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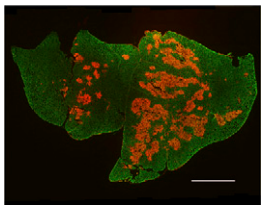
Cooperative Costimulation in Thymus



Crosstalk between medullary thymic epithelial cells (mTEC) and mature single positive (SP) thymocytes is essential to the development of mTEC, cells integral to self-tolerance induction during thymocyte development. Costimulatory CD28–CD80/86 and CD40–CD40L interactions are also involved in the thymic tolerization process, but the extent to which they affect maintenance of the thymic medulla is not fully known. To determine this, Williams et al. (p. 630) examined the thymic lobes of mice singly or doubly deficient for CD40 and CD80/86 and found that CD40/CD80/86 knockout (KO) mice exhibited an even more dramatic reduction in mTEC numbers than did CD40 KO mice, which are known to have defects in mTEC development. Gene expression analyses revealed that mTEC from CD40/CD80/86 KO compared with wild-type mice had reduced expression levels of molecules critical for mTEC formation, including lymphotoxin (LT) β and receptor activator of NF κ-B (RANK). These results suggest that costimulatory receptor interactions may play a role in mTEC development. $CD4^+$ thymocytes from CD40/CD80/86 KO mice were found to be autoreactive, as adoptive transfer of these cells (but not CD40 or CD80/86 KO thymocytes) resulted in lymphadenopathy, splenomegaly, and death of congenic athymic nude recipients by two months posttransfer. Together, these data suggest that the CD40–CD40L and CD28–CD80/86 pathways cooperate to regulate normal medullary epithelial development and consequent induction of self-tolerance in thymocytes.

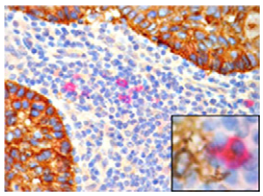
Insulin AKTs on Tregs

Obesity-associated chronic inflammation is characterized by the accumulation of proinflammatory immune cells and cytokines and a deficiency in regulatory T cells (Tregs) within obese visceral adipose tissue (VAT). The AKT pathway plays a role in both insulin-mediated glucose uptake and Treg function, leading Han et al. (p. 623) to hypothesize that insulin may exacerbate inflammation in obesity by modulating Treg development and function through the AKT/mTOR pathway. Upon stimulation with insulin, purified murine $FOXP3^+$ Tregs demonstrated enhanced AKT Ser^{473} and ribosomal protein S6 phosphorylation compared with $FOXP3^-$ T cells, indicating Tregs can activate the AKT pathway in response to insulin. Insulin-induced AKT activation in Tregs inhibited their IL-10 production without altering TGF-β production or the expression of FOXP3, CTLA-4, CD25, CD39 or LAP. Treg-derived IL-10 suppressed the production of TNF-α by bone marrow-derived macrophages (BMDMs); however, incubation of BMDMs with insulin-conditioned Treg media reduced Treg suppression of BMDM-derived TNF-α. Consistent with in vitro data, VAT Tregs in a model of diet-induced obesity produced less IL-10 and more IFN-γ than Tregs from mice fed a normal diet, suggesting a shift toward a Th1-like phenotype. Taken together, these data indicate that insulin may promote chronic inflammation in obesity by modulating the suppressive function of Tregs.

Age and Infection Influence Immunity

Human humoral immunity decreases with age, enhancing the susceptibility of the elderly to viral pathogens, such as CMV and EBV. Aging alone or in the context of chronic viral infection may alter the B cell repertoire, but the role these factors play in shaping the B cell population of the elderly has not been thoroughly investigated. Wang et al. (p. 603) used high-throughput DNA sequencing of IGH in PBLs of healthy individuals between 20 and 89 years of age to study IGH gene rearrangements. They found that B cell IGH V, D, and J usage varied among individuals, but was comparable between younger and older people. Elderly patients had increased numbers of B cells with long CDR3 regions, tended to accumulate more highly mutated IgM and IgG genes, and harbored a higher proportion of persistent clonal B cell populations in the blood compared with young people. Regardless of an individual's age, IGHV sequence analysis revealed that CMV seropositivity correlated with increased mutations in this gene region, and EBV seropositive patients exhibited increased persistent clonal B cell expansion compared with seronegative individuals. Together, these data suggest that the B cell repertoire is influenced by both age- and chronic viral infection–related factors that may have implications for vaccine design and infection studies in aged adults.

Tumor Ags Cross-Dress pDCs



Expansion of tumor Ag-specific, cytotoxic $CD8^+$ T cells can occur in vivo through 1) "cross-priming", when exogenous Ags are acquired from dead or dying tumor cells by dendritic cells (DCs) and presented in the context of MHC class I; and 2) "cross-dressing", when membrane peptide–MHC complexes are exchanged between immune cells. Although these phenomena have been clearly demonstrated for conventional myeloid DCs, the ability of plasmacytoid DCs (pDCs), which are thought to be less phagocytic than typical DCs, to acquire and

cross-present tumor Ags remains to be determined. Using fluorescently labeled cancer cell lines incubated with pDCs, Bonaccorsi et al. (p. 824) determined that pDCs could acquire cancer membrane components within 30 minutes. However, cancer cell labeling with a dye that only fluoresces in acidic endosomal compartments indicated that pDCs were not acquiring tumor cell components via phagocytosis, and that the transfer of tumor material occurred only from viable tumor cells. Further experiments indicated that the transfer of cell membrane components was dependent on both IL-3, which is necessary for pDC viability in vitro, and cell-to-cell contact, but was unaffected by surface inhibitory molecules present on pDCs. Incubation of pDCs with a B cell–derived cancer cell line or a colon carcinoma cell line led to the appearance on pDCs of the B cell marker CD19 and the epithelial cell adhesion molecule (EpCAM), respectively, indicating that acquired cell components were presented on pDCs. Similarly, in patients with colon carcinomas, an increase in the presence of pDCs in contact with $EpCAM^+$ cells in the tumor and of $EpCAM^+$ pDCs was observed. Additionally, pDCs from donors expressing HLA-B8 or HLA-A2 molecules induced IFN-γ production by HLA-B8/A2–restricted $CD8^+$ T cell clones. Thus, despite the limited phagocytic capacity of pDCs, these cells can acquire tumor cell membrane components and efficiently present tumor cell-derived Ags.

Corrections

In This Issue. 2014. *J. Immunol*. 192: 549.

An error was made in the summary titled "Age and Infection Influence Immunity."

The first sentence in the summary should read: "Human humoral immunity decreases with age, enhancing the susceptibility of the elderly to viral pathogens, such as CMV and EBV."

The penultimate sentence in this summary should read: "Regardless of an individual's age, IGHV sequence analysis revealed that CMV seropositivity correlated with increased mutations in this gene region, and EBV seropositive patients exhibited increased persistent clonal B cell expansion compared with seronegative individuals."

The online version has been changed to reflect this correction and, as such, differs from the print version.

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