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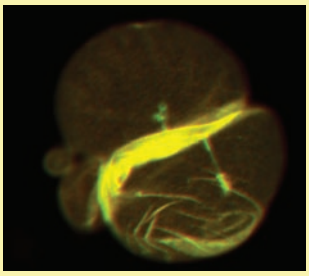
In this issue

Tregs are not defective in patients with MS MS is a chronic inflammatory disease thought to be caused by self-reactive T cells. Previous studies have indicated that the suppressive function of natural Tregs (characterized as CD4+CD25high) is defective in individuals with MS. However, Michel and colleagues have found that if cells expressing high levels of the α-chain of the receptor for IL-7 (CD127) are excluded from the analysis (because they have recently been shown to be activated T cells and not Tregs), natural Tregs from individuals with MS and healthy controls exhibit equivalent suppressive capacity (pages 3411–3419). Thus, although the authors observed a marked defect in the suppressive function of unseparated CD4+CD25high T cells isolated from MS patients, when CD127high cells were removed, the remaining cells inhibited T cell proliferation and cytokine production equally as well as CD4+CD25highCD127low cells from healthy individuals. These data indicate that the suppressive function of natural Tregs (when characterized as CD4+CD25highCD127low) is not defective in individuals with MS. Further, as CD4+CD25highCD127high cells from individuals with MS proliferated more and secreted more IFN-γ and IL-2 than the same cells from healthy individuals, the defect in CD4+CD25high T cell suppressive function in patients with MS is probably due to increased activation of CD127high T cells. Premature aging with or without farnesylation Hutchinson-Gilford progeria syndrome (HGPS), a childhood […]

Premature aging with or without farnesylation

Hutchinson-Gilford progeria syndrome (HGPS), a childhood disease with features resembling premature aging, is caused by a point mutation in the *LMNA* gene that leads to the production of progerin — a mutant form of prelamin A. Although the carboxyl-terminal domain of both progerin and wild-type prelamin A are farnesylated, this domain is not cleaved from progerin. The accumulation of farnesylated progerin has been linked to the pathogenesis of HGPS; however, Yang and colleagues have now shown that a nonfarnesylated form of progerin can elicit disease in mice (pages 3291–3300).



They generated mice with a mutant *Lmna* allele ($Lmna^{nHG}$) encoding progerin that cannot be farnesylated and found that these mice developed HGPS-like disease phenotypes, although these phenotypes were somewhat milder than those observed in mice that were identical except that they had a mutant allele ($Lmna^{HG}$) encoding progerin that can be farnesylated, rather than the $Lmna^{nHG}$ allele. Further analysis revealed that mouse embryonic fibroblasts and tissues from $Lmna^{nHG/+}$ mice contained lower levels of progerin than the cells and tissues of $Lmna^{HG/+}$ mice, suggesting an explanation for the milder phenotype. These findings suggest that farnesyltransferase inhibitors, which are currently being evaluated in children with HGPS, may have rather limited therapeutic benefits.

Tregs are not defective in patients with MS

MS is a chronic inflammatory disease thought to be caused by self-reactive T cells. Previous studies have indicated that the suppressive function of natural Tregs (characterized as $CD4^+CD25^{high}$) is defective in individuals with MS. However, Michel and colleagues have found that if cells expressing high levels of the α-chain of the receptor for IL-7 (CD127) are excluded from the analysis (because they have recently been shown to be activated T cells and not Tregs), natural Tregs from individuals with MS and healthy controls exhibit equivalent suppressive capacity (pages 3411–3419). Thus, although the authors observed a marked defect in the suppressive function of unseparated $CD4^+CD25^{high}$ T cells isolated from MS patients, when $CD127^{high}$ cells were removed, the remaining cells inhibited T cell proliferation and cytokine production equally as well as $CD4^+CD25^{high}CD127^{low}$ cells from healthy individuals. These data indicate that the suppressive function of natural Tregs (when characterized as $CD4^+CD25^{high}CD127^{low}$) is not defective in individuals with MS. Further, as $CD4^+CD25^{high}CD127^{high}$ cells from individuals with MS proliferated more and secreted more IFN-γ and IL-2 than the same cells from healthy individuals, the defect in $CD4^+CD25^{high}$ T cell suppressive function in patients with MS is probably due to increased activation of $CD127^{high}$ T cells.

Insight into HIV-1 transmission and interaction with the immune system

Despite many years of intensive investigation, there is still no drug to cure individuals infected with HIV-1 and no vaccine or therapeutic to prevent infection. To facilitate the development of such public health tools, many researchers believe we need more insight into the mechanisms underlying the transmission of HIV-1 and the interactions between the human immune system and the virus. Steps forward in both of these areas are provided by two studies in the current issue. In the first study, de Jong and colleagues have detailed one mechanism by which genital coinfections could increase an individual's risk of becoming infected with HIV-1 (pages 3440–3452). In an ex vivo human skin explant model, it was found that although immature immune cells known as Langerhans cells (LCs) captured HIV-1, they did not efficiently transmit the virus to T cells, something that is important for the initiation of systemic disease. By contrast, efficient virus transmission was observed if LCs were activated by inflammatory stimuli. Interestingly, different inflammatory stimuli (TNF-α and a ligand for the TLR1/TLR2 heterodimer) increased HIV-1 transmission by distinct mechanisms. As the genital pathogens *Candida albicans* and *Neisseria gonorrhea* triggered TLRs and induced TNF-α production in vaginal and skin explants, the authors suggest that in the presence of a genital pathogen, LCs might be activated directly by pathogenic structures and indirectly by inflammatory cytokines, thereby increasing an individual's risk of becoming infected with HIV-1. In the second study, Manches and colleagues have found that HIV-1–stimulated human immune cells known as plasmacytoid DCs (pDCs), which are known to potentiate antiviral innate and adaptive immune responses, also limit the extent of the antiviral immune response by inducing the generation of Tregs from naive $CD4^+$ T cells (pages 3431–3439). The ability of HIV-1–stimulated pDCs to induce naive $CD4^+$ T cells to become Tregs was dependent on their expression of the enzyme indoleamine 2,3-dioxygenase, which was induced following triggering of TLR7 by HIV-1 genomic RNA. Further analysis indicated that pDC-induced Tregs inhibited the maturation of bystander conventional DCs, providing insight into one mechanism by which these cells could dampen the antiviral immune response. These studies further our understanding of the biology of HIV-1 transmission and interaction with the immune system, but many questions remain to be answered if we are ever to overcome the HIV/AIDS pandemic.