The Journal of Immunology

# IN THIS ISSUE

*J Immunol* 2006; 177:2737-2738; ;
doi: 10.4049/jimmunol.177.5.2737
http://www.jimmunol.org/content/177/5/2737



*The Journal of Immunology* is published twice each month by
The American Association of Immunologists, Inc.,
1451 Rockville Pike, Suite 650, Rockville, MD 20852

Print ISSN: 0022-1767 Online ISSN: 1550-6606.

THE JOURNAL OF IMMUNOLOGY

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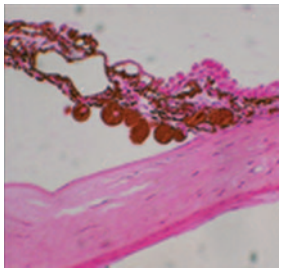
## Spotting Vitiligo T Cells



Although the depigmentation that characterizes human vitiligo is caused by autoreactive T cells that target melanocyte-specific Ags, it is difficult to isolate the roles of central and peripheral tolerance in the disease. Lambe et al. (p. 3055) developed mice double transgenic for a neo Ag (hen egg lysozyme (HEL)) expressed only within melanocytes plus a CD4 TCR specific for HEL. Skin and eye lesions similar to those seen in humans spontaneously developed in 87% of animals. $CD4^+$ T cells reactive with HEL were reduced in thymus and peripheral organs, whereas the clonotype-specific $CD4^+CD25^+$ T cell fraction was enriched among peripheral $CD4^+$ T cells. $CD4^+$ T cells from the double transgenic mice had a 1000-fold lower ability to provide in vivo help to anti-HEL Ig transgenic B cells in partially irradiated HEL-expressing recipients. Vitiligo developed in double transgenic mice deficient in MyD88, Rag, or perforin but not in those lacking Fas ligand (FasL). Elevated total $CD4^+$ T cell numbers were found only in spleens of the FasL-deficient animals. The authors show in this mouse model of spontaneous autoimmune vitiligo that $CD4^+$ T cells initiate destruction of MHC class II-expressing melanocytes via Fas-FasL interactions.

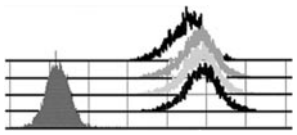
## IgE Response to Diesel Exhaust

Diesel exhaust particles (DEPs) induce production of IgE, induction of reactive oxygen species (ROS), and activation of antioxidant response elements (AREs) in airway allergic responses. However, it is not known how ROS in B cells are regulated by DEPs. Wan and Diaz-Sanchez (p. 3477) demonstrated a dose-response increase in mRNA and protein for the phase II enzyme NAD(P)H:quinone oxidoreductase (NQO1) in fresh human PBMCs and a B cell line after DEP stimulation in vitro. A similar response to DEP extract (DEPX) was seen for a reporter gene with an ARE in the NQO1 promoter transfected into a B cell line; ARE activity was partially blocked by pretreatment of the transfected cells with an antioxidant that antagonized cellular ROS. Inhibitors of p38 MAPK and PI3K, but not of PKC or MAPK/ERK, blocked DEPX-induced ARE activity and mRNA and protein expression of NQO1. DEPX increased B cell IgH $\varepsilon$ germline transcription. Addition of a potent activator of transcription factor Nfr2 plus an inducer of phase II antioxidant enzymes to DEPX-exposed primary B cells, PBMCs, or the established B cell line led to increased *NQO1* mRNA expression and reduced IgE production compared with controls. The data show both activation of IgE production and expression of phase II drug metabolizing enzymes in human B cells exposed to DEPX. Protection against ROS is mediated by p38 MAPK and PI3K and is enhanced by stimulating ARE-induced expression of the phase II enzymes.

## Splenic Architecture in Viral Infections

The filtering of blood-borne pathogens through the marginal zone (MZ) of the spleen is critical in controlling infections. However, it is not known which MZ cells are involved in producing type 1 IFNs that control virus infections. Louten et al. (p. 3266) determined that mouse strains lacking B cells, but not those lacking T cells, failed to produce IFN-$\alpha\beta$ in response to lymphocytic choriomeningitis virus (LCMV) infection; their IFN-$\alpha\beta$ responses to murine cytomegalovirus (MCMV) infection were normal. The IFNs were not detected in LCMV-infected strains of mice with disrupted splenic organization and were not produced by B cells from LCMV-infected control mice. Pretreatment of mice with clodronate-containing liposomes to deplete MZ phagocytic cells resulted in reduced type 1 IFN levels in spleen and serum after LCMV, but not MCMV, infection. Immunohistochemical analyses on clodronate-depleted spleens during natural repopulation showed that reappearance of IFN-$\alpha\beta$ responses coincided with restoration of cells with C-type lectin receptors ($SIGN\text{-}R1^+$) almost to control levels, whereas control of LCMV replication required $CD11c^+$ cells. The authors conclude that intact splenic architecture and $CD11c^+$ cells in the MZ are important in early defense against LCMV, but not MCMV, infection and that $SIGN\text{-}R1^+$ cells are required for a late IFN-$\alpha\beta$ response.

