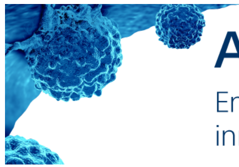
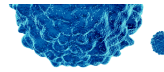

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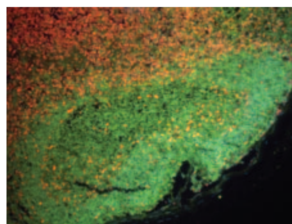
THE JOURNAL OF IMMUNOLOGY

IN THIS ISSUE

Few $CD4^+$ T Cells but No AIDS



Clinical AIDS in humans is associated with a loss of peripheral $CD4^+$ T cells. In contrast, SIV infection of its natural primate host usually does not result in decreased $CD4^+$ T cells, opportunistic infections, lymphomas, or other signs of clinical AIDS. In two of six sooty mangabeys injected with SIV, Milush et al. (p. 3047) noted a dramatic $CD4^+$ T cell decline in blood, lymph nodes, lungs, and GALT at 37 and 51 wk postinfection (p.i.). Viral plasma titers also decreased. However, lymph node architecture, SIV envelope protein-specific Ab responses, SIV-specific $CD8^+$ T cell levels, and $\gamma\delta$ T cell responses were not affected. SIV coreceptor usage expanded from recognition of CCR5 to an additional three coreceptors at 43 wk p.i. in one of the two mangabeys with decreased $CD4^+$ T cell levels and at 71 wk p.i. in the other. This multitropic phenotype was maintained beyond 195 wk p.i. and was associated with amino acid changes that localized within the V3 region of the SIV envelope gene. The $CD4^+$ T cell-low animals remained healthy nearly 6 years after SIV infection. The authors propose that $CD4^+$ T cell depletion induced by SIV is not sufficient to induce AIDS in the natural primate host. They propose that the low levels of $CD4^+$ T cells are adequate to maintain health in the absence of dysfunction of other immune cell subsets.

IgA in Cancer Immunotherapy

Targeted clinical therapy against several types of cancer expressing the epidermal growth factor receptor (EGF-R) involves tyrosine kinase inhibitors or human IgG isotype anti-EGF-R mAbs. Yet triggering of Ab-dependent cellular cytotoxicity (ADCC) by polymorphonuclear cells (PMN) is more effective via the IgA receptor than the IgG receptor. Dechant et al. (p. 2936) compared chimeric isotype switch variants of an EGF-R Ab and found that IgA_1 and IgA_2, but not IgG_1, isoforms bound FcαRI-transfected cells and freshly isolated PMNs. The two IgA isoforms also inhibited EGF binding to cells expressing EGF-R. All three EGF-R Ab variants inhibited ligand-induced receptor phosphorylation and cell growth. Only the IgA isoforms triggered PMN-mediated ADCC, with IgA_2 more effective at low E:T cell ratios. Target cell killing was mediated via the FcαRI, as shown by the ability of an anti-CD89 Ab to block it. The human IgA_2 isoform triggered a high level of PMN-mediated ADCC killing of tumor cells in vitro using human whole blood from healthy donors or from G-CSF-primed donors as the effector source. The experiments demonstrate that recombinant human IgA anti-EGF-R Abs are more effective at ADCC-mediated PMN killing of EGF-R-expressing human tumor cells than their human IgG1 counterparts.

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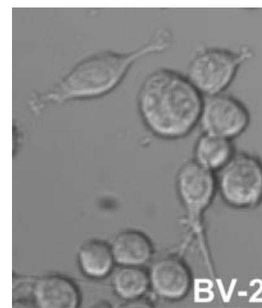
PGD_2 Suppresses NK Type 1 Responses

Suppression of NK cell functions such as migration and cytotoxicity is seen in asthma. Although the lipid mediator PGD_2 is produced in asthmatic lungs, it is not known if PGD_2 directly suppresses NK cells. Chen et al. (p. 2766) detected expression of two PGD_2 receptors on primary human NK cells by RT-PCR and immunoblotting. Most NK cells expressed high levels of the D prostanoid receptor (DP) but very low levels of the chemoattractant receptor-like molecule on Th2 cells (CRTH2). Addition of PGD_2 or a DP receptor agonist, but not a CRTH2 agonist, before NK interaction with target cells inhibited NK cytotoxicity. NK cells pretreated with PGD_2 or the DP receptor agonist decreased the production of IFN-γ, TNF-α, and GM-CSF type 1 cytokines by activated NK cells and blocked NK cell migration in response to a chemokine compared with controls. Intracellular levels of cAMP were elevated in NK cells treated with PGD_2 or the DP receptor agonist; a cAMP antagonist reversed the inhibition of cytotoxicity by PGD_2- or DP receptor agonist-treated NK cells. Intracellular Ca^{2+} concentrations in NK cells activated through the CD16 receptor were reduced by the addition of PGD_2 or DP receptor agonist; control or CRTH2 agonist had no effect. The authors conclude that PGD_2 inhibits human NK cell functions via the cAMP-dependent pathway of the DP receptor, thus inducing a type 2-biased immune response.

