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A 2-hit model for chronic GVHD

Robertson Parkman1,2 1CHILDREN’S HOSPITAL LOS ANGELES; 2UNIVERSITY OF SOUTHERN CALIFORNIA KECK SCHOOL OF MEDICINE

In this issue of Blood, Dertschnig and colleagues1 demonstrate in mice that acute graft–versus-host disease (GHVD) results in a marked reduction of autoimmune receptor–expressing medullary thymic epithelial cells (Aire+ mTEC) and a decrease in the diversity of Aire-dependent tissue-restricted peripheral self-antigens (TRAs) required for effective negative thymic selection. Both of these abnormalities are reversed by the peritransplant administration of effecter T cells. J Exp Med. 2008;205(1):699-710.

Chronic GVHD continues to be a major cause of both morbidity and mortality after allogeneic hematopoietic stem cell transplantation (HSCT).2 Chronic GVHD has been assumed to be caused by the continuation of the pathogenic mechanisms that cause acute GVHD, primarily donor-derived T lymphocytes specific for histocompatibility antigens uniquely expressed by recipient cells.3 As a consequence, therapy for chronic GVHD has traditionally been directed at suppressing the donor antirecipient immune response. However, during the last 25 years, a series of murine experiments have indicated that donor-derived, autoreactive T lymphocytes (ie, T lymphocytes specific for antigens expressed by both donor and recipient cells) are present in murine HSCT recipients with chronic GVHD and that the chronic GVHD could be transferred by the donor-derived T lymphocytes into both donor and recipient mice.4-6

More recently, a clinical trial of low-dose subcutaneous IL-2 in human HSCT recipients with established chronic GVHD demonstrated that an increase in circulating regulatory T lymphocytes (Treg) resulted in clinical improvement, suggesting that deficiencies in Treg lymphocytes play a role in the pathogenesis of human chronic GVHD.7

Dertschnig et al report that mice with acute GVHD have a profound decrease in the frequency of Aire+ mTEC, which are necessary for the thymic production of naturally occurring Treg lymphocytes. Other investigators have previously demonstrated that the diverse expression of TRA by Aire+ mTEC is required for the effective thymic elimination of autoreactive T lymphocytes by negative selection.8 Using microarray analyses of isolated Aire+ mTEC, the present investigators report the decreased expression and diversity of TRA with a selective decrease in the TRA associated with the tissues that are the target organs of human chronic GVHD (skin, liver, salivary glands, lung, eye, and gastrointestinal tract). The result of the restricted diversity of TRA expression would be the extrathymic presence of autoreactive T lymphocytes. Their present results suggest a 2-hit model for chronic GVHD, in which the presence of extrathymic autoreactive T lymphocytes (Hit 1) in the context of immune dysregulation (deficiencies in Treg lymphocytes, Hit 2) can result in the development of chronic GVHD.

The peri-HSCT administration of the epithelial protectant drug, Fgf7, does not affect the initial post-HSCT decrease in mTEC but does hasten the recovery of Aire+ mTEC and improves the diversity of TRA expression. Fgf7 acts by stimulating the proliferation and differentiation of TEC progenitors and the proliferation of residual mTEC.9 The relative contribution of the 2 populations to the recovery of Aire+ mTEC is unclear. The presence of normal numbers of Aire+ mTEC with normal TRA diversity during the recapitulation of immunologic ontogeny, which occurs after the engraftment of donor hematopoietic stem cells, may result in the presence of adequate numbers of circulating Treg lymphocytes and effective negative thymic selection, which would eliminate the peripheral presence of autoreactive T lymphocytes, and an absence of chronic GVHD. As such, clinical trials to determine whether the peritransplant administration of Fgf7 results in a decreased incidence of chronic GVHD in human HSCT recipients are indicated.

