Comment on Licht et al, page 4538

Platelet CFH: in search of the source

Jan Willem N. Akkerman UNIVERSITY MEDICAL CENTER UTRECHT

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 α-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 canalicular 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 α-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.
Transplantation is immense. The application of this approach to other diseases cured by allogeneic stem cell transplantation has demonstrated after 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.1 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.

Conflict-of-interest disclosure: The author declares no competing financial interests.

REFERENCES
Platelet CFH: in search of the source

Jan Willem N. Akkerman

Updated information and services can be found at:
http://www.bloodjournal.org/content/114/20/4323.full.html
Articles on similar topics can be found in the following Blood collections

Information about reproducing this article in parts or in its entirety may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#repub_requests

Information about ordering reprints may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#reprints

Information about subscriptions and ASH membership may be found online at:
http://www.bloodjournal.org/site/subscriptions/index.xhtml