Transplantation

Comment on Kelly et al, page 5734

High-TECh thymus

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In this issue of Blood, Kelly and colleagues provide a possible solution to poor thymic function and prolonged immune deficiency following allogeneic BMT by demonstrating the additive benefit of combining KGF with androgen blockade to speed recovery of thymic function and reconstitution of functional T cells after BMT.

The thymus is a dynamic organ with regard to both the lymphoid and stromal compartments. The 3-dimensional thymic stromal compartment, composed primarily of cortical and medullary thymic epithelial cells (TECs), fibroblasts, and endothelial cells, directly supports thymocyte development and selection.1 Myeloablative conditioning prior to hematopoietic stem-cell transplantation (HSCT) damages and depletes TECs. Because T-cell reconstitution and the generation of a broad T-cell repertoire require factors supplied by TECs, prolonged T-cell immunity deficiency due to TEC injury predisposes patients to infections. Adults who undergo allogeneic HSCT, and who typically have poor age- and chemotherapy-related TEC support of thymopoiesis, are especially vulnerable.2 Low TEC levels would impede T-cell reconstitution, regardless of the number of stem and thymic progenitor cells infused.

Hormonal factors can inhibit thymopoiesis. Androgens (eg, testosterone) strongly suppress thymopoiesis via effects on TECs and other androgen receptor–bearing cells in the thymus. Physical castration of old mice can reverse thymic atrophy linked to age-related increases in androgen levels.3 In addition, androgen ablation has been reported to enhance thymopoiesis and reduce costimulatory thresholds for peripheral T-cell activation, possibly resulting in enhanced host immunity.4 Consistent with this, initial clinical studies have indicated that pretransplant castration may improve patient thymopoiesis and T-cell recovery.5,6 TECs also may be positively regulated by thymic proteins. Keratinocyte growth factor (KGF), also known under the generic drug name palifermin, is a member of the fibroblast growth factor family that binds FGFR2-IIIb expressed by TECs. Studies in mice and rhesus macaques have demonstrated that thymic injury and T-cell deficiency can be partially ameliorated by KGF pretreatment; however, maximal benefit was not observed until relatively long after bone marrow transplantation (BMT).7,8

The individual thymopoietic effects of KGF and physical castration, and the broad distribution of cognate receptors for KGF as well as androgen within thymic tissues, led the authors to pretreat allo-BMT recipients with both KGF to induce TEC mitogenesis and a chemical luteinizing hormone–releasing hormone supra-agonist, leuprolide (Lupron; TAP Pharmaceutical Products, Lake Forest, IL), to block the androgen-inhibitory pathway. Prior to conditioning, these agents, when given together but not individually, normalized TEC subset numbers and thymic architecture, led to supranormal thymopoiesis and accelerated peripheral CD4/CD8 T-cell reconstitution, facilitated CD8 T-cell–mediated clearance of a live pathogen, and augmented a CD4 T-cell–dependent B-cell humoral response. Distinct TEC subsets were protected by each reagent. Importantly, palifermin is approved for use in HSCT patients to prevent mucositis, and various chemical luteinizing hormone–releasing hormone supra-agonists including leuprolide acetate (ie, Lupron) have been used for several decades to treat prostate cancer. Each agent is under separate investigation in clinical studies to determine its potential for enhancing T-cell reconstitution in patients undergoing HSCT. While future clinical trials arising from these provocative preclinical studies will need to be performed to determine whether the incidence of infectious complications can be diminished without adverse effects on graft-versus-host disease or tumor recurrence, it is likely that multimodal therapy targeting TEC subsets and other thymic stromal cells holds the key to reducing the profound immune deficiency that accompanies allogeneic HSCT.

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Blood to brain yet again

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Cell traffic from the BM to remote body sites, and the local differentiation of these cells into often-unexpected cell types, have been independently reported by several laboratories. Toth and colleagues now show that, following stroke, a significant fraction of brain endothelial cells are of BM origin.

Toth and colleagues report in this issue of Blood on an experimental model that was chosen so as to ensure feasibility of tracking the origin of cells found in the brain. First, bone marrow (BM) from green fluorescence protein (GFP) transgenic male mice was transplanted into female C57Bl recipients. Cerebral artery occlusion in these radiation chimeras caused frontal and parietal cortical brain injury. Upon combined cytokine treatment with G-CSF and SCF, an overall improvement and partial correction of brain damage was observed in the cytokine-treated group compared with controls, and was associated with angiogenesis. Some of the blood vessels contained GFP-positive endothelial cells harboring the Y chromosome, substantiating their BM origin. The study therefore suggests that a cell population within the BM is capable of responding, either directly or indirectly, to G-CSF/SCF. This population consequently leaves the BM microenvironment and migrates, via an unknown route, to the brain (see figure).

Probably, the cells must then cross the blood–brain barrier and settle in the brain, where they participate in formation of new vessels.

These findings are of value as regards therapeutic brain regeneration following ischemic insult. Further analysis is called for regarding the cytokines involved in brain angiogenesis. In addition, and not less important, is the impression that the BM serves as a reservoir of cells that are recruited to various body sites upon need. Such sites include tumors, gastric ulcers, and wounds, to mention just a few examples. One major question raised by these studies is the nature of the cell(s) within the complex BM population endowed with migratory and tissue-repair capacities. In view of previous reports, precursors of brain endothelial cells could be hematopoietic, mesenchymal, or endothelial progenitors, or still-unidentified cells. This issue is not resolved by the present report.

Along with these main findings, the study by Toth and colleagues highlights a major technical limitation in the use of GFP-labeled cells. About 10% of the cells containing the Y chromosome were GFP negative. GFP analysis therefore may underestimate cell frequency, and this problem could account for some of the discrepancies found between studies using this and other methodologies. Related to this point is an issue mentioned by the authors in passing: GFP-positive cells bearing neuronal or glial markers were detected in the ischemic brain at 2 months after treatment. Past reports on the transformation of BM-derived cells into brain neuronal cells evoked controversy. This issue must, however, be revisited, because the incidence of such cells might be higher than estimated given the limitations of GFP analysis. It should further be examined whether the use of various cytokine combinations, as one option, might shift the balance toward increased production of nerve cells from BM-derived precursors.

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REFERENCES

Cells of bone marrow origin give rise to endothelial cells in the brain following ischemia-induced damage. HSC indicates hematopoietic stem cell; MSC, multipotent stromal cell; EPC, endothelial progenitor cell; ?, uncertainly as to the nature of the bone marrow cell that gives rise to brain endothelium and as to the exact target for the action of granulocyte colony-stimulating factor (G-CSF) and stem-cell factor (SCF).
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