## HLA/Tapasin/TAP Binding



Binding of MHC class I molecules to TAP in the endoplasmic reticulum (ER) requires tapasin. There are reports that residue 116 of HLA-B*44, located within the F pocket of the peptide binding groove of MHC class I molecules, affects HLA/tapasin/TAP binding and renders HLA-B*4402 tapasin-dependent compared with HLA-B*4405, which differs at aa 116. Thammavongsa et al. (p. 3150) determined by immunoprecipitations, immunoblotting, and thermostability measurements that HLA-B*4405 expressed in human lymphoma cells bound more tapasin and was peptide loaded and transported to post-ER compartments more rapidly than HLA-B*4402. Pulse-chase experiments indicated rapid formation and disassociation of HLA-B*4405/TAP complexes. Under conditions of peptide deficiency in a $TAP1^{-/-}$ human melanoma cell line, both HLA allotypes bound tapasin with similar efficiencies and were equally unstable. Both HLA allotypes were thermally stable in lysates of insect cells containing two HLA-B*44-specific nonapeptides, but thermostability of only HLA-B*4405 increased in the presence of random nonapeptides or of nonapeptides containing glutamic acid at aa 2. No significant differences in stability of surface HLA-B*4405 or HLA-B*4402 were detected in the lymphoma cells. The data indicate that, rather than being tapasin-independent, HLA-B*4405 is incorporated into tapasin/TAP complexes efficiently but transiently in a process dependent on





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peptide supply and loading kinetics. The observed tapasin dependency of HLA-B*4402 is due to inefficient peptide loading.

## Forming Granulomas

Granuloma formation in *Mycobacterium tuberculosis* infections is an attempt by a host to sequester the invading pathogen. It also offers the bacterium protection from host defenses and, as such, bacterial factors could play a role in its formation. Rojas et al. (p. 2959) incubated $CD4^+$ T cells from PBMCs of healthy individuals with cell wall/membrane or cytosolic fractions of disrupted *M. tuberculosis* and *M. bovis* bacilli. Only the cell wall/membrane fraction induced homotypic T cell aggregates. Aggregate formation tracked with a biphasic column- and PAGE-separated low molecular mass glycolipid identified by thin layer chromatography as phosphatidylinositol mannoside (PIM). A combination of PIMs caused T cells to aggregate in the presence of serum or plasma fibronectin, but not BSA, and induced T cell adhesion to plate-bound fibronectin. Addition of EDTA or pretreatment of cells with an antagonist of actin polymerization inhibited aggregation; a mAb directed against the $\alpha_5\beta_1$ integrin receptor or an RGD-containing peptide blocked PIM-induced T cell adhesion to fibronectin. Direct interaction of PIM with $\alpha_5\beta_1$, but not fibronectin, was established by immunoprecipitation and immunoblotting experiments and confirmed by PIM adhesion to plate bound $\alpha_5\beta_1$ integrin. The authors demonstrate that a *M. tuberculosis* cell wall/membrane glycolipid binds and activates $\alpha_5\beta_1$ integrin on $CD4^+$ T cells to induce cell adhesion to fibronectin in the extracellular matrix and to promote granuloma formation.