Regulating Microglia Apoptosis



Activated microglia help to resolve CNS injury, but uncontrolled microglia activation can be destructive. Lee et al. (p. 3231) selected mouse microglia cells resistant to NO-induced apoptosis to study the molecular mechanisms by which activated microglia are removed to resolve neuroinflammation. Lipocalin-2 (*lcn2*) mRNA expression was greatly reduced in the apoptosis-resistant cells treated with NO compared with controls. Apoptosis sensitivity to NO and to other cytotoxic agents was enhanced in microglia cells stably transfected with a vector expressing the *lcn2* gene compared with nontransfected control cells. In contrast, microglia cells transfected with an *lcn2* short interfering RNA had decreased NO sensitivity that was reversed by addition of recombinant mouse LCN2 protein. The LCN2 protein sensitized cultured and primary mouse microglia cells to NO donors; addition of a siderophore-iron complex abolished the sensitization. Expression of *lcn2* mRNA and secretion of LCN2 protein were induced by several stimuli, including LPS, serum withdrawal, and PMA. Along with increased apoptosis, LCN2 protein induced a morphological change in the microglia from ramified to ameboid. A calcium ionophore induced deramification, increased NO-induced cell death, and increased intracellular *lcn2* mRNA levels. The authors

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conclude that the LCN2 protein produced by microglia may act in an autocrine fashion to deramify activated microglia and sensitize them to apoptosis as a means to regulate CNS inflammation.

The Importance of Introns in FcRn

The neonatal Fc receptor for IgG (FcRn) facilitates transport of maternal IgG to a fetus or newborn. FcRn is expressed in a variety of cell types and controls IgG levels in tissues and in blood, but its regulation during immune responses or inflammatory reactions is not known. On p. 2999, Liu et al. detected up-regulation of *FcRn* mRNA and FcRn protein in a human macrophage cell line, an intestinal epithelial cell line, and freshly isolated human monocytes after TNF-α or IL-1β treatment or in response to CpG or PMA/vitamin D3/LPS. Cytokine stimulation increased the formation of FcRn-IgG complexes. Stimulated *FcRn* mRNA levels were reduced in cells treated with an inhibitor of NF-κB p65 nuclear translocation and DNA binding or by overexpression of a mutated IκBα. Three *FcRn* gene intronic regions that bound NF-κB proteins were identified by chromatin immunoprecipitation assays and confirmed by EMSA. Stimulation of luciferase reporter genes driven by the FcRn promoter plus each of the intron sequences separately occurred in TNF-α-treated cells cotransfected with a plasmid expressing NF-κB proteins. A chromosome conformation capture assay demonstrated interactions between the NF-κB binding sequences and the FcRn promoter. Human IgG added to either side of polarized human intestinal epithelial cells was transported in both directions after exposure of the cells to TNF-α. The data indicate that FcRn expression in human cells stimulated by cytokines or TLR ligands is regulated by NF-κB binding to three *FcRn* gene intronic regions.

