bind to platelets through TLR2 and/or TLR4 leading to aggregation and heterotypic aggregate formation as well as activation of the coagulation pathway to form thrombi. This reaction could lead to a myriad of pathophysiologic events depending on the specific clinical setting, including unstable coronary syndromes or sepsis-induced vascular occlusion. The next step will be demonstrating the presence and importance of these pathways in vivo, particularly in clinical settings. Understanding the specific clinical role of the complex interaction between histones, platelets, and immune receptors will continue to add to our understanding of thrombotic disease and the interaction of inflammation and platelets.

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Comment on Zlotoff et al, page 1962

Supply-side economics finds the thymus

Jarrod A. Dudakov and Marcel R. M. Van den Brink MEMORIAL SLOAN-KETTERING CANCER CENTER

In this issue of Blood, Zlotoff and colleagues demonstrate that despite relaxed entry requirements after irradiation and hematopoietic stem cell transplantation (HSCT), insufficient supply of bone marrow (BM) T-cell progenitors acts as a limiting factor to thymic reconstitution,1 contributing toward delayed T-cell recovery.

The thymus contains no self-renewing T-cell progenitors, but instead relies on the importation of BM-derived precursors from the circulation. The identity of this blood-borne progenitor, and in particular the extent of its lineage commitment, remains elusive and even controversial.2 However, mounting evidence suggests that there may actually be multiple progenitors with T lineage and thymic seeding capacity, which all contribute to thymopoiesis.3,4 Interestingly, while the precise identity of the thymus-seeding T-cell progenitor remains contentious, the mechanism by which these cells gain entry to the thymus and differentiate into mature T cells has been surprisingly consistent (see figure).4,6 Expression of several molecules had previously been postulated for their importance in this process; however, only recently have studies emerged, including others by Bhandoola and colleagues, that have offered significant insight into the molecular pathways of thymic importation. The receptor-ligand interactions between p-selectin glycoprotein ligand-1 (PSGL-1)/p-selectin,7 CCL25/CCR9, and CCL19-CCL21/CCR76,9 have all been identified as fundamental in this active process of thymic importation. Although in single knockout animals it appears that there is at least some redundancy in these pathways, in CCR7 and CCR9 double knockout (DKO) animals, this redundancy is dispensed and thymic settling is almost completely blocked. This was shown in studies of both the prevascular fetal setting as well as in postnatal thymus importation.8,9

The thymus is exquisitely sensitive to damage and regeneration can be severely impaired, particularly after immunodepletion such as after cytoreductive chemotherapy or the myeloablative conditioning required for successful HSCT. While previous studies have pointed toward both damage to the supporting thymic stromal microenvironment and reduced T-lineage potential of hematopoietic progenitors as fundamental factors in this delayed regeneration, the underlying mechanisms and their relative contribution to posttransplantation thymopoiesis are poorly understood.10 Here, Zlotoff et al address the biologically and clinically relevant issue of thymic reconstitution after irradiation, ultimately offering potential targets for improving long-term T-cell recovery after HSCT. The key findings demonstrate that after irradiation there is: (1) an uncoupling of the steady-state...
thymic importation regulatory processes, (2) a significant defect in regeneration of the BM progenitor pool capable of thymic seeding, and (3) intrathymic niches remain unsaturated for extended periods.

Using the same CCR7/CCR9 DKO animals this group used previously to demonstrate their importance for steady-state thymic importation of progenitors, Zlotoff and colleagues found that after lethal irradiation and HSCT there is a brief window where the regular dependence of thymic entry on CCR9 and CCR7 is broken. In assessing the kinetics of this uncoupling they found that while there was reduced reconstitution from CCR7/CCR9 DKO cells up to 3 weeks after transplantation, after which their relative contribution declined considerably. Interestingly, the importance of PSGL-1 in this process of thymic importation was maintained even after irradiation. Zlotoff et al then go on to show that the BM-resident Lin− c-kit+ Flt3+ fraction, which contains most T-lineage progenitors after transplantation, was significantly depleted for at least 4 weeks after transplantation. This finding indicates that increasing the supply of progenitors could considerably enhance thymic reconstitution. Indeed this was the case, and thymic reconstitution was significantly increased in a dose-dependent fashion.

These findings suggest that even despite the uncoupling of CCR7 and CCR9 from the process of thymic seeding, deficiency in the supply of progenitors from the BM leads to unsaturated thymic niches for at least 10 weeks after transplantation, ultimately causing delayed reconstitution. Moreover, taken together with the prolonged availability of intrathymic niches, the uncoupling of the processes regularly used in steady-state thymopoiesis could provide further evidence at the molecular level of the regulation of thymic “gates” and the periodic entry of precursor T cells postulated by Goldschneider and colleagues—an process that is likely disrupted after irradiation. It will be of considerable interest to identify the regulating factors at play in the irradiated setting and, critically, how these can be manipulated to enhance thymic reconstitution after HSCT.

These studies by Zlotoff et al represent an important advance in furthering our understanding of the processes underpinning thymic seeding, particularly in the context of the clinically relevant situation of immune reconstitution after HSCT. Their findings highlight that in attempting strategies to enhance thymic reconstitution we must not only focus on the thymus and its ability to support T-cell development, but also on the supply of BM-resident progenitors that can seed the thymus. These crucial insights will not only aid in developing strategies to enhance thymic reconstitution using precursor T cells,12 but also offer an important target for manipulation of thymic importation of progenitors for achieving tolerance to solid organ transplants and generating efficient and effective antitumor responses.

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Comment on Miller et al, page 1971

X-ALD: centralize care in an international network

Jaap J. Boelens UMC Utrecht

In this issue of Blood, Miller et al describe the efficacy of hematopoietic cell transplantation (HCT) in 60 patients with childhood cerebral adreno-leucodystrophy (ALD).1 To further improve the outcomes of cellular treatment options in this very rare disease, there is need for coordination of care and a well-functioning international clinical and research network.

After the first report from Aubourg in 1990 and a 2004 international report from Peters et al (n = 126 of whom only 94 with complete dataset were analyzed),1 the data from Miller et al once again demonstrate efficacy of transplantation for otherwise rapidly fatal childhood neurodegenerative disease. The outcomes from this recent (2003-2009) single-center cohort are encouraging, with an overall survival rate of ~ 80%, with ~ 90% survival for those who receive a transplant when minimally affected (absent neurologic disease or Loes score < 10). In line with previous reports,2-5 predictors for poor survival/disease progression after HCT were high Loes scores (> 10) or having neurologic dysfunction before HCT. Miller and colleagues speculate that better supportive care in the past decade and better patient selection are the main causes of improved survival rates in this recent cohort. Several centers, most notably the University of Minnesota, have been leaders in advancing the care of patients with inherited metabolic diseases (IMDs). In
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