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THE JOURNAL OF IMMUNOLOGY

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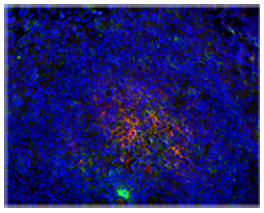
Neonatal Immune Booster



In human neonates, germinal center (GC) responses are impaired due to delayed maturation of follicular dendritic cells (FDCs), necessitating repeated vaccinations to induce protective immunity. Bjarnarson et al. (p. 1265) previously found that the adjuvant LT-K63 could enhance pneumococcal vaccine efficacy in neonatal mice and have now used this system to investigate whether adjuvants can reverse defects in the immature immune system. Indeed, administration of LT-K63 together with a protein-conjugated pneumococcal polysaccharide vaccine (Pnc1-TT) enhanced GC formation in neonatal mice, compared with Pnc1-TT immunization alone. LT-K63 promoted maturation of FDCs that was associated with upregulation of TNF-α and the FDC-M2 marker, which are required for FDC development and linked to immune complex retention, respectively. Addition of LT-K63 to the Pnc1-TT vaccine also stimulated the migration of marginal metallophilic macrophages, which are involved in immune complex deposition on FDCs, into GCs. Accelerated development of FDCs and GCs was associated with an increased frequency of vaccine-specific Ab-secreting cells and the promotion of their long-term persistence in the bone marrow. Unlike LT-K63, the CpG1826 adjuvant did not augment Pnc1-TT–induced GC formation or FDC maturation. This study suggests that the addition of LT-K63 can improve neonatal vaccine efficacy by overcoming GC defects of the immature immune system.

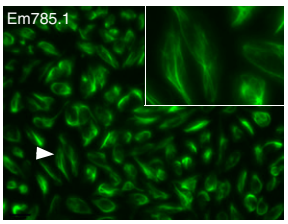
Overactive STAT1

The heterogeneous primary immunodeficiency diseases grouped together as chronic mucocutaneous candidiasis (CMC) are often associated with autoimmune diseases and endocrine disorders. Patients with CMC have chronic, recurrent infections of the skin, nails, and oropharynx with the fungus *Candida*. Gain-of-function mutations in the coiled-coil (CC) domain of STAT1 have recently been identified as causes of CMC in some patients. In this issue, Takezaki et al. (p. 1521) identified a heterozygous point mutation in the DNA-binding domain of *STAT1* in two unrelated CMC patients. This mutation, 1153C>T, caused the amino acid substitution T385M and augmented STAT1 function, as indicated by hyperphosphorylation of STAT1 following stimulation of cells with IFN-γ, IFN-α, or IL-27. Like gain-of-function mutations in the STAT1 CC domain, the T385M mutation impaired STAT1 dephosphorylation and was associated with a dramatic reduction in Th17 differentiation compared with controls. Interestingly, one of the T385M patients, unlike patients with mutations in the CC domain, developed hemophagocytic lymphohistiocytosis, which might be related to the mutation's effect on STAT1 activity. This report indicates that mutations in the DNA-binding domain of *STAT1*, not just the CC domain, may cause the development of CMC.

The Need for NKG2D

NK cells are important cytotoxic effector cells in tumor immunity that recognize cancer cells through activating receptors such as NKG2D. One mechanism by which tumor cells may evade NK cell immunosurveillance is through the proteolytic shedding of NKG2D ligands (NKG2DL) and the subsequent downregulation of NKG2D expression. To resolve conflicting data regarding this mechanism and clarify the role of NKG2D in leukemia, Hilpert et al. (p. 1360) analyzed primary cells from 205 leukemia patients. Surface expression of at least one of the 5 NKG2DLs analyzed, most frequently MICA, was observed on leukemia cells of 75% of patients, and these ligands were important for NK cell cytotoxicity and IFN-γ production. Sera from all patients contained elevated levels of at least one soluble NKG2DL, compared with sera from healthy controls, and again MICA was the most frequently represented ligand. Sera from leukemia patients with active disease could downregulate NKG2D expression on PBMCs from healthy controls or patients in remission, and this downregulation was blocked by an NKG2D-Fc fusion protein. Downregulation of NKG2D by soluble NKG2DL was confirmed to impair NK cytotoxicity and IFN-γ production in response to NKG2DL-expressing target cells. Taken together, these data present a comprehensive picture of the importance of NKG2D–NKG2DL interactions in NK cell regulation in leukemia.

New Players in Polyreactivity



Polyreactive natural IgM molecules are produced by B-1 cells and are thought to serve as innate mediators that help neutralize pathogens early in infection. Jones et al. (p. 1440) have now found that Ag-specific B cells can also produce polyreactive IgM Abs in response to intracellular bacterial infection. CD11c-expressing splenic plasmablasts produced T cell-independent IgM in response to infection of mice with *Ehrlichia muris*, and these Abs were able to bind a variety of self and foreign Ags bearing distinct structures. The majority of the polyreactive IgM Abs recognized *Ehrlichia*-derived Ags, suggesting that they were pathogen specific and not produced via nonspecific B cell activation. Polyreactive Abs were encoded by a variety of germline V, D, and J segments, indicating that polyreactivity was not a characteristic of a specific clonotype, although it was particularly enriched in Abs reactive to the immunodominant Ag outer

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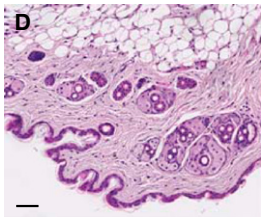
membrane protein (OMP)-19. In immunodeficient mice, polyreactive OMP-19–specific IgM was sufficient to protect from lethal *E. muris* infection. However, these Abs could bind to nuclear Ags, suggesting an increased risk of autoimmunity. Human ehrlichiosis patients also produced polyreactive IgM that exhibited autoreactive potential. Thus, polyreactive IgM Abs can be produced in an Ag-specific manner and may affect the development or attenuation of autoimmune disease during bacterial infections.