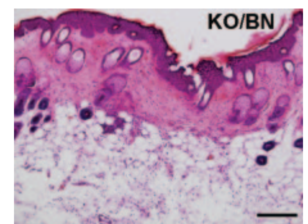
Rethinking Preclinical Safety Testing

Although extensively tested in vitro and in Cynomolgus macaques, the CD28-specific mAb TGN1412 induced a life-threatening cytokine storm (cascade of proinflammatory cytokines) in six volunteers in a phase I clinical trial. In a follow-up to their confirmation of the purity of the superagonist used in the trial, Stebbings et al. (p. 3325) at the National Institute for Biological Standards and Control in the United Kingdom exposed human PBMCs or whole blood to the mAb under a variety of conditions. They found that TGN1412, air dried onto the wall of microtiter wells, induced TNF-α, IL-6, and IL-8 production from human, but not macaque, PBMCs or 20% blood coincubated for 24 h. Similar results were noted after the addition of TGN1412 to a coculture of human PBMCs plus endothelial cells. Intense CD4$^+$ T cell proliferation occurred in the human cultures. Proliferation of macaque lymphocytes exposed to immobilized TGN1412 in the presence of human IL-2 was modest but increased in the presence of rhesus anti-CD3 mAb. High levels of IL-2 and modest levels of IFN-γ and TNF-α from human lymphocytes were measured after only 6 h of incubation with immobilized TGN1412 or with TGN1412 captured by immobilized anti-human Fc Ab. Maximum proliferation and IL-2 and IFN-γ production were achieved in vitro with a concentration of TGN1412 equivalent to the dose administered during the clinical trial. The authors caution that in vitro protocols should mimic in vivo presentation conditions and that Cynomolgus macaque lymphocyte responses to reagents may be different than those of human lymphocytes. Tolerance in macaques does not necessarily mean tolerance in humans.

TLR4 and Susceptibility to RSV

Either of two single nucleotide polymorphisms (SNPs) in the ectodomain region of the *TLR4* gene increases the risk of respiratory syncytial virus (RSV) disease in full-term infants. Although premature infants are at high risk for RSV disease, any correlation with the *TLR4* SNPs is unknown. On p. 3171, Awomoyi et al. found that 94 of 105 (90.2%) archived nasal lavages of high-risk children from early clinical trials of Ab-mediated prophylaxis for RSV were heterozygous for one SNP and 92 of 105 (90.2%) were heterozygous for the other SNP. Heterozygosity was 10.5 and 6.5%, respectively, for healthy controls from pooled data of 25 studies, 13.5 and 7.7%, respectively, for 52 contemporary healthy controls, and 4.4 and 2.2%, respectively, for pediatric controls presenting with respiratory symptoms but not RSV infection. Among the high-risk children, 92 of 105 samples carried both SNPs heterozygously. No homozygosity for either SNP was detected. Samples were analyzed by PCR amplification and confirmed by DNA sequence analysis. In 12 of 13 samples randomly chosen from the 92 double heterozygous case specimens, both SNPs were within the same chromosomal homologue. The authors conclude that the two cosegregating *TLR4* gene polymorphisms predispose premature infants to RSV infection, possibly through defective TLR4 signaling during lung development in utero.

Genetic Control of Psoriasis



Although IFN-α/β and IFN-γ are reported to play roles in human psoriasis, the polygenic nature of this autoimmune skin disease has made its study difficult. Arakura et al. (p. 3249) looked at genetic control of inflammatory skin disease in mice lacking the IRF-2 (IFN regulatory factor-2) transcription factor that attenuates IFN-α/β signaling. *IRF-2*$^{-/-}$ mice on a C57BL/6 background (*IRF-2*$^{-/-}$BN) developed the disease, whereas *IRF-2*$^{-/-}$ mice on a BALB/c or a C57BL/6 $\times$ BALB/c F_1 background did not. Increased skin disease severity mapped strongly to loci on chromosomes 4 and 10 and less strongly to loci on chromosomes 1, 2, and 16; loci on chromosomes 4 and 10 from BALB/c mice down-modulated disease severity. RT-PCR of mRNAs from the skin of the three *IRF-2*$^{-/-}$ strains showed up-regulation of two IFN-inducible genes, IFN-α/β, IFN-γ, and STAT1 only in *IRF-2*$^{-/-}$BN mice. *IRF-2*$^{-/-}$BN mice, also lacking either RAG-1 or β2m, did not have skin disease, and *IFN-γ* mRNA was not up-regulated in their skin. *IRF-2*$^{-/-}$BN mice lacking the α-chain of IFN-γR also did not develop skin inflammation, although ~20% of the animals developed a milder disease at old age. *IRF-2*$^{-/-}$BN mice lacking IFN-α/βR or β2m remained disease-free and did not have elevated expression of the two IFN-inducible genes, STAT1, or IFN-γ. This study identifies chromosomal loci that dominantly modulate the severity of inflammatory skin disease in an *IRF2*$^{-/-}$ mouse model of psoriasis and indicate that IFN-γ up-regulation by CD8$^+$ T cells is downstream of an IFN-α/β response.

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

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