reactivity. Megakaryocytes equip platelets with RNA and microRNA, thereby allowing platelets to mirror the condition of their progenitors. Platelets further take up various RNAs from cells they encounter within the circulation. Platelets also transfer mRNA and microRNAs from one cell to another via release of microvesicles, which allows platelets to communicate with a variety of different cell types, thereby modulating target cell effector functions in various diseases.[6] Emerging lines of evidence indicate that platelet microRNAs are biologically and clinically relevant regulators of protein translocation and may serve as biomarkers for thrombotic disease and platelet reactivity, with possible therapeutic applications in the future.[4]

Zhang et al show for the first time that anti-microRNA therapy can inhibit platelet function in vivo. In an animal model, the authors demonstrate that anti–miR-148a enhances TULA-2 expression in bone marrow cells. This results in a strong reduction of microvessel occlusion and thrombotic events after use of an immune complex–induced in vivo platelet stimulation model. This model mimics the pathological situation of HIT in high responders and demonstrates the importance of TULA-2 function in FcγRIIA-mediated platelet signaling.

Whether the in vivo effects observed by anti–miR-148a are solely the result of FcγRIIA signaling in platelets or whether other cells are also involved remains to be determined. Recently, it was also shown that FcγRIIA signaling in monocytes contributes to thrombotic complications. Monocyte FcγRIIA signaling induces tissue factor production and subsequent thrombin generation in an Syk-dependent fashion.[7] Therefore, anti–miR-148a treatment might also have beneficial antithrombotic effects on cell types other than platelets.

The study by Zhou et al brings us one step closer to understanding the underlying mechanism of inter-individual differences in response to FcγRIIA-mediated signaling in platelets. TULA-2 and miR-148a could potentially serve as predictive markers to identify patients at risk of HIT. However, the utility of anti–miR-148a as a therapeutic target is doubtful, because miR-148a has many crucial functions in other cell types. It was previously reported that miR-148a is a tumor-suppressive microRNA that potently induces apoptosis of tumor cells.[8] Therefore

miR-148a itself has been suggested as a therapeutic target, which, given the effects of this microRNA on platelet activation and subsequent thrombotic complications demonstrated by Zhou et al, should be reconsidered.

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● ● ● TRANSPLANTATION

Comment on Hiwarkar et al, page 2882

Cord blood T cells are "completely different"

Juliet Barker and Alan Hanash   MEMORIAL SLOAN-KETTERING CANCER CENTER

According to some, one of Britain's significant contributions to the modern world is the comedy of the Monty Python Flying Circus. One of their films employed the memorable catchphrase, *"And now for something completely different…."* Now, decades later, in this issue of *Blood*, the work of Hiwarkar et al represents another notable English export.[1] This group of investigators has begun to dissect the differences in graft-versus-tumor effects of adult donor peripheral blood (PB) and cord blood (CB) T cells, and the findings are quite remarkable.

For many years, CB transplantation (CBT) clinicians have observed and reported upon the unique nature of CBT biology based on observations on the transplant floor and in the clinic, as well as findings from single-center and registry studies of adult and pediatric CBT. The first remarkable feature of CBT is that the incidence of severe acute graft-versus-host disease (GVHD) is much lower than would be expected based on the high degree of donor-recipient human leukocyte antigen (HLA) mismatch. For example, the median 8 HLA-allele match of CB units transplanted at Memorial Sloan-Kettering Cancer Center (MSKCC) is 5/8 with grafts as mismatched as 3-4/8 frequently being administered to adult patients. And yet, the incidence of severe acute GVHD in CBT recipients is no greater than

that of HLA-matched adult donor allografts in many series. Recent MSKCC and University of Minnesota analyses have shown a day 100 grade 2 to 4 acute GVHD incidence of <15% in double-unit CB recipients who were transplanted with adequately dosed mycophenolate mofetil.[2,3] The manifestations of chronic GVHD in CBT recipients are also different from that of adult donor PB allograft recipients with severe chronic GVHD being quite uncommon.[4]

It would be logical to assume that a less than expected GVHD risk would be associated with an increased incidence of relapse. In fact, the opposite has been observed, with multiple reports demonstrating that T-replete CBT with either single- or double-unit grafts is associated with a robust graft-versus-leukemia

(GVL) effect.[5-8] However, despite this tremendously important advantage, relatively little laboratory investigation has been performed to explain this biology. The study by Hiwarkar et al thus represents a long-awaited "bedside-to-bench" investigation of CB T-cell–mediated antitumor responses.

The investigators examined CB and PB T-cell antitumor responses in a xenogeneic nonobese diabetic/severe combined immunodeficiency/interleukin-2rg^{null} model. They found that CB T cells mediated enhanced clearance of human Epstein-Barr virus-driven B-cell lymphomas as compared with adult PB T cells. The CB T cells mediating this effect did so based on alloreactivity, as CB T cells that were syngeneic to the tumors demonstrated little to no antitumor immunity at all. CB T cells demonstrated rapid tumor infiltration with a preponderance of CD8$^+$ T cells within the tumor. This was in contrast to PB T cells that exhibited delayed tumor infiltration and a greater proportion of CD4$^+$ T cells, even though both T-cell groups initially demonstrated similar CD4:CD8 ratios.

This provocative study, arguing that CB T cells are intrinsically more effective at GVL, generates a host of important questions. First, it is surprising that the PB T cells did not have greater antitumor potency. Additionally, the tumor model used is distinct from most clinical CBT settings, other tumors may have different responses to the T-cell populations being studied, and it is conceivable that the methods used for injecting the tumors could arbitrarily favor one T-cell population over the other.

Furthermore, there are inherent limitations of xenograft models, particularly for studies of immunology and transplantation, so the findings must be appreciated in this context and cannot automatically be applied to the human (or a standard alloreactive) setting. Beyond the xenogeneic antigenic differences and issues related to mixing cells across species, given the lack of donor (and possibly host) antigen-presenting cells (APCs) in this system and the importance of APCs for mediating GVL,[9,10] it is possible that the findings in this model may be distinct from what is occurring in clinical or other experimental transplant settings. Further mechanistic studies are thus needed to better understand the differences in the neonatal vs adult T-cell sources that are reported here.

Nonetheless, these authors' findings are novel and intriguing, and they should prompt further investigation, both in the laboratory and in clinical correlative studies. Of great interest would be to better understand the seeming separation of GVHD vs GVL that has been observed in many human CBT recipients. Whether differences in GVL potency could be demonstrated against different malignancies (eg, myeloid vs lymphoid), in subcutaneous vs marrow-based disease, and after transplantation of single- vs double-unit grafts, are all of great interest. In the interim, thanks to this exciting study, we can agree that when considering the biology of CB T cells, as stated by the Monty Python comedians, we are now talking of "…*something completely different*… ."

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