Approaching Vaccines from Within

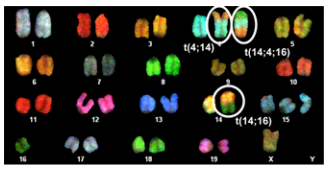


Endogenous retrotransposable elements (EREs) have been found to be aberrantly expressed in HIV-infected individuals and cancer patients. T cells specific for ERE Ags can effectively attack tumors or HIV-infected cells, suggesting the potential of EREs as vaccine targets. Sacha et al. (p. 1467) therefore assessed the safety and immunogenicity of ERE-targeting vaccines in mouse and macaque models. The authors first measured the expression of the EREs, long interspersed nuclear element-1 open reading frame 2 (L1O2) and human (or simian) endogenous retrovirus-K (HERV-K or SERV-K), in healthy mouse, human, and nonhuman primate tissues. Immunization of mice with fragments of LIO2 via a variety of homologous and heterologous prime-boost regimens demonstrated that L1O2 vaccination could stimulate $CD8^+$ T cell responses without inducing detectable autoimmunity. In the more clinically relevant rhesus macaque model, vaccination with L1O2, SERV-K Gag, or SERV-K Env Ags induced multifunctional responses by both $CD4^+$ and $CD8^+$ T cells. SERV-K Env immunization also induced IgG responses. Macaques immunized with EREs in an SIV challenge model demonstrated no autoimmunity or other adverse reactions to vaccination. Taken together, this study explores the potential for immunization against self Ags in the treatment or prevention of HIV infection or cancer. The safety of the regimens tested here supports further investigation of this approach in preclinical models.

Committing to CD8 Suppression

For thymocytes to commit to either the CD4 or CD8 lineage, they must upregulate the expression of one of these surface markers while suppressing the other. Although much is known about *Cd4* downregulation during $CD8^+$ T cell development, the mechanism by which *Cd8* is suppressed in $CD4^+$ single-positive thymocytes is less clear. Rui et al. (p. 1380) have found that the transcription factor ThPOK, which is known to be a $CD4^+$ T cell commitment factor, is responsible for directly repressing CD8 expression in the thymus. ThPOK directly associated with and repressed *Cd8* enhancers and the *Cd8a* promoter. This repression required the recruitment of class II histone deacetylases (HDACs) via the ThPOK BTB domain. Mutations in the ThPOK binding sites of the *Cd8* locus or the DNA-binding domain of ThPOK confirmed that ThPOK binding to DNA was also necessary for *Cd8* transcriptional suppression. Analysis of ThPOK-transgenic mice revealed that ThPOK mediated the deposition of HDAC4 and consequent histone deacetylation at *Cd8* loci, leading to the suppression of *Cd8a* and *Cd8b* transcription and the repositioning of these loci near heterochromatin. Conversely, *Cd8* loci became more accessible in ThPOK-deficient mice, resulting in enhanced expression of CD8 on $CD4^+CD8^{low}$ thymocytes, relative to controls. These data reveal a mechanism by which ThPOK directly silences *Cd8* expression during $CD4^+$ T cell development.

Variety in ATM Transactions



During the DNA damage response to double strand breaks (DSBs), the ataxia telangiectasia mutated (ATM) kinase phosphorylates histone H2AX to maintain genomic stability and protect against lymphoma resulting from chromosomal translocations. Some data suggest that ATM and H2AX also have independent functions; however, this has been difficult to assess because deficiency in both *Atm* and *H2ax* results in embryonic lethality. To address these potential nonredundant functions in T cells, Yin et al. (p. 1372) generated $Atm^{-/-}$ mice with a conditional deletion in *H2ax* in αβ thymocytes (*LAH* mice). Compared with mice lacking only ATM, *LAH* mice had defective expansion of double-positive thymocytes but no additional defects in V(D)J recombination during the G1 phase of the cell cycle. Defects in coding joint formation were similar in *LAH* and $Atm^{-/-}$ thymocytes. Both *LAH* and $Atm^{-/-}$ mice developed thymic lymphomas with a similar incidence and mortality rate, and these lymphomas had similar phenotypes and harbored similar patterns of chromosomal translocations. Spectral karyotyping revealed increased genomic instability in splenic *LAH* T cells versus T cells lacking either *Atm* or *H2ax* alone, which suggested nonredundant roles for these molecules in proliferating mature αβ T cells and in the repair of DSBs on nonselected TCRβ alleles. These data clarify the redundant and nonredundant roles of ATM and H2AX in the DNA damage response and may promote the understanding of human cancers arising in patients with ATM mutations.

Summaries written by Jennifer Hartt Meyers, Ph.D.