupled receptor, such as the rat basophilic leukemia cell line RBL-2H3 and mouse bone marrow–derived mast cells, made them responsive to the effects of hBDs. Thus, the authors conclude that hBDs activate human mast cells through MrgX2 and, potentially, use signaling pathways involving Gαq and Gαi for degranulation.