



mal scarring (8). Some of the clinical features of EDS are actually evident in the families with ICH studied by Gensure et al. (6), and this makes sense. But the reason why some ICH patients also develop acute bone lesions at a specific age is not clear. The authors hypothesize that periosteum is only loosely attached to the underlying bone structure in infants and that periosteum detachment (perhaps facilitated by the collagen mutation) would be the *primum movens* leading to increased bone formation. Such a hypothesis is not entirely consistent with the histologic studies done sequentially in cases of ICH (3), which clearly indicate that inflammation is the initial event, in agreement with the clinical and PGE-related observations. It is noteworthy that Gensure et al. found that 79% of the individuals studied who were heterozygous for the *COL1A1* mutation had an episode of cortical hyperostosis, while 21% of the subjects carrying the R836C substitution do not develop disease, which confirms

the clinically observed reduced penetrance at the molecular level. Many unresolved questions regarding the pathology of this disease may have to wait for the engineering of an appropriate mouse model.

In conclusion, by showing convincingly that Caffey disease is associated with a *COL1A1* missense mutation, Gensure et al. (6) have once again demonstrated the power of linkage analysis. They have lifted the lid of a black box, but what is inside the box remains to be discovered.

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A tax on luxury: HTLV-I infection of CD4⁺CD25⁺ Tregs

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Almost a quarter of a century ago, Oldstone and colleagues proposed that infection of cells by noncytopathic viruses may lead to an alteration of the cells’ ability to produce certain products or perform certain tasks, i.e., inhibition of “luxury function.” In this issue of the *JCI*, this topic has been revisited by Yamano et al., who demonstrate that human T cell lymphotropic virus type I (HTLV-I) infection of CD4⁺CD25⁺ Tregs in patients with HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP) results in a decrease in *FOXP3* mRNA and protein expression (see the related article beginning on page 1361). This leads to the inability of HTLV-I-infected CD4⁺CD25⁺ Tregs to inhibit the proliferation of CD4⁺CD25⁻ Tregs, due to the effect of the HTLV-I *tax* gene. Defects in the Treg population could be responsible for the large numbers of virus-specific T cells and occurrence of lymphoproliferation and inflammatory autoimmune disease in HAM/TSP patients.

Nonstandard abbreviations used: AC, asymptomatic HTLV-I-infected individual; HAM, HTLV-I-associated myelopathy; HD, healthy donor; HTLV-I, human T cell lymphotropic virus type I; TSP, tropical spastic paraparesis.

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Several years ago, Uchiyama (1) provided interesting insight into the workings of human T cell lymphotropic virus type I (HTLV-I) infection. He stated that “The interaction between HTLV-I-infected cells with dysregulated function and different kinds of cells in the host, such as lymphocytes and vascular endothelial cells through viral peptides, antigen receptors, cell adhe-

sion molecules, and cytokines, appears to be one of the basic mechanisms underlying the development of HTLV-I-associated diseases.” In this issue of the *JCI*, the study by Yamano et al. (2) provides an interesting confirmation of Uchiyama’s précis. The authors present data showing that the *tax* gene of HTLV-I can cause dysfunction of infected CD4⁺CD25⁺ Tregs and that the interaction between these HTLV-I-infected Tregs and other CD4⁺CD25⁻ T cells is dysregulated. One could infer from the study by Oldstone et al. (3) that viral infection of differentiated cells can lead to different outcomes, which depend on what type of cell is infected and what gene product expression is turned off.

HTLV-I is a human retrovirus that is the etiologic agent for HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP). The prevalence of HAM is about 2.4–3.8% in HTLV-I-positive individuals (4, 5). Therefore, only a minority of infected individuals go on to develop HAM. Yamano et al. (2) explored HTLV-I infection

