Comment on Licht et al, page 4538

Platelet CFH: in search of the source

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CFH protects platelets against complement attack. In this issue of Blood, Licht and colleagues unexpectedly identify CFH at intracellular localizations other than alpha granules, where CFH had previously been thought to localize. They show accumulation of exogenous CFH in the platelet cytoplasm, as well as production of endogenous CFH by megakaryocytes.

Complement factor H (CFH) is a member of the regulator of complement activation gene cluster and an essential component of the alternative pathway, directing it toward pathogens and protecting host tissue. CFH is produced by the liver. Extrahepatic synthesis occurs in peripheral blood lymphocytes, endothelial cells, and fibroblasts. These cells supply the CFH that accumulates at sites of infection and inflammation and protect the endothelium. Defects in CFH caused by mutations or autoantibodies result in cellular damage. Destruction of glomerular endothelial cells exposes subendothelial matrix, inducing platelet adhesion, microthrombi, and the atypical hemolytic uremic syndrome (HUS).

Platelets have been known previously to contain CFH and secrete it upon activation, a process long interpreted as secretion of alpha-granule contents. These secretory granules store 3 types of proteins: First, proteins synthesized by the platelet progenitors, the megakaryocyte. An example is von Willebrand factor, which assists in platelet adhesion to the damaged vessel wall. Second, proteins taken up from the surrounding plasma by receptor-mediated endocytosis and stored in concentrations higher than in plasma. An example is fibrinogen taken up through binding to the fibrinogen receptor. Third, proteins taken up through fluid-phase endocytosis and stored in concentrations lower than in plasma. Examples are albumin and immunoglobulins. Granule contents are released through the open canalicul system (see figure).

As in any nucleated cell, the megakaryocyte transcribes message from genes in the nucleus, translates it into proteins in the cytosol, and transports signal peptide–containing proteins to the endoplasmic reticulum and Golgi. Here, they are packaged in granules that fuse either directly with the plasma membrane (constitutive secretion) or upon later activation (regulated secretion). Proteins lacking a signal peptide stay behind in the cytosol.

The exciting findings of Licht et al do not appear in line with the conventional secretory pathway. First, there is the extensive accumulation of CFH in the cytosol of platelets in healthy persons visualized by a beautiful laser fluorescence confocal microscopic approach. Second, platelets from a patient with ARC (arthrogryposis, renal tubular dysfunction, cholestasis) lack alpha-granules but contain a normal amount of CFH, as do normal megakaryocytes. Third, platelets from an HUS patient with complete CFH deficiency accumulate CFH on transfusion with normal plasma. Fourth, normal platelets take up extracellular CFH but do not store it in granules.

CFH is encoded by a single gene (HFI) and it contains a signal peptide.
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 tumor-specific antigen for which no endogenous immune tolerance was present, the absence of costimulatory molecules on the tumor cells, release of immunosuppressive chemokines, and associated expansion of regulatory T 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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REFERENCES

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