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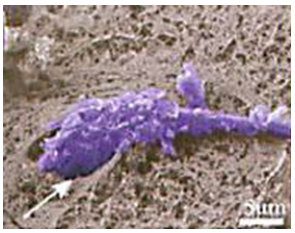
THE JOURNAL OF IMMUNOLOGY

In This Issue

The Hows of Macrophage Migration



The ability of monocyte-derived macrophages (MDMs) to infiltrate tissues is a key feature of the innate immune response but can also be damaging to tissues. To better understand the controlling factors of MDM tissue infiltration, Van Goethem et al. (p. 1049) investigated human MDM three-dimensional migration through various acellular extracellular matrix (ECM) materials. When MDMs migrated through laminin- and collagen IV-rich Matrigel, they tended to adopt the strongly adhesive and proteolytic mesenchymal mode of motility and became elongated with long membrane protrusions. In contrast, MDMs migrating through fibrillar collagen I, a highly porous matrix compared with the dense material of Matrigel, adopted the nonproteolytic, round-shaped amoeboid mode. However, MDMs switched to the mesenchymal mode of migration in fibrillar collagen I that was induced to polymerize into a dense gel. Further experiments showed that the architecture of the ECM determined the migratory mode employed by MDMs. Thus, these experiments reveal that human MDMs can employ either proteolytic or nonproteolytic modes to migrate through three-dimensional ECM materials, and the mode of migration is dictated by the architecture and not by the composition of the ECM material.

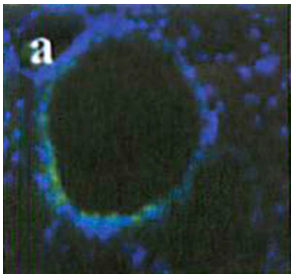
The Highs and Lows of Insulin

Type 1 diabetes (T1D) results from a T cell-mediated autoimmune response to insulin-producing pancreatic islet β cell Ags, including insulin. Carriers of insulin gene alleles that correlate with low levels of thymic insulin expression are predisposed for the strongest T1D susceptibility. To determine if thymic insulin levels modulate the magnitude of $CD8^+$ T cell responses to insulin in T1D, Jarchum and DiLorenzo (p. 658) first examined the impact of thymic insulin deficiency on the prevalence of insulin-specific $CD8^+$ T cells. Comparisons were made between T1D-susceptible NOD mice, which express insulin forms Ins1 and Ins2, and NOD.$Ins2^{-/-}$ mice, which have markedly reduced thymic insulin expression and show accelerated T1D development. It was found that *Ins2* deficiency caused increased numbers of insulin-specific T cells to infiltrate pancreatic islets. To similarly investigate human T1D, a humanized mouse model, NOD.$\beta 2m^{-/-}$.HHD.$Ins2^{-/-}$, was generated. These mice, which express the T1D-associated human class I MHC molecule HLA-A*0201, showed a rapid onset of T1D and an increased proportion of HLA-A*0201–restricted insulin-reactive $CD8^+$ T cells relative to control mice. These data indicate that insulin-specific $CD8^+$ T cell responses in T1D are augmented in response to deficient thymic insulin expression levels and thereby provide a credible explanation for the observed link between insulin gene alleles and T1D susceptibility.