The present murine experiments, however, do not address several potentially important clinical questions: (1) What would be the impact of the administration of Fgf7 to patients with established chronic GVHD?; (2) Do HSCT recipients with established chronic GVHD have an adequate number of TEC progenitors and residual mTEC for the Fgf7 to be effective?; (3) Do the TEC progenitors and mTEC in chronic GVHD patients become refractory to the action of Fgf7?; and (4) Is the loss of Aire+ mTEC during acute GVHD paralleled by a decrease in TRA diversity, or are they separable biological processes? If they differ, then some HSCT recipients may have a deficiency of Treg lymphocytes without the concomitant presence of peripheral autoreactive T lymphocytes, whereas other recipients may have adequate numbers of Treg lymphocytes with the presence of peripheral autoreactive T lymphocytes. Only HSCT recipients with both the presence of peripheral autoreactive T lymphocytes (Hit 1) and deficiencies in Treg lymphocytes (Hit 2) would be at risk of developing chronic GVHD. The immunophenotypic identification of functional human Treg lymphocytes will aid in the evaluation of
human chronic GVHD; however, the inability to identify immunophenotypic human autoreactive T lymphocytes is still a major limitation to our better understanding.10

Finally, the present results suggest that the focus of future research into new therapies to prevent or treat chronic GVHD should be directed at the thymic microenvironment rather than at lymphohematopoietic cells.

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VASCULAR BIOLOGY

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The endothelial protein C receptor and malaria

Tom van der Poll1 1UNIVERSITY OF AMSTERDAM

In this issue of Blood, Moxon et al provide novel insight into the pathogenesis of cerebral malaria, linking loss of the endothelial protein C receptor (EPCR) on brain vessels, caused by cytoadherent infected erythrocytes, with localized coagulation, inflammation, and disruption of endothelial barrier function.1

Malaria is caused by parasites of the genus Plasmodium, of which P falciparum is the most virulent.2 One of the most fatal manifestations of P falciparum infection is cerebral malaria, which especially affects children <6 years of age and is responsible for an annual death toll of nearly a million infants in Africa alone. In recent years, the cycle of coagulation and inflammation has emerged as a pivotal component of malaria pathogenesis.3 In normal homeostasis, activation of coagulation is compensated by concurrent induction of anticoagulant mechanisms.4 In areas of excessive activation of the clotting cascade, thrombin acts as a feedback inhibitor of coagulation by binding to the endothelial receptor thrombomodulin (see figure). The thrombomodulin-thrombin complex converts the zymogen protein C into activated protein C (APC), a reaction that is greatly accelerated by EPCR.5,6 APC acts as an anticoagulant by virtue of its capacity to proteolytically inactivate clotting factors Va and VIIIa. When attached to EPCR, APC in addition can exert anti-inflammatory, antiapoptotic, and vasculoprotective signals via protease activated receptor (PAR).1. In case of impaired function of the protein C system, high thrombin levels can activate PAR1, resulting in effects that are opposite to those transduced by APC, disrupting endothelial barrier function.

A hallmark feature of severe malaria is sequestration of infected erythrocytes in blood vessels.2 The elegant investigations by Moxon et al provide a long-sought explanation of why red blood cell sequestration especially leads to damage in the brain.1 In postmortem studies in children that had died of cerebral malaria, endothelial sites of adherent erythrocytes were shown to colocalize with loss of EPCR. Moreover, the authors developed a novel approach that enabled examination of blood vessels with relevance for the brain vasculature in children with cerebral malaria directly after admission to the hospital. For this, they used subcutaneous tissue microvessels as an ex vivo surrogate for brain endothelium and demonstrated reduced expression of both EPCR and thrombomodulin in cerebral malaria patients compared with healthy controls. Children with cerebral malaria had higher levels of soluble EPCR and thrombomodulin in their cerebrospinal fluid than febrile control patients, suggesting that the loss of these receptors at least in part was caused by shedding. Importantly, in plasma, the balance between the production of thrombin (measured by the levels of the prothrombin F1+2 fragment) and APC was not altered in cerebral malaria compared with healthy children and children with mild febrile disease or uncomplicated malaria, indicating that at the systemic level, coagulation activation was compensated. Together, these data strongly suggest that cerebral malaria is associated with a localized disturbance of coagulation and inflammation caused by a local loss of EPCR and thrombomodulin initiated by sequestration of infected erythrocytes, changes that damage the brain due to the already low constitutive expression of EPCR and thrombomodulin in healthy brain vessels.1,7

Another recent study has implicated EPCR in the pathogenesis of malaria by a completely different mechanism.8 In malaria, adherence of red blood cells to endothelium is caused by an interaction between P falciparum erythrocyte membrane protein-1 ( PfEMP1) family members, transported to the erythrocyte membrane as a consequence of parasite infection, and receptors on the vascular endothelium.2 In this respect, PfEMP1 subtypes containing domain cassettes 8 and 13 are important for sequestration of infected erythrocytes in severe childhood malaria.9 Turner et al very recently revealed EPCR as the endothelial receptor for PfEMP1 domain
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