Furthermore, because GO is effective in only a portion of patients with AML, these findings suggest that multiple therapies may be required to effectively eradicate LSCs.4

The emerging field of cancer stem cells provides a challenge to cancer therapeutics: selective and effective manipulation of cancer stem cells. Identification of cell surface molecules and biochemical pathways unique to cancer stem cells will facilitate the development of cancer stem cell–directed therapies. Clinical studies such as the GAIN Trial of GO by the Southwest Oncology Group (SWOG) and of bortezomib (Velcade; Millennium Pharmaceuticals, Cambridge, MA) by the Cancer and Leukemia Group B (CALGB) in AML will test whether therapies capable of targeting the cancer stem cell result in clinical benefit. ■

REFERENCES

A great incentive to study platelets from patients with ARC syndrome is that the genetic lesion responsible for the phenotype has been defined. The disorder is caused by mutations in the VPS33B gene.3 All subjects studied by Lo et al carried mutations in this gene. The VPS33B gene product is a member of the Sec-1/Munc18 family, which is involved in vesicular trafficking. Sec-1/Munc18 family members modulate membrane fusion events via their strong interaction with members of the syntaxin family of soluble N-ethylmaleimide-sensitive fusion attachment protein receptor (SNARE) proteins. Functions for Sec-1/Munc18 family members in platelet membrane fusion events have previously been shown. One such example is VSP33A, a homolog that shares 31% identity to VPS33B. VSP33A-deficient mice demonstrate a bleeding phenotype and a dense granule deficiency.4 Munc-18a, b, and c are also members of the Sec-1/Munc18 family and have been shown to regulate platelet granule secretion.5,6 However, a role for VPS33B in platelet membrane trafficking had not previously been studied.

Knowing the molecular identity of the platelet defect, the investigators were able to make several observations regarding the role of VPS33B in α-granule biogenesis. Their immunofluorescence studies of normal megakaryocytes demonstrate that VPS33B colocalizes with α-granule precursors. In contrast, VPS33B does not show significant colocalization with dense granule precursors. The investigators also show that VPS33B is found in megakaryocytes, but not in mature platelets. This result demonstrates that VPS33B is not involved in platelet granule secretion (or other functions of mature platelets).

Although these studies do not conclusively demonstrate that VPS33B is involved exclusively in α-granule and not dense granule biogenesis, they raise this possibility. The prominent role of VPS33B in α-granule biogenesis may enable identification of protein complexes (as described in dense granule biogenesis) that mediate α-granule biogenesis. Such information could lead to the generation of animal models to directly compare and contrast the respective roles of α-granule and dense granules in thrombus formation and inflammation. ■
T-cell therapy for viral and fungal infections

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Perruccio and colleagues demonstrate feasibility and efficacy of adoptive immunotherapy with donor-derived T-cell clones in controlling viral and fungal infection following haploidentical stem cell transplantation.

In spite of an increasing number of volunteer unrelated donors in the various international donor registries, there is still a significant percentage of patients for whom no human leukocyte antigen (HLA)-matched related or unrelated donor is available. Transplantation of hematopoietic stem cells from full HLA haplotype-mismatched (haploidentical) family donors is an option for these patients but requires extensive T-cell depletion of the graft, leading to a delayed immune reconstitution following transplantation. Thus, after haploidentical transplantation, patients are at very high risk of developing severe infectious complications.

Adoptive transfer of donor-derived virus-specific CD8+ T cells has been shown to be safe and effective in prophylaxis and treatment of cytomegalovirus (CMV) and Epstein-Barr virus (EBV) infection following stem cell transplantation from an HLA-identical related and unrelated donor. Due to the high degree of mismatching between donor and patient in haploidentical transplantation, transfer of donor T cells to improve immune reconstitution in these patients is associated with a high risk of severe acute graft-versus-host disease (GVHD). But immunotherapy with highly enriched polyclonal virus-specific CD4+ T cells has been reported to be safe and effective in a small cohort of patients, including one recipient of a haploidentical transplant. Here, Perruccio and colleagues report the safe and effective transfer of donor-derived pathogen-specific T cells to recipients of a haploidentical transplant.

There are 2 important messages. No infection-related toxicity nor induction of GVHD were reported in any of the previous studies using adoptive transfer of donor-derived T cells and even more important in none of the 35 recipients of a haploidentical transplant in the study by Perruccio et al when less than 10^6 donor CD4+ T cells/m2 were transferred. Thus, transfer of highly enriched pathogen-specific T cells even from haploidentical donors is safe. In spite of the fact that only a small number of pathogen-specific T cells was administered, specific T-cell responses could be detected in most of the patients in the previous studies and all patients in the trial reported here. All of the patients in this study showed a surprisingly prompt increase in CD4+ as well as CD8+ T-cell responses to CMV as soon as 3 weeks after transfer. Obviously, even extensively in vitro–cultured T cells were able to rapidly expand in vivo when administered to lymphopenic patients not receiving immunosuppressive medication for GVHD prophylaxis. When compared with a control group, patients receiving CMV-directed immunotherapy had a lower risk of CMV reactivation and disease.

It has been shown before that patients with Aspergillus-specific T helper 1 (TH1) responses have a better chance to survive invasive aspergillosis. But this is the first study that describes adoptive T-cell therapy not only for viral but also for invasive fungal infection. Aspergillus-directed CD4+ TH1 responses were detected in all recipients as soon as 3 weeks after the transfer, and 9 of 10 treated patients showed a decrease in their galactomannan antigenemia and resolution of pulmonary infiltrates. Thus, Perruccio and colleagues for the first time also document antifungal efficacy of T-cell therapy.

There are several issues to be resolved before adoptive transfer of pathogen-specific T cells will become routine therapy in recipients of an allogeneic stem cell graft. First, more efficient culture and stimulation techniques or improved selection devices are needed to reduce long-term in vitro culture and to allow enrichment of pathogen-specific T cells under GMP (Good Medical Practice) conditions. Only then will it be possible to conduct clinical trials with highly enriched pathogen-specific T cells that contain not only terminally differentiated effector cells, but also central memory T cells, which are essential to build up a memory T-cell response in the recipient. If so, adoptive immunotherapy will be increasingly used to prevent or control various infectious complications after transplantation.

REFERENCES

Comment on Perruccio et al, page 4397

TRANSPLANTATION
VPS33B: let there be α-granules

Robert Flaumenhaft

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