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THE JOURNAL OF IMMUNOLOGY

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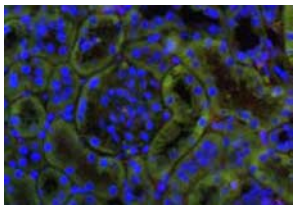
Chemokines and Lupus Pathogenesis



Drawn by a previous observation that CXCR4 was dysregulated in the murine BXSB model of spontaneous lupus, Wang et al. (p. 4448) examined the role of this G protein-coupled chemokine receptor in lupus pathogenesis. Among models of lupus with active nephritis, B6.*Sle1Yaa*, BXSB, and MRL.*lpr* CXCR4 cell surface expression was found to be up-regulated on monocytes, neutrophils, B cells, and plasma cells. This increased expression was attributed to the presence of the inflammatory cytokines IL-1β, IL-6, and TNF-α, as well as the stimulation of TLR4 signaling. The increase in CXCR4 found in lupus models was associated with an increase in the ability of neutrophils, monocytes, and B cells to migrate. B cells from these mice also had enhanced survival characteristics. The expression of the CXCR4 ligand CXCL12 was increased in the nephritic kidneys of mice with spontaneous lupus. When mice with lupus were treated with a peptide antagonist of CXCR4, the animals exhibited reduced lupus pathogenesis as characterized by prolonged survival times, reduced autoantibodies, and reduced renal lymphocytic infiltrates. This peptide agonist treatment also caused a reduction in splenomegaly and end-stage organ disease. Thus, the data demonstrate that CXCR4 and its ligand CXCL12 play an important pathogenic role in the lymphoproliferative and nephritic aspects of lupus and point to these molecules and pathways as potential therapeutic targets.

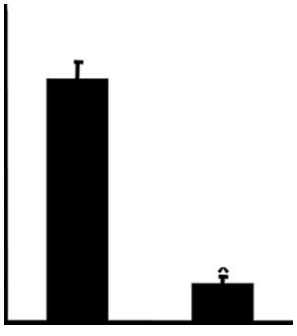
The Innate Importance of Taking Your Vitamins

Vitamin D, known most widely for its importance to bone health and the prevention of rickets in children, is also important for maintaining innate immunity. Bioactive vitamin D, 1,25-dihydrovitamin D (1,25$(OH)_2$D), induces production of the human cathelicidin antimicrobial peptide (hCAP). Within monocytes and macrophages, the stimulation of TLRs can induce the expression of the vitamin D receptor and localized expression of the vitamin D precursor 25-hydroxyvitamin D_3 (25OHD). This in turn causes induction of hCAP. Using patients that were attending a bone clinic, Adams et al. (p. 4289) examined the changes in hCAP expression both in vivo and ex vivo. Thirty-eight percent of patients in the study had vitamin D deficiency and were receiving vitamin supplementation. No correlation was found between the serum concentration of vitamin D metabolites and the serum levels of hCAP in these patients. However, patient monocytes stimulated ex vivo with the TLR1/2 ligand 19-kDa lipoprotein or the TLR4 ligand LPS in "vitamin D-insufficient" conditions showed an increase in the expression of the vitamin D-activating enzyme CYP27b1 and a decrease in the expression of hCAP. Thus, stimulation of the TLR pathway demonstrated how vitamin D deficiency can affect hCAP expression. After monocyte treatment with the 19-kDa ligand, a correlation between the expression of hCAP and serum 25OHD supplementation levels was observed. This expression could be enhanced by the addition of 25OHD, as well as by the addition of serum from patients receiving vitamin D supplements. Together, these results suggest that vitamin D enhances innate immunity by providing for the local production of hCAP in response to TLR stimulation.

