levels of endogenous α-granule proteins (PF4 and β-thromboglobulin) supports a packing or sorting defect rather than a defect in protein synthesis.5-7 By analogy, mice lacking chondroitin sulfate have α-granules deficient in PF4, β-thromboglobulin, and platelet-derived growth factor because of a granule-packing defect8 and patients lacking the vesicle-sorting protein VPS33B have α-granule deficiency.10 Defects in protein packing, vesicle trafficking, granule acidification, membrane retrieval, or protein processing could prevent normal granule maturation and result in shunting to a default pathway of constitutive secretion. The large number of genes that could potentially contribute to α-granule maturation complications identification of likely culprits from the long list of candidate genes located in the linked interval on chromosome 3. We can only hope that improvements in sequencing technologies will make identification of the causative gene in GPS more black and white.

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REFERENCES

“default” thinking, Huang and coworkers now demonstrate that IVIg-primed DCs mediate an anti-inflammatory activity at the level of the platelet itself rather than an effect on the phagocytic cell in a murine model of ITP (see figure).

DCs purified from the spleens of naive mice were incubated in vitro with IVIg and adoptively transferred into recipient ITP mice, similar to a previous study. After 24 hours, the degree of thrombocytopenia was assessed in the recipient mice, the spleen removed, and a binding interaction assay performed with CD14+ monocyte/macrophages (Mϕ) and opsonized platelets from selected groups of mice. The authors assessed the ability of Mϕ from IVIg-DC–primed mice versus Mϕ from naive mice to engage opsonized platelets from IVIg-DC–primed mice versus those from naive mice. This novel approach allowed the authors to map whether the downstream effects of IVIg-DC priming orchestrate a change in the attributes of the phagocytic Mϕ versus the platelet. Surprisingly, only under conditions where the platelets were isolated from mice treated with IVIg-primed DCs did the number of interactions between the opsonized platelets and Mϕ decrease. This is the first clear indication that IVIg targets (or marks) the platelets rather than phagocytic cells.

Although details on how the platelets are marked or affected by this IVIg pathway remain to be solved, IVIg appeared to have an absolute requirement for P-selectin in the recipient mice: P-selectin or P-selectin glycoprotein ligand-1 (PSGL-1) expression by platelets, DCs, or other cells involved in IVIg action (such as endothelial cells) could interact together to either further complicate these IVIg-directed nuptials or help provide clues as to how or why IVIg works in the myriad of diseases where it is beneficial.

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Off-the-shelf T-cell therapy

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In this issue of Blood, Barker et al demonstrate that third-party non-neonatal T cells specific for Epstein-Barr virus (EBV) can be safely used to treat EBV-associated disease after allogeneic umbilical cord blood (UCB) transplantation (UCBT). This is made possible by the a priori generation ofcryopreserved banks ofEBV-specific T cells from peripheral blood.

An algorithm for treating EBV-associated clinical disease after transplantation. Frontline treatment (Option #1) and second-line therapies (Option #2) are widely practiced. Option #3 is to be considered experimental, but encouraging, at this time.

The clinical benefits of infusing third-party T cells is predicted from extensive nonhuman and human experiences demonstrating that the adoptive transfer of antigen-specific T cells from a donor can successfully augment an immune response protecting and treating a designated recipient against pathogens and tumors after allogeneic hematopoietic stem cell transplantation (HSCT). What is only recently becoming apparent is that one donor can be used to generate antigen-specific T cells that can be infused into multiple recipients.

The report in this issue joins a growing list of clinical trials in which previously generated cryopreserved third-party EBV-specific T cells have been adoptively transferred. Multiple infusions were administered to achieve a clinical response with thawed T cells given every week, every 2 weeks, or every 3 weeks, at intravenous doses of 10^6/kg/infusion to 2 to 10^6/kg/infusion based on recipient weight. These data describe clinical responses to opportunistic EBV infection and associated disease that were apparently long-lasting and significantly were not associated with severe adverse effects. The anonymity, small size, and functional naivete of the UCB graft typically preclude isolation of clinical-grade T cells with desired specificity and suitable for adoptive immunotherapy. Thus, the testing of third-party EBV-specific T cells from non-neonatal donors is particularly compelling in this clinical context. In aggregate, Barker’s data highlight that third-party
IVIg conducts DC-platelet nuptials

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