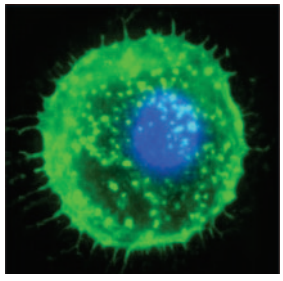
## Dual Attack on Influenza Virus

Vaccines against human influenza virus focus on eliciting neutralizing Abs that target two prominent outer membrane proteins. Stimulating $CD4^+$ T cell immunity to highly conserved internal proteins might provide more protection against emergent strains. Brown et al. (p. 2888) showed that mice injected with influenza hemagglutinin (HA) peptide-specific TCR transgenic (Tg) $CD4^+$ T cells primed in vitro with HA peptide survived a lethal virus challenge. Adoptively transferred effector $CD4^+$ T cells were recovered from lungs of wild-type or T cell-deficient mice between 1 and 4 days postinfection (p.i.), and less viral RNA was detected in wild-type lungs compared with control animals. Wild-type mice injected with wild-type or *IFN-*$\gamma^{-/-}$ effector T cells, primed or not with IFN-$\gamma$, survived a lethal virus infection. Beginning 5–10 days p.i., wild-type or *IFN-*$\gamma^{-/-}$ recipients of wild-type effector T cells developed higher serum levels of anti-influenza IgG Ab in response to lethal infection than controls. *IFN-*$\gamma^{-/-}$ effector T cells delayed time to death in B cell-deficient mice over controls given wild-type cells. Both recipients exhibited a plateau in weight loss at 5–10 days p.i. and had high survival rates when given sera from wild-type survivors of infection. Wild-type and *IFN-*$\gamma^{-/-}$, but not perforin-deficient, effector T cells killed HA peptide-coated target cells in vitro and in vivo. B cell-deficient mice given wild-type, but not perforin-deficient, effector T cells survived infection with a low dose of virus. The data indicate that perforin-dependent $CD4^+$ T cell cytotoxicity reduces early influenza virus titers in the lung and that effector $CD4^+$ T cell-driven Ab production clears residual virus.

## IL-12 and Polymicrobial Sepsis

Neutrophils protect against bacterial sepsis by phagocytosis, NO production, and killing of bacteria. Both IL-12 and IL-18 are important in neutrophil migration to the infection site; however, the separate roles of the cytokines in neutrophil activation have not been investigated. Moreno et al. (p. 3218) found 100% mortality of *IL-12*$^{-/-}$ mice, but 100% survival of *IL-18*$^{-/-}$ and wild-type mice, in a polymicrobial model of septic peritonitis induced by sublethal cecal ligation and puncture (SL-CLP). All mice died after lethal CLP (L-CLP). The three strains of mice had comparable levels of neutrophil migration into peritoneal cavities after SL-CLP, and all had impaired migration after L-CLP. Lung neutrophil numbers and TNF-$\alpha$ serum levels were higher, and IFN-$\gamma$ levels in peritoneal exudates and serum were lower, in *IL-12*$^{-/-}$ mice compared with *IL-18*$^{-/-}$ and wild-type mice after SL-CLP; *IL-12*$^{-/-}$ neutrophils exhibited reduced phagocytic activity and NO production vs controls. Neutrophils from *IFN-*$\gamma^{-/-}$ mice had less phagocytic and microbicidal activity and lower NO production after LPS stimulation than wild-type neutrophils, and only 65% of *IFN-*$\gamma^{-/-}$ mice survived SL-CLP. IFN-$\gamma$ restored in vitro phagocytic, microbicidal, and NO-producing activities of *IL-12*$^{-/-}$ neutrophils to wild-type levels, and 100% of SL-CLP-treated *IL-12*$^{-/-}$ mice injected with IFN-$\gamma$ survived. The experiments indicate that resistance to SL-CLP in this mouse model of polymicrobial sepsis is due to stimulation of neutrophils via IL-12 induction of IFN-$\gamma$.

## Arsenic and Old Macrophages



Inorganic arsenic is known to alter $CD4^+$ T cell function and inhibit in vitro differentiation of human monocytes. However, the full impact of arsenic on macrophage function has not been explored. Lemarie et al. (p. 3019) documented loss of adhesion, assumption of a rounded morphology, reorganization of the F-actin cytoskeleton, reduced surface expression of integrins and a differentiation marker, increased surface expression of CD14, and decreased endocytosis and phagocytosis in human blood monocyte-derived macrophages treated for 6 days with a low concentration of arsenic trioxide ($As_2O_3$) comparable to that found in chronically exposed individuals. $As_2O_3$ enhanced secretion and mRNA levels of TNF-$\alpha$ and IL-8 in LPS-treated macrophages. These effects were reversed by GM-CSF treatment of cells grown in arsenic-free medium for an additional 6 days; addition of IL-4 to the GM-CSF yielded $CD1a^+$ dendritic-like cells from the "de-differentiated" macrophages. Macrophages pretreated with an inhibitor of a Rho-associated kinase involved in cytoskeleton regulation did not exhibit the $As_2O_3$-induced changes in morphology and increased activation of RhoA and phosphorylation of the cytoskeletal adaptor moesin (membrane-organizing extension spike protein) seen in controls. The experiments show that a nontoxic concentration of $As_2O_3$ de-differentiates human macrophages into monocyte-like cells via activation of a RhoA/RhoA kinase signaling pathway.

**Summaries written by Dorothy L. Buchhagen, Ph.D.**