Helpless Memory T Cells

Every immunologist is instilled with the knowledge, early in their careers, that CD4 help is important for proper CD8 T cell memory development and recall responses. Fuse et al. (p. 4244) have determined one of the molecular mechanisms by which CD4 T cells help CD8 T cells to become effective memory cells by looking at the phenomenon of the "helpless memory T cell" in a model of vaccinia virus infection. They found that CD4 help is necessary during the priming of CD8 T cells for memory cell differentiation. However, in the absence of CD4 helper T cells, the helpless phenotype can be rescued by stimulation of CD40 without CD4 T cells. The lack of recall response from helpless CD8 T cells was due neither to apoptosis nor to TRAIL expression but was correlated with increased programmed death (PD)-1 expression. Conversely, enhancement of the recall response from helpless memory T cells was achieved through blockade of PD-1. IL-2 signaling provided in vivo through immune complexes of α-IL-2:IL-2 also rescued the virally induced recall responses of helpless memory T cells and reduced PD-1 expression. Taken together, the data demonstrate a molecular mechanism for the generation of memory CD8 T cells that is independent of TRAIL and indicate that the "helpless" phenotype can be reversed at several stages during the immune response to viruses.

The Travels of MDP



Muramyl dipeptide (MDP) is an agonist of the nucleotide-binding oligomerization domain (NOD)-like receptor (NLR) 2 (NOD2). MDP stimulation of NOD2 causes the activation of NF-κB and MAPK, leading to an antimicrobial and proinflammatory immune response. However, the mechanism by which MDP is endocytosed into acidified macrophage vesicles necessary for its function is still unknown. In this study, Marina-Garcia et al. (p. 4321) have shown that this endocytic process and subsequent NOD2 activation is mediated by the action of clathrin and dynamin. The intracellular targeting of MDP was blocked by chlorpromazine, which inhibits clathrin-dependent endocytosis. Molecules that blocked pinocytosis or scavenger and mannose receptors did not effect MDP internalization. Both MDP endocytosis and the

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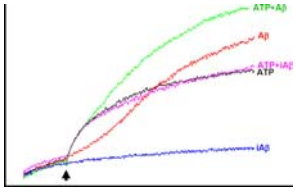
subsequent NOD2-dependent signaling events were unaffected in peptide transporter PepT1-deficient macrophages. This was a surprising finding, as PepT1 had previously been implicated in the endocytosis of MDP. The blocking of MDP internalization by chlorpromazine or the reduction of expression of clathrin by RNA interference also hindered the NF-κB and MAPK signaling events normally induced by MDP. Inhibition of dynamin, a GTPase required for clathrin-coated vesicle budding, prevented the endocytosis of MDP as well. Thus, these experiments show that clathrin and dynamin are necessary for the endocytic pathway that allows the trafficking of MDP through macrophage vesicles and signaling through NOD2.

How Amyloid β Triggers Neuroinflammation



During Alzheimer's disease, accumulation of amyloid β (Aβ) has been identified as a key pathogenic event. However, the mechanism linking this protein to inflammation in the brain has remained a mystery. Taking the knowledge that the nucleotide receptor $P2X_7$ was up-regulated in brain tissue during neuroinflammation and that Aβ causes ATP release from microglia, Sanz et al. (p. 4378) investigated how this plays a role in Alzheimer's. $P2X_7$ is known for its proinflammatory activity and is found to be up-regulated in a transgenic model of Alzheimer's disease as well as in brain samples from Alzheimer's patients. The authors demonstrated that Aβ treatment was responsible for an increase in intracellular Ca^{2+}, microglial-plasma cell permeabilization, ATP release, and IL-1β secretion in wild-type mice. These effects were absent in $P2X_7$-deficient mice. In addition, when Aβ was injected into the intra-hippocampus there was an increase in IL-1 β in wild-type mice, but this increase was not seen in $P2X_7$-deficient mice. The authors concluded that these data indicated an autocrine/paracrine loop activated by Aβ-mediated stimulation of $P2X_7$. Thus, the $P2X_7$ receptor on microglia is identified as potential target for the inflammation caused by Aβ and becomes a potential target in Alzheimer's disease.

