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Dry Eye Demystified

Dysfunctional tear syndrome, also known as dry eye, is a high-prevalence ocular disease that can cause debilitating eye pain and reduced vision. $CD4^+$ T cells are known to be involved in the pathogenesis of the disease. In this issue, Schaumburg et al. (p. 3653) report that APCs are required for the development of dry eye in a mouse model of T cell-mediated autoimmune lacrimal keratoconjunctivitis induced by desiccating stress (DS). Production of proinflammatory cytokines within the cervical lymph nodes was observed soon after exposure to DS and was associated with an accumulation of mature DCs that preceded $CD4^+$ T cell activation. Depletion of conjunctival APCs induced a significant reduction in the number of infiltrating $CD4^+$ T cells and preservation of the goblet cells within the conjunctiva. Nude mice receiving $CD4^+$ T cells from APC-depleted/DS-treated donor mice presented a markedly reduced ocular inflammation relative to recipients of cells from nondepleted/DS-treated controls. APC-depleted recipient nude mice had a lower number of DS-specific $CD4^+$ T cells in the conjunctiva. Finally, mice subjected to surgical removal of the cervical lymph nodes did not develop the disease. This study enhances our understanding of the pathogenesis of dry eye and might help in devising therapeutic strategies targeting these pathways.

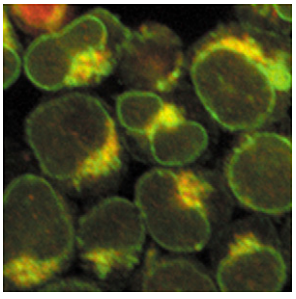
Double Agent T Cells

As Th17 cells regulate inflammatory processes, including lung allergic inflammation, Lemaire et al. (p. 3530) analyzed the immune response of transgenic DO11.10 mice in a classic experimental model of OVA-induced asthma. In this model, the transgenic mice, which express a TCR specific for an OVA peptide, are known to develop neutrophilic lung inflammation with high levels of IFN-γ and IL-17, instead of the expected Th2 response and eosinophilia. The authors discovered that the neutrophilic response was mainly mediated by a population of T cells with a memory phenotype, which expressed a dual TCR that included an endogenous TCRα chain. The cells overexpressed the transcription factors RORγt and T-bet; thus they were preferentially polarized toward the Th17 and Th1 subsets. The neutrophilia was a consequence of increased IL-17A and IL-17F production, whereas the presence of IFN-γ in the lung inhibited eosinophil recruitment, as demonstrated by the use of neutralizing mAbs. Interestingly, oral antibiotic treatment to reduce gut bacterial microflora strongly inhibited IL-17 production and lung neutrophilia. These data suggest that enteric Ags might affect the response to subsequently encountered airway allergens in the context of dual TCR expression.

Clonal Convergence

A hallmark of the humoral response is the ability to generate a vast range of Ab specificities. To explore the molecular mechanisms of B cell repertoire diversification, Krause et al. (p. 3704) derived a panel of five human mAbs (4A10, 2O10, 4K8, 6D9, and 2K11) from a donor exposed to the 2009 H1N1 influenza. All mAbs bound to the viral Sa antigenic site and neutralized several H1N1 strains, including 2009, 1918, and, interestingly, USSR/77, which has glycosylation sites within its Sa. Sequence analysis of the variable regions showed that the mAbs shared the use of V_H3–7*01 and J_H6*02 gene segments. Generation of escape mutants provided evidence that they recognized a common epitope. The mAbs represented four distinct clones, as 4K8 and 6D9 were found to be clonally related. To further characterize the repertoire encoded by the V_H3 gene, ultradeep sequencing was used on a blood sample collected from the same donor 6 mo after hybridoma generation. The results showed interclonal convergence toward a similar amino acid sequence, indicating selection for optimal Ag binding sites. Concomitantly, within the clones, sequence divergence from the germline sequence was wide, suggesting the presence of persistent low-affinity memory populations. These studies represent a step forward in understanding how the B cell repertoire is formed and functions.

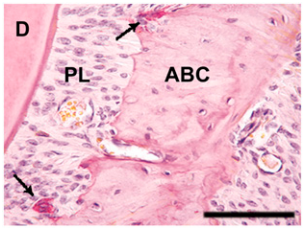
Tiam1 Takes Aim at Integrins



Lymphocyte function-associated antigen 1 (LFA-1) is a member of the integrin family of molecules that mediate leukocyte adhesion. Ligation of T cell surface receptors, including TCR and chemokine receptors, causes phosphorylation of aa T758 in the LFA-1 β2-chain, enabling the integrin to bind its ligands. Intracellular signaling generated by LFA-1 activation and leading to cytoskeletal reorganization is quite complex and involves the recruitment of 14-3-3 proteins and activation of the small GTPase Rac-1. The aim of the study by Grönholm et al. (p. 3613) was to identify the guanine nucleotide exchange factor (GEF) that could activate Rac-1 downstream of LFA-1 T758 phosphorylation. T lymphoma invasion and metastasis protein 1 (Tiam1), a Rac-specific GEF, was chosen as a prospective candidate because of its ability to associate with 14-3-3. The authors demonstrated that Tiam1 forms a complex with 14-3-3 and the LFA-1 β2-chain, and that β2 T758 phosphorylation enhances Tiam1 binding to 14-3-3 in

TCR-stimulated T cells. A functional Tiam1 is necessary for Rac1 activation of T cells, and blocking Tiam1 reduces T cell adhesion and migration. Similar results were obtained when T cells were activated by the chemokine SDF-1α. This study therefore contributes to our understanding of the sequential events involved in integrin activation and implicates Tiam 1 as a novel central player.

