(MRLLAKICLMLWAICVA, UniProtKB/Swiss-Prot P08603, CFAH_HUMAN). Thus, CFH is a protein released through the secretory pathway, probably including α-granules. These granules might well accumulate extracellular CFH, but whether this involves receptor-mediated or fluid-phase endocytosis depends on concentrations of granular and extracellular CFH. Thus, a next step to understand these intriguing findings should focus on the presence of membranes that surround secretable proteins and proteins taken up from the medium (not detectable with the present approaches), the quantitative aspects of CFH accumulation (difficult but essential to identify uptake phenomena), conformation of CFH presence in other patients lacking α-granules (eg, Gray platelet syndrome), and identification of the receptor for CFH-mediated endocytosis (if present). Should all attempts fail to explain CFH localization and transport in models of conventional secretory and uptake pathways, CFH will be one of the first proteins in megakaryocytes subject to regulated, unconventional protein secretion. This is again a starting point for new and exciting research.

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REFERENCES

Comment on Baskar et al, page 4494

Hunting for the Achilles’ heel of CLL

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Baskar and colleagues take translational immunology to another level by applying a sophisticated antibody library cloning process to identify a novel tumor-specific antigen derived from CLL patients cured by allogeneic stem cell transplantation. The application of this approach to other diseases cured by allogeneic stem cell transplantation is immense.

The immunologic response to exposure to foreign or tumor-specific antigens can occur through cellular and humoral specific pathways. This is the proposed mechanism by which antitumor responses have been demonstrated after allogeneic stem cell transplantation in multiple diseases including chronic lymphocytic leukemia (CLL). Whereas much effort has been directed toward understanding the T cell–specific responses following allogeneic stem cell transplantation, the contribution of donor B cells in both eliminating and preventing tumor recurrence has been relatively unexplored. The classic response to tumor that an allogeneic B cell would generate is against a tumor-specific antigen for which no endogenous immune tolerance was present.

In thinking about why both autologous (from the CLL patient) and allogeneic (from donor) B cells might not effectively respond to CLL cells, many different features of these tumor cells are an impediment. These include the absence of costimulatory molecules on the tumor cells, release of immunosuppressive chemokines, and associated expansion of T regulatory cells that becomes more pronounced with disease progression. Settings to reverse this balance in B-cell suppression including allogeneic stem cell transplantation, CD154 gene therapy, or other therapeutics that effectively activate CLL cells thereby making them better antigen–presenting cells offer opportunity to fully exploit this approach.

Using a very novel technology and serial CLL patient samples obtained before and long after completion of successful allogeneic stem cell transplantation, Baskar and colleagues have in fact identified an antibody to what appears to be directed at a CLL–specific tumor-derived antigen. The paper describing this work in this issue of Blood sequentially outlines development of an assay to measure tumor-specific antibodies on primary CLL cells that lacks interference with surface immunoglobulin on these respective tumor cells. This allows for tumor-specific antibody screening using primary CLL cells. The authors then generated a human Fab library from normal cells derived from peripheral blood mononuclear cells and selected it on primary B-CLL cells by phage display. From this very technically derived work has come a Fab that binds predominantly to CLL cells but not to normal B cells. Much work remains for these authors including identification of the potential tumor-specific antigen, its true selectivity for CLL cells, and relevance as either a drug or an immunologic target. However, this paper is very important to the field of CLL, allogeneic transplantation, and immunology in general, as it allows us to use a very sophisticated technology to better understand how the immune system has prevented recurrence of a specific malignancy using material derived from potentially cured patients. One can hope that information derived from such investigation will result in both antibodies that may be used therapeutically and also peptide antigens that may be effective for vaccination of both donors (in the setting of allogeneic stem cell transplantation) and patients undergoing this procedure as an adjuvant to improve the humoral response. In addition, it is possible that this approach may also be active in other immune modulating therapies, not requiring allogeneic stem cell transplantation.

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