A Most In-Gene-ious Paradox

The *Mclk1* gene encodes a mitochondrial enzyme that is required for the biosynthesis of ubiquinone and its decreased expression results in reduced mitochondrial function and increased oxidative stress. Paradoxically, age-associated loss of mitochondrial function is also reduced in heterozygous $Mclk1^{+/-}$ mice, and they enjoy a prolonged lifespan. Wang et al. (p. 582) employed the $Mclk1^{+/-}$ mice to investigate the relationship between mitochondrial ROS (mROS) and the regulation of hypoxia inducible factor 1α (HIF-1α) expression. Compared with control littermates, HIF-1α levels were elevated in $Mclk1^{+/-}$ peritoneal macrophages, and HIF-1α levels further increased under hypoxic conditions. $Mclk1^{+/-}$ peritoneal macrophages were classically activated with a reduced ability to be alternatively activated by IL-4. Compared with controls, some $Mclk1^{+/-}$ animals were hypersensitive to LPS treatment, and some showed spontaneously elevated cytokine levels, but $Mclk1^{+/-}$ animals did not exhibit an increased incidence of chronic or acute tissue damage. Small interfering RNA-mediated knockdown of *Mclk1* in RAW264.7 cells confirmed that decreased *Mclk1* levels induced elevated mROS levels, and further experiments established a causal link between increased mROS levels and enhanced HIF-1α expression. Taken together, these data suggest that HIF-1α–mediated alterations of immune function may positively impact longevity.

Advantageous Autoantibodies



Inflammatory mediators (IMs) associated with autoimmune disorders can sometimes elicit an IM-specific autoantibody response. To determine if cancer of the prostate (CaP)-associated IM expression induces an autoantibody response, Izhak et al. (p. 1092) analyzed human sera and prostate tissue sections from normal donors and individuals with benign prostate hypertrophy or CaP. The chemokine CCL2 was singularly expressed at significantly elevated levels in patients with CaP and at slightly elevated levels in benign prostate hypertrophy donors compared with normal donors. Accordingly, patients with CaP showed a significant CCL2-specific Ab response that neutralized CCL2-induced migration of both prostate and macrophage cell lines. When prostate cell lines C1 (tumorigenic) and C3 (non-tumorigenic) were administered to immunocompetent mice, both cell lines expressed CCL2 but only C1 induced a CCL2-specific Ab response. Vaccination of C1-treated mice with a CCL2-encoding DNA plasmid enhanced CCL2 Ab production and significantly inhibited tumor growth and progression. These

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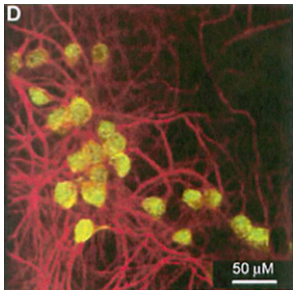
data suggest that an anti-CCL2 Ab response is tumorgenicity dependent and may serve as a reliable diagnostic marker for CaP. Furthermore, vaccination-induced amplification of the anti-CCL2 Ab response shows potential as a therapeutic intervention.

HANDs Down to CEP-1347



The causative factors of HIV-1–associated neurocognitive disorders (HANDs) are not known, but the presence of HIV-infected mononuclear phagocytes within the gray matter of HIV-1 encephalitic brains suggests a role for virus-induced neuroinflammation (NI). If this is true, adjunctive treatment with an anti-inflammatory drug may decrease the extent of neurotoxicity and, concomitantly, the incidence of HAND. To this end, Eggert et al. (p. 746) tested the multilineage kinase inhibitor CEP-1347. In vitro, CEP-1347 treatment of HIV-1–infected myeloid-derived monocytes (HIV-1-MDMs) reduced expression of various monocyte-derived inflammatory proteins. Furthermore, when cultured with conditioned supernatants from HIV-1-MDMs, primary murine cortical neurons exhibited effects of neurotoxicity, whereas murine cortical neurons cultured with conditioned supernatants from CEP-1347–treated HIV-1-MDMs did not. To investigate CEP-1347's effects on HIV-induced NI in vivo, mice were injected with HIV-1-MDM in the basal ganglia followed by treatment with CEP-1347 or vehicle alone. Compared with vehicle-alone mice, the brains of CEP-1347–treated mice exhibited decreased evidence of neurotoxicity, despite similar viral loads between the two groups. These data indicate that CEP-1347 treatment decreases HIV-1-MDM–mediated NI and associated neurotoxicity, thereby providing promise as an adjunct medicine to antiretroviral drug treatment.