Arthritis Sullies Gums



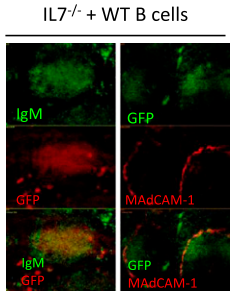
Periodontitis (PD) and rheumatoid arthritis (RA) share several inflammatory hallmarks. Epidemiologic studies have indicated higher prevalence of the oral infectious disease in patients with RA. Causal and non-causal mechanisms, including genetic and environmental factors, have been suggested for this association. To clarify the potential connection between these diseases, Queiroz-Junior et al. (p. 3821) employed a model of Ag-induced arthritis (AIA) triggered by intra-articular Ag challenge in immunized mice. Disease was characterized by severe inflammation localized in the challenged joint and the presence of serum autoantibodies and acute phase proteins. Concurrently with the progression of the autoimmune disease, and independently from oral bacterial load, the mice developed PD with alveolar bone loss, elevated numbers of osteoclasts, and increased local expression of proinflammatory mediators. Interestingly, both diseases were ameliorated by the administration of an anti–TNF-α mAb. In contrast, topical application of an antiseptic greatly improved periodontal conditions without decreasing the joint destruction caused by AIA. These results indicate that oral microbiota are triggered to induce PD by arthritic inflammation, thus supporting the existence of a causal link between the two diseases.

CD8 Stage by Stage

During thymocyte development, double positive cells become committed to either the CD4 or the CD8 single positive lineage, in which reciprocally exclusive expression of the two coreceptors is regulated by several *cis*-regulatory elements. Locus control regions (LCRs) are regulatory elements that can have long-distance effects and can be used to generate transgenic mice. For example, human CD2-LCR, composed of three DNase I-hypersensitive regions (HS1–3), directs T cell-specific expression of linked genes. Previous studies established that insertion of the full-length hCD2-LCR gene into the murine CD8 locus induced the expression of CD8 in $CD4^+$ T cells. In this issue, Menzel et al. (p. 3712) expanded their earlier study by generating floxed mCD8-(hCD2-LCR) knockin mice, in which deletion of the inserted LCR could be achieved at specific hematopoietic developmental stages by crossing the mice to transgenic mice with lineage- and stage-specific expression of *Cre*. The authors demonstrated that the continuous presence of hCD2-LCR is required to maintain CD8 expression in $CD4^+$ T cells and that the CD8 expression pattern is not affected by the presence of CD2-LCR in early stages of thymocyte development. Moreover, the authors tested the function of HS regions in individual LCRs and concluded that, in contrast to the HS1,2 region, HS3 is not sufficient to drive CD8 expression. This study, therefore, improves current understanding of the commitment steps to CD8 expression.

B Cells and IL-7

In this issue, two reports highlight the roles played by IL-7 in B cell lymphopoiesis and function. Corfe et al. (p. 3499) examined the proliferative effect of the cytokine on progenitor B cells from primary cultures and cell lines that included the novel line B62.1 IND, which has a pre-B phenotype and is IL-7 independent. The authors found that, during the B cell lineage maturation process, $CD2^+IgM^-$ small pre-B cells lose the capacity to signal through the IL-7R, although they maintain receptor expression. The unresponsive state was caused by increased expression of SOCS-1, which in turn inhibited JAK/STAT phosphorylation of the IL-7R. Of interest, SOCS-1 expression was upregulated by IL-7 in combination with other cytokines, such as IFN-γ or IL-21, indicating that distinct signal pathways can cooperate to regulate responsiveness to IL-7. In additional experiments, increased expression of Gfi-1b, a SOCS transcriptional repressor, correlated with enhancement of IL-7–induced proliferation. The authors propose that during B cell development, IL-7–induced proliferation is tightly regulated and is completely inhibited by SOCS-1 at the pre-B cell stage. This inhibition allows signals mediated by the pre-BCR to promote cell maturation and the rearrangement of light chain genes.



The second report, by Willems et al. (p. 3587), focuses on mature B cells, specifically the marginal zone B (MZB) cells of the spleen. These B cells respond rapidly to bacterial infections by producing Abs to pathogen-derived polysaccharide Ags independent of T cell help. The authors previously showed that concordant xenogeneic Ags behave as T-independent type II Ags and induce the production by MZB cells of IgM xenoantibodies (XAb), which can mediate the rejection of hamster heart transplants in mice. In the present study, they showed that IL-7 signaling was essential for MZB-induced xenograft rejection. IL-7–deficient mice were unable to mount IgMXAb responses and did not reject transplanted hamster hearts, whereas wild-type (WT) and $TCR\beta^{-/-}$ mice had high IgMXAb serum levels and quickly rejected the transplants. The inability of the IL-7–deficient mice to reject the transplant was found to correlate with a lack of proper MZ microarchitecture, involving both B cell areas and the adjacent macrophage and sinus-lining areas. In addition, the $IL\text{-}7^{-/-}$ splenic microenvironment was unable to support the homing of WT MZB cells to the MZ areas. In conclusion, the two studies indicate that IL-7 signaling is essential for at least two stages of B cell development, regulating cell maturation and responsiveness to Ags.

Summaries written by Bernardetta Nardelli, Ph.D.