altered life span or the potential of acquiring the ability to interact with the other components of the immune system? Do similar events occur in other immune cells on aging and with what consequences? An affirmative answer to the latter question would indicate that treatments targeting the PtdIns(1,4,5)P_3 pathway would have consequences on the immune system broader than just the restoration of migration accuracy of neutrophils.

By identifying specific PI3Ks involved in the ability of neutrophils to migrate appropriately, these studies go beyond a descriptive analysis of a phenomenon of basic, as well as clinical and societal, relevance. The reversal of the old phenotype by PI3K inhibitors suggests avenues of research for improving disease outcomes in aging patients.

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

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● ● ● TRANSPLANTATION

Comment on Schuetz et al, page 281

Tearing RAGs apart

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In this issue of *Blood*, Schuetz et al analyze the immunologic and nonimmunologic outcomes in cohorts of severe combined immunodeficiency (SCID) patients with either RAG or ARTEMIS mutations following allogeneic hematopoietic stem cell transplantation (HSCT).[1] The authors show that full immunologic recovery is more likely to be achieved if myeloablative conditioning is used; additionally, they show that in ARTEMIS patients, the use of alkylating chemotherapy agents is associated with a higher incidence of nonimmunologic complications. The challenge remains, especially in ARTEMIS deficiency, to achieve full immunologic recovery without long-term complications. The use of novel conditioning agents or the development of gene therapy strategies may help improve overall outcome for these patients.

Very few articles have the ability to change clinical practice. This article by Schuetz et al makes a strong argument to be one on not just 1, but 2, clinical issues.

SCIDs are a genetically heterogeneous group of conditions characterized by the absence of T cells, varying degrees of B-cell development (often categorized as T-B+ or T-B- forms), and presentation with severe recurrent infections in the first year of life. Definitive treatment by HSCT has shown increasing success over the years[2] and the absence of adaptive T-cell immunity in SCID has allowed HSCT to be undertaken without any chemotherapy conditioning, especially if a matched sibling donor is available.

Until very recently, the data on SCID HSCT outcome have been pooled together for all forms of SCID. However, treating physicians have long recognized that some SCID forms do better than others and also that long-term outcomes are different. Furthermore, in this genomic era and with the recognition of 20 different SCID gene defects[3] (at the last count), there is a need to tailor treatments and analyze outcomes according to the genetic form of SCID. The collaborative efforts of 3 centers in Ulm, Paris, and San Francisco finally allow us to make more rational treatment decisions and understand outcomes more clearly for the RAG and ARTEMIS forms of SCID.[1]

In both RAG and ARTEMIS SCID, the underlying molecular defect is associated with DNA breakage and repair. Importantly, RAG genes are lymphoid specific and are involved in the process of V(D)J recombination whereas ARTEMIS is ubiquitously expressed and is part of the nonhomologous end-joining (NHEJ) repair mechanism of all cells.[4] Nevertheless, both forms are immunologically characterized by the absence of T and B cells (T-B- SCID) and so have been treated similarly.

In this study, the overall survival outcomes are equivalent between the RAG and ARTEMIS types. However, the first major issue that this article highlights is the poor immunologic recovery in both these SCID forms following unconditioned HSCT. Without conditioning in the matched sibling/relative donor setting, only 50% of patients achieved T cells of >1000 cells per μL, only 42% had CD4 T cells >600 cells per μL, and 44% still receive immunoglobulin replacement. It is also likely, though not measured in this study, that there was minimal naive T-cell recovery. In both SCID forms, the molecular defect results in impairment of V(D)J recombination in thymocyte and B-cell progenitors. Thus, although thymocyte development is very abnormal, the thymic niche remains occupied and, similarly, B-cell progenitors occupy the bone marrow (BM) but do not develop. HSCT without chemotherapy conditioning is therefore unable to allow effective engraftment of donor progenitor cells in the thymus and even less so in the BM. As might be predicted, immune recovery is limited to mature T cells, which have a limited repertoire and provide limited B-cell help. In the haploidentical setting for both RAG and ARTEMIS SCID, HSCT with no or limited conditioning has even worse outcomes with very poor levels of engraftment and T-cell recovery, no B-cell recovery, a high rate of second HSCT, and poor overall survival.

