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July 08, 2015 // By Karen Kreeger // Comments

What's Eating the Erythrocytes?

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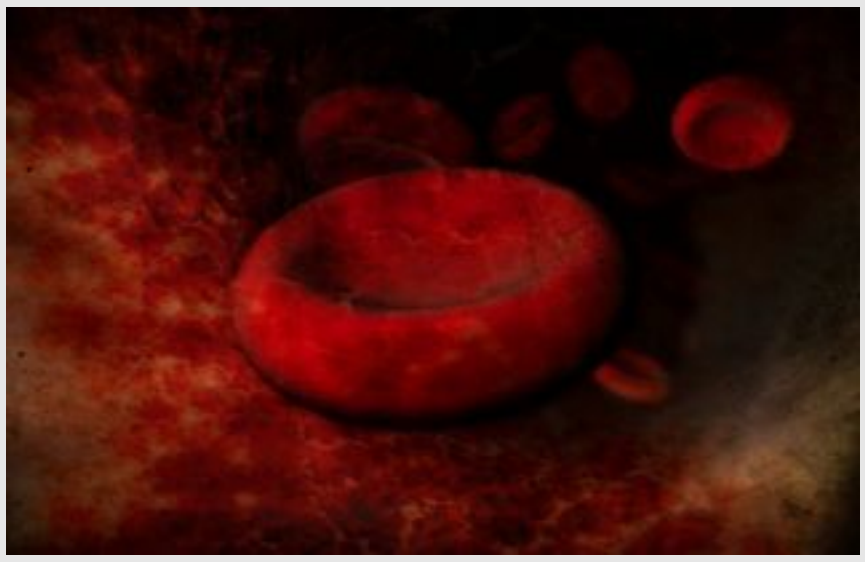

In the rare, life-threatening disease called paroxysmal nocturnal hemoglobinuria (PNH), patients are stricken with chronic anemia and blood clots, when the oldest part of the immune system -- known as complement -- turns against its own red blood cells, or erythrocytes.

Complement is a network of more than 50 proteins in the blood and on cell surfaces that quietly cruise the body, keeping a low profile until triggered into action. But this defense system can also be inappropriately activated and attack cells, contributing to a broad spectrum of immune, inflammatory, and age-related diseases. Current treatments for PNH include frequent blood transfusions and the drug eculizumab, which binds to one part of complement, called C5, and blocks its assault on red blood cells. However, this therapy is effective in 70 to 75 percent of PNH patients.

PNH affects between 1 and 5 per million people and is caused by a defective expression of regulatory proteins on the surface of blood cells, leaving them vulnerable to complement attack. This can lead to premature death of the red blood cells, a process called hemolysis, which results in the severe anemia and contributes to the high risk of clotting.

Now, for the first time, Penn Pathology and Laboratory Medicine investigators **Daniel Ricklin, PhD**, a research associate professor; **John Lambris, PhD**, the