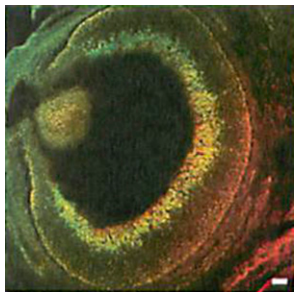
Vitamin D Balances Inflammation

Vitamin D deficiency has been associated with increased susceptibility to severe respiratory viral infections. Confoundingly, it also depresses the NF-κB signaling pathway, which plays an important positive role in antiviral immune responses. To clarify vitamin D's role in respiratory viral infections, Hansdottir et al. (p. 965) examined vitamin D's effects on NF-κB signaling in human tracheobronchial epithelial (hTBE) cells. Vitamin D treatment of hTBE cells increased NF-κB inhibitor IκBα protein levels, and increased IκBα levels were maintained even after subsequent respiratory syncytial virus (RSV) infection, which is known to trigger TLR-mediated degradation of IκBα. Overexpression of a nondegradable form of IκBα in hTBE mimicked the effects conferred by vitamin D treatment. Moreover, vitamin D's immunomodulatory effects were abolished by small interfering RNA-mediated silencing of vitamin D receptor expression. Despite its depressive effects upon the NF-κB pathway, vitamin D treatment did not increase RSV replication or load in hTBE. In light of these findings, it appears that vitamin D inhibits NF-κB–mediated inflammatory responses to RSV infection of airway epithelium without detrimentally affecting antiviral immunity.

Dually Dynamic IL-4Rα in Control

Th2 cells are key responders to helminth infections but are also negatively associated with allergy and asthma. Thus, elucidating how Th2 activity is controlled in vivo is of great interest. Th2 differentiation and function is largely directed by IL-4. Accordingly, Perona-Wright et al. (p. 615) investigated IL-4Rα expression and IL-4 responsiveness during the Th2 response. To create an in vitro draining lymph node model, sort-purified naive $CD4^+$ T cells from two different TCR-transgenic (Tg) mice were cocultured in the presence of irradiated APCs. In culture, all cells initially expressed low levels of IL-4Rα and upregulated its expression with IL-4 treatment. However, when either Tg cell population's cognate peptide was introduced, the responder (Ag-specific) Tg cells ceased to express IL-4Rα, whereas the bystander Tg cells upregulated IL-4Rα expression. The analysis of $CD4^+$ T cells harvested from the draining mesenteric lymph nodes of mice infected with an enteric helminth confirmed the same modulations of IL-4Rα expression in vivo. Further studies revealed that local IL-4 production by responder T cells was necessary and sufficient for IL-4Rα upregulation on bystander T cells. Thus, the effects of Ag-induced IL-4 expression are tightly regulated via the differential modulation of IL-4Rα expression on responder and bystander $CD4^+$ T cell populations.

Self-Guidance by MHC I



The expression of MHC I differentially regulates the cytolytic activities of $CD8^+$ T cells and NK cells. The former's activities rely upon MHC I:peptide specificities, whereas NK cell activity is dictated solely by MHC I expression levels. MHC I expression is tightly regulated in the CNS, and now experiments by Escande-Beillard et al. (p. 816) suggest that this may be, at least in part, due to a regulatory role for MHC I in neurodevelopment. When embryonic retina explants were exposed to self-MHC I loaded with a ubiquitously expressed Ag peptide, neurite outgrowth was inhibited. Inhibition was dependent upon proper folding of the MHC I molecules but was peptide independent, as neurons did not discriminate between self- and nonself peptides. Furthermore, neuroinhibitory activity required a self-MHC I allele. Interestingly, retinal neurons of MHC I-deficient mice were insensitive to exogenous MHC I, suggesting that endogenous MHC I might be necessary for MHC I sensitization of embryonic retinal neurons. In support of this notion, both MHC I molecules and their receptors were expressed early in retina development. Thus, taken together, these data suggest that MHC I plays a role in neurodevelopment and neuronal sensitivity to MHC I may require a MHC I-dependent selection process for MHC I receptors.

Summaries written by Meredith G. Safford, Ph.D.