significantly elevated IL-6, and IFN-treated patients had significantly elevated IL-1Rα. There was no significant difference in cytokine profile comparing ECD patients treated with IFN-α to untreated patients. Furthermore, cytokine profiles were relatively unchanged over months in individual patients on whom serial plasma samples were available. The authors conclude that these data reveal ECD as a condition characterized by specific systemic proinflammatory activation that is not affected by treatment with IFN-α.

Previous studies demonstrated that histiocytes in ECD are clonal, consistent with a neoplastic process.[11,12] However, the absence of Ki67$^+$ cells suggests that they accumulate rather than proliferate within the lesions.[7] In a single patient study, increased cytokine expression (IL-1α, IL-1β, IL-2, and IL-8) was noted in peripheral blood mononuclear subsets by quantitative polymerasechain reaction, demonstrating that cells other than the ECD histiocytes may contribute the proinflammatory plasma cytokine profile.[13] The relative culpability of the ECD lesion histiocytes, peripheral blood dendritic cell precursors, circulating monocytes, or other cells in cytokine production, lesion formation, and disease progression remains to be determined. With this report, Arnaud et al's study supports a model in which the ECD cytokine microenvironment develops within a complex systemic inflammatory atmosphere. The ECD cytokine signature may provide further clues to pathogenesis as well as tools for diagnosis and targeted therapy.

Conflict-of-interest disclosure: The authors declare no competing financial interests. ■

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● ● ● CLINICAL TRIALS

Comment on Allers et al, page 2791

The power of 1 in HIV therapeutics

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In this issue of *Blood*, Allers and colleagues describe the long-term follow-up of their previously reported HIV+ patient who was treated with allogeneic CCR5Δ32/Δ32 stem cell transplantation (SCT) for relapsed acute myeloid leukemia (AML).[1,2] The patient has since remained off antiretroviral therapy (ART) and without evidence of HIV disease for 45 months after the SCT despite relapse of his AML, which necessitated a second successful transplantation.

During the additional follow-up reported here, CD4 T-cell reconstitution has reached normal values in peripheral blood with 100% donor chimerism as confirmed by absent CCR5 expression. The CD4 T cells of the patient, similarly to other SCT recipients, had a higher proportion of activated effector memory cells and a lower proportion of naive cells compared with healthy controls. CD4 T-cell reconstitution was also achieved in the gut mucosa in the reported patient, again to a similar degree as that observed in other SCT recipients. HIV RNA and DNA have not been detected in plasma and several tissues obtained to evaluate symptoms of graft-versus-host disease (GVHD; gut, liver) and leukoencephalopathy (brain). These biopsies showed that tissue macrophages were eventually replaced by donor-derived macrophages lacking CCR5 expression. The T cells of the patient do express normal levels of CXCR4 and appear fully susceptible to X4-tropic HIV in vitro, a relevant observation considering that 2.9% of the isolated viruses before transplantation were X4 or dual-tropic. Finally, HIV-specific antibodies (Ab) continued to wane with only envelope Ab remaining detectable at the end of follow-up.

This single-patient study is important in more than one way. It is hard to prove with certainty the complete eradication of HIV and its latent reservoirs and thus the possibility that residual X4 strains could at some point reactivate and lead to HIV disease progression. Yet it is still reasonable to conclude that CCR5Δ32/Δ32 SCT has probably led to a cure of HIV infection in this particular case. This lends further support to the evaluation of therapeutic strategies that can generate the delta32 phenotype, known to confer resistance to primary infection and slow disease progression in established HIV infection. One of the most encouraging findings of the report is that the SCT allowed over time the replacement of one of the challenging and resilient cells for HIV eradication: the tissue macrophages. This case also highlights how SCT, a high-mortality procedure for HIV+ patients in the past, has gained ground with the advent of ART for appropriate underlying diseases.[3,4] In addition, T-cell reconstitution can be achieved in HIV+ patients after SCT, as was recently shown in a series of autologous SCT in HIV patients with relapsed lymphoma.[5]