Thus, clinical practice message 1 is that, in RAG and ARTEMIS SCID, myeloablative conditioning is required to achieve long-term T- and B-cell recovery. Unconditioned HSCT allows only limited immune recovery in the matched sibling/related donor

setting and should be avoided altogether if using haploidentical donors.

The other striking finding from this study is the significantly increased incidence of late complications in ARTEMIS patients in comparison with RAG SCIDs. Noninfectious and nonautoimmune complications were exclusively seen in ARTEMIS patients and included central growth hormone deficiency, central hypothyroidism, insulin-dependent diabetes, renal tubulopathy, pancreatic exocrine insufficiency, and pulmonary fibrosis. Abnormal permanent teeth development was also seen in 10 ARTEMIS patients. Univariate and multivariate analysis identified the use of alkylating agents as a significant predictive factor for the development of these abnormalities. Furthermore, analysis of growth in both cohorts showed that ARTEMIS patients who had received alkylating agents had significant growth failure in comparison with patients who had not received alkylating agents. Together, these data show a significant vulnerability of ARTEMIS patients to conditioning with alkylating agents that may relate to the underlying defect in systemic NHEJ repair.

Thus, clinical practice message 2 is that when transplanting ARTEMIS SCIDs, the use of alkylating agents is likely to result in significant late complications and growth failure.

Together, these messages seem at odds with each other because clearly, myeloablation is necessary for full immunologic recovery; but in ARTEMIS SCID, this is associated with late complications. Alternative approaches to myeloablation are not easy to find. Total body irradiation is likely to be more harmful although the use of targeted radioimmunotherapy to BM cells may have some utility.[5] Similarly, hematopoietic progenitor cell depletion by administration of specific antibodies may be an important development.[6] Gene therapy strategies for ARTEMIS[7] and RAG[8,9] deficiencies have shown proof of concept in murine models and clinical trial protocols are in development. This may provide an option when compatible donors are unavailable but will still need to be coupled in ARTEMIS SCIDs with an appropriate conditioning regime.

Clearly challenges remain, but this study and others[10] highlight the problems faced by specific SCID forms and make the case for us to deliver more gene-specific transplant strategies.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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● ● ● VASCULAR BIOLOGY

Comment on Aird et al, page 163

EPCR: holy grail of malaria cytoadhesion?

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In this issue of *Blood*, Aird et al[1] review recent findings that suggest the endothelial protein C receptor (EPCR), known for its pivotal role in mediating cytoprotection against coagulopathy, proinflammatory cytokines, and vascular permeability, may serve as a receptor for *Plasmodium falciparum*–infected red blood cells (IRBCs) in the brain.[2] In the process, coagulation is allowed to proceed unchecked and contributes to the pathogenesis of cerebral malaria.[3]

Over a century ago, Marchiafava and Bignami made the seminal observation that IRBCs are sequestered in the capillaries and postcapillary venules of the brain to create a mechanical obstruction to blood flow (see figure). Quantitative autopsy studies in the 1980s showed that sequestration is in fact widespread in infected patients, and the degree and organ specificity of sequestration correlated with clinical manifestations.[4] Since then, research efforts have focused on the identification of the endothelial receptor (s) and parasite ligand(s) involved in the process of cytoadhesion to develop antiadhesive therapies. Such a therapeutic approach could be lifesaving in the first 24 to 36 hours of hospitalization during which most deaths occur.

The cytoadherent ligand *P falciparum* erythrocyte membrane protein 1 (PfEMP1) is a 200- to 350-kDa, antigenically diverse protein encoded by ~60 copies of the *var* gene scattered throughout the *P falciparum* genome. Structurally, PfEMP1 consists of a conserved transmembrane and cytoplasmic domain, as well as highly variable extracellular domains assembled from an N-terminal segment, 2 to 7 Duffy-binding–like domains (DBLs), 1 to 2 cysteine-rich interdomain region, and C2 domains. PfEMP1 variants containing a combination of adhesion domains, termed domain cassettes (DCs) 8 and 13, have been