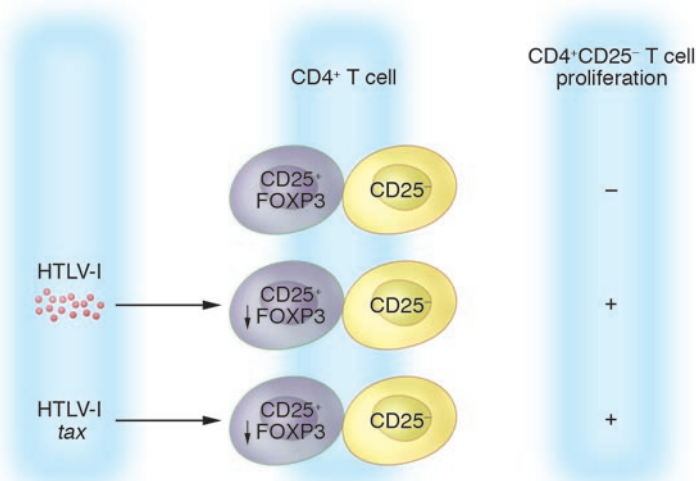


Figure 1

CD4⁺CD25⁺ Tregs limit the proliferation of stimulated CD4⁺CD25⁻ T cells. Studies have shown that lack of these regulatory cells can lead to lymphoproliferative disease and autoimmunity. In this issue of the *JCI*, Yamano et al. (2) report that CD4⁺CD25⁺ T cells infected with HTLV-I (from HAM/TSP patients) have decreased levels of FOXP3 expression and lack the ability to suppress CD4⁺CD25⁻ T cell proliferation. CD4⁺CD25⁺ T cells transfected with the HTLV-I *tax* gene also have decreased levels of FOXP3 expression and lack the ability to suppress the proliferation of stimulated CD4⁺CD25⁻ T cells.

of CD4⁺CD25⁺ Tregs in HAM/TSP patients and the possible immunological consequences of downregulating the function of regulatory cells. HTLV-I primarily infected CD4⁺ T cells, particularly the CD4⁺CD25⁺ T cell subset (6–8). It may be possible that infected CD4⁺CD25⁺ T cells are partly responsible for the chronic expansion of the population of Tax-specific CD8⁺ T cells often observed in HAM/TSP patients (8). This expansion of the T cell population can lead to a circumstance in which 30% of the CD8⁺ T cells in the peripheral blood mononuclear cell population are Tax specific. Tax is generally thought to transactivate transcription of regions of the HTLV-I genome as well as numerous cellular genes and is a major viral protein recognized in infected individuals. The expansion of the CD8⁺ T cell population could be due in part to dysregulation of infected CD4⁺CD25⁺ T cells (9).

Various investigators have found a high provirus load in individuals with inflammatory diseases such as HAM/TSP and HTLV-I-associated uveitis (10–13). A significant number of HAM patients also suffer from other inflammatory organ diseases such as leukoencephalopathy, infiltrates in the lungs, Sjögren syndrome, and arthropathy (14). One of the reasons for the increase in inflammation and lymphoproliferation could be the dysregulation of the CD4⁺CD25⁺ Treg population due to Tax

expression, which leads to the unregulated expansion of either CD4⁺ or CD8⁺ T cells.

Tregs and FOXP3

CD4⁺CD25⁺ Tregs express various cell-surface markers including CD62 ligand, CD103, CD152, and glucocorticoid-induced TNF receptor family-related protein (GITR; reviewed in ref. 15). In humans, these cells express the forkhead transcription factor gene *FOXP3* (the mouse homolog is *Foxp3*). *FOXP3* encodes a forkhead/winged-helix family transcriptional repressor known as Scurfin (reviewed in ref. 16). These Tregs have the ability to decrease proliferation of and IL-2 production by CD4⁺CD25⁻ T cells as well as expansion of CD8⁺ T cells. Humans with mutations or defects within the *FOXP3* gene or its regulatory elements develop lymphoproliferative disease, which leads to autoimmune diseases such as dermatitis, type 1 diabetes, thyroid disease, anemia, and thrombocytopenia (16). Induction of FOXP3 in CD4⁺CD25⁻ T cells can convert these cells into a suppressor or regulatory phenotype (17). Therefore, expression of FOXP3 correlates with their regulatory activity.

Tax regulates the regulator

Yamano et al. found increased levels of expression of *FOXP3* mRNA in CD4⁺CD25⁺ T cells compared with the expression levels in the CD4⁺CD25⁻ T cells of HAM/TSP patients,