Many questions still remain: Could more sensitive techniques studying a much larger number of cells or specific subsets of CD4 T cells be more revealing in finding latently infected cells, and would the virus be replication-competent? Considering the

anticipated extremely low number of cells with latent virus, sampling error when accessing peripheral blood samples or tissue biopsies is a considerable limitation. But does it really matter if this is a "sterile" cure, if the patient is clinically well and not receiving antiretroviral medications? It is uncertain at this point what interval without signs of virus in the absence of ART will eventually be broadly accepted as HIV cure. Is it possible that the "donated" immune system's innate and adaptive immune responses to HIV contribute to the control of residual low levels of virus as a graft-versus-virus phenomenon? Experience so far would suggest that latent viruses typically reactivate in the setting of GVHD. Chemotherapeutic regimens have previously been used in HIV+ patients to treat malignancies, but did the preparative and conditioning regimens in this case, which included total body irradiation and antithymocyte globulin, contribute to the possible elimination of resistant reservoirs such as resting CD4 T cells and macrophages? Or could gemtuzumab, a monoclonal anti-CD33 Ab combined with a cytotoxic antibiotic (calicheamicin), have played a role, considering that CD33 is expressed not only on myeloid precursors but also granulocytes, monocytes, macrophages, and mast cells?

Dramatic decreases in allogeneic transplantation-related mortality reflected by all-around decreases in infections, GVHD, and end-organ damage despite increasing age and disease severity of transplantation recipients have been recently reported.[6] Despite these improvements, the risk is still unacceptably high for chronically ART-treated HIV+ patients in the absence of an underlying malignancy that would require SCT as therapy. It is thus obvious that such an invasive, long, and expensive procedure cannot be proposed as a reasonable strategy to treat the majority of HIV-infected patients who can live long, healthy lives with the use of ART, nor is it feasible to find HLA-matched donors with Δ32/Δ32 mutation for the majority of people. Yet this study, the first of its kind, provides a proof of concept for further evaluation of strategies involving antiviral gene modification of SCTs in nonhuman primate models and HIV+ patients.[7,8] It is uncertain that autologous SCT with CCR5 manipulation alone would achieve the same effect as allogeneic transplantation in the latent viral reservoirs. It is likely that a combination of strategies aiming both to limit CD4 T-cell targets and targeting viral reservoirs may be required to succeed in reproducing the unique combination of events that led to this cure.

The cure of HIV now has a face and a name after a 3-decade fight with HIV. The quest for more practical options for the remaining 33 million people living with HIV worldwide has to continue.

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● ● ● IMMUNOBIOLOGY

Comment on Takagi et al, page 2887, and on Niemela et al, page 2883

Oncogenic Ras scales the ALPS

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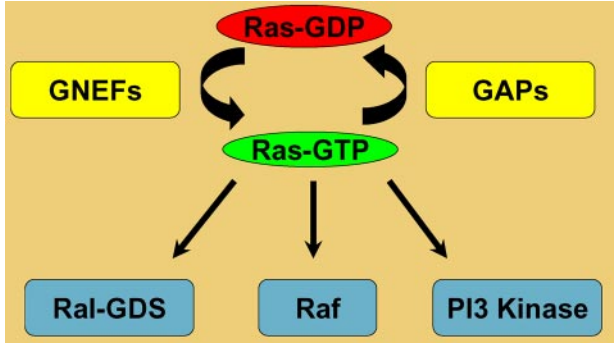
In this issue of *Blood*, 2 studies identify somatic *KRAS* mutations in pediatric patients who presented with features of autoimmune lymphoproliferative syndrome (ALPS), hyper γ globulinemia, and autoimmune cytopenias.[1,2] With a previous report of an *NRAS* mutation in an adult with lifelong lymphoproliferation,[3] these cases define a new and unexpected role of mutant *RAS* in hematologic disorders, furthering our understanding of lymphoid growth control and raising the possibility of therapeutic intervention.

Ras proteins regulate cell fates by cycling between active guanosine triphosphate–bound and inactive guanosine diphosphate–bound conformations (Ras-GTP and Ras-GDP; see figure). Ras activation is mediated by guanine nucleotide exchange factors (GNEFs). These proteins induce guanine nucleotide dissociation in response to extracellular stimuli, which allows Ras to associate with GTP. Upon GTP binding, Ras undergoes a conformational change and can interact productively with Raf1, phosphoinositide-3-OH (PI3) kinase, Ral-GDS, and other effectors. Ras-GTP is hydrolyzed to Ras-GDP through an intrinsic GTPase activity. This reaction is greatly augmented by GTPase-activating



Overview of the Ras cycle showing major classes of effectors.