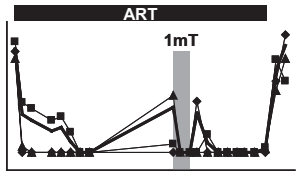
Vitamin D_3, Directing Traffic

Using a minimally toxic derivative of LPS, monophosphoryl lipid A (MPLA), Enioutina et al. (p. 4296) wanted to determine whether they could use this adjuvant to stimulate both mucosal and systemic responses to an s.c. administered Ags. They found that the addition of MPLA elicited both mucosal and systemic immune responses to vaccination and that this was due to the local production of calcitriol. MPLA caused the up-regulation of 1α-hydroxylase, the enzyme responsible for converting inactive vitamin D_3 into the active calcitriol form. The locally produced calcitriol caused the migration of myeloid dendritic cells from the cutaneous site of vaccination to both draining and nondraining lymph nodes. Both B and T cells responses were effectively triggered, and both serum IgG2a and mucosal IgA were identified. The production of calcitriol was mediated through the up-regulation of 1α-hydroxylase expression by a type I IFN response and was "TIR-domain-containing adapter-inducing IFN-β" (TRIF)-dependent. The ability of dendritic cells to respond to calcitriol and type I IFN was necessary for their ability to migrate to nondraining lymph nodes. Taken together, the data demonstrate that MPLA, through the action of vitamin D_3, was capable of acting as an excellent adjuvant and stimulated both systemic and mucosal immune responses to an s.c. administered Ag.

Before T Cells Become Double Positive

There is a small population of thymocytes that rearrange the TCRα gene before the double positive stage. However, what happens to these T cells in the periphery is unknown. To answer this question, Hendricks et al. (p. 4267) developed a mouse in which TCRα rearrangement occurs at the double negative stage of development. This was achieved through the use of mice carrying floxed *RAG2* alleles and Cre recombinase directed by the CD4 promoter (Cre(+)$RAG2^{fl/fl}$). These Cre(+)$RAG2^{fl/fl}$ mice had compromised T cell development with a limited TCRα repertoire in the TCRαβ^+ T cells that successfully developed. These T cells preferentially used the early-rearranging Vα genes. Thy-1^+TCRαβ^+ intraepithelial lymphocytes were present in the guts of these mice, but not the Thy-1^-TCRαβ^+ subset, leading the authors to propose that differences in Thy-1 expression correlated with the usage of distinctive TCR α-chains and TCR-stimulated activation. However, when T cell progenitors from Cre(+)$RAG2^{fl/fl}$ mice were tested in bone marrow chimeras, they could not compete with wild-type T cell progenitors. Thus, the authors conclude that the normal peripheral T cell population contains very few cells from those that undergo only early TCRα rearrangements. However, when these cells were able to populate the intraepithelial lymphocyte compartment, they were able to generate a relatively normal Thy-1^+TCRαβ^+ pool.

The Power of IDO



During HIV and SIV infection there is increased IDO activity. IDO, which catalyzes the degradation of tryptophan (Trp) to kynurenine (Kyn), has been hypothesized to suppress anti-HIV/SIV T cell responses. The IDO inhibitor 1-methyl-D-tryptophan (D-1mT) is currently undergoing testing in cancer immunotherapy clinical trials. Boasso et al. (p. 4313) treated SIV-infected rhesus macaques receiving antiretroviral therapy (ART) with D-1mT for 13 days. They found that D-1mT treatment increased plasma levels of Trp with no concomitant reduction in Kyn levels, indicating that the IDO pathway in some way compensated for the effects of the inhibitor. However, in ART refractory animals, D-1mT reduced plasma and lymph node virus to undetectable levels. This D-1mT-mediated viral suppression was not seen in ART-untreated animals and the inhibitor had little effect on either Trp or Kyn levels without ART treatment. To clarify these effects, the authors looked at IDO and TGF-β mRNA levels in the lymph nodes of ART-treated animals and found that both the enzyme and the cytokine were increased with D-1mT treatment. This suggested that there was a compensatory mechanism for IDO expression but also that D-1mT was having a more general immunomodulatory effect. However, D-1mT did not interfere with the action of ART on T cells, as it did not change the ART-mediated increase in CD4 or CD8 T cells or cells expressing Bcl2 or change the reduction in regulatory T cells. Thus, the authors demonstrated that D-1mT suppressed viral replication in a synergistic fashion with ART. The mechanism by which this occurs still remains to be elucidated.

Summaries written by Kira R. Gantt, Ph.D.