asymptomatic HTLV-I-infected individuals (ACs), and uninfected healthy donors (HDs), as expected (2). However, they also found a significantly lower level of FOXP3 expression in HAM/TSP CD4⁺CD25⁺ T cells compared with that in CD4⁺CD25⁺ T cells from the HD group (Figure 1). In addition to conducting mRNA expression studies, the authors examined FOXP3 protein expression levels by flow cytometry. FOXP3 protein levels were found to correlate with mRNA expression, in that CD4⁺CD25⁺ Tregs from HAM/TSP patients contained less FOXP3 than did CD4⁺CD25⁺ cells from the HD group. These data indicate that HTLV-I-infected CD4⁺CD25⁺ Tregs have reduced *FOXP3* mRNA and protein expression. They also suggest that HTLV-I-infected CD4⁺CD25⁺ Tregs cannot modulate the proliferation of CD4⁺CD25⁻ T cells. In coculture studies, Yamano et al. showed that this was indeed the case (Figure 1). Mixing irradiated HTLV-I-infected CD4⁺CD25⁺ T cells (from HAM/TSP patients) with uninfected, stimulated (via anti-CD3), nonirradiated CD4⁺CD25⁻ T cells (from HDs) resulted in decreased suppression of CD4⁺CD25⁻ T cell proliferation compared with the suppression seen in irradiated control CD4⁺CD25⁺ T cells mixed with stimulated CD4⁺CD25⁻ T cells (both from HDs). They found that transfection of the HTLV-I *tax* gene into purified CD4⁺CD25⁺ T cells from HDs caused a decrease in FOXP3 expression, whereas transfection with the HTLV-I *env* gene did not (Figure 1). Interestingly, the CD4⁺CD25⁺ T cells from HDs transfected with the HTLV-I *tax* gene lost their ability to suppress anti-CD3-induced CD4⁺CD25⁻ T cell proliferation, whereas untransfected CD4⁺CD25⁺ T cells were able to mediate this suppression.

Conclusions

It has been suggested that the tax-mediated mechanism described by Yamano et al. could be one of the reasons why HTLV-I-specific CD8⁺ T cells are so numerous in HAM/TSP patients (18). In HAM/TSP patients in whom a high proportion of the CD4⁺CD25⁺ Tregs are infected with HTLV-I, the cells' ability to suppress the proliferation of viral-specific CTLs would be limited. It has been previously shown that CD4⁺CD25⁺ Tregs can inhibit the proliferation of CD8⁺ T cells (9). Another hypothesis is that the inflammatory diseases associated with HTLV-I infection are related to defects in the ability of infected CD4⁺CD25⁺ Tregs to modulate or regulate autoreactive CD4⁺CD25⁻ T cells. The lack of suppression of these autoreactive



cells could lead to an autoimmune component in HTLV-I infection. For example, Sjögren syndrome, which is associated with HAM/TSP, might be a result of unregulated expansion of autoreactive CD4⁺ T cells leading to increased numbers of autoantibodies as well as lymphoproliferation and systemic inflammatory changes and the presence of infiltrating T cells. Viruses have evolved to subvert the host cells they infect, leading to unexpected consequences. The findings by Yamato et al. could help explain why certain viral infections are often associated with autoimmune diseases through their inhibition of cellular luxury function.

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A seek-and-hide game between Cd1-restricted T cells and herpesviruses

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T and NK cells collaborate to control viral infections, discerning minute differences between infected and uninfected cells. At the same time, viruses have evolved to escape this discovery. In this issue of the JCI, Ganem and colleagues show that Kaposi sarcoma-associated herpesvirus (KSHV) inhibits CD1d presentation to T cells (see the related article beginning on page 1369). This novel immune evasion strategy highlights the importance of CD1d-restricted T cells in controlling viral infection and raises an interesting question: how do T cells recognize viruses in the context of CD1 molecules that bind lipids? In the case of herpesviruses, alterations in endosomal trafficking might trigger redistribution of CD1/lipid complexes to cell surfaces, thereby promoting recognition by CD1d-restricted T cells.

Nonstandard abbreviations used: HCMV, human cytomegalovirus; HSV, herpes simplex virus; KSHV, Kaposi sarcoma-associated herpesvirus; MIC, MHC class I chain-related; MIR, modulator of immune recognition; TGN, trans-Golgi network; ULBP, UL16-binding protein; US2, unique short region open reading frame 2.

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Recognition of viruses

Control of viruses by the immune system is critically dependent upon recognizing differences between infected and uninfected cells. It is also imperative that immune cells identify viruses inside cells before progeny are produced and can spread. Early recognition relies on detecting the appearance of new cell-surface markers or the loss of oth-

ers. The classic examples are MHC class I and MHC class II molecules, which present peptides derived from viral proteins to T lymphocytes, which use variable TCRs to discern the viral peptides against a huge background of cellular peptides. NK cells recognize cells that lack cell-surface MHC class I molecules, a situation caused by viral inhibition of the class I pathway. Viral infection can also trigger the appearance of new molecules detectable by NK cells. For example, genes encoding MHC class I chain-related-A (MIC-A) and MIC-B proteins and UL16-binding protein (ULBP) are coupled to hair-trigger promoters that are “tripped” by viruses so that cell-surface MIC proteins and ULBPs are detected by NK group 2D (NKG2D) receptors on NK and CD8⁺ T cells (1).

Viral immune evasion

As the immune system endeavors to recognize the presence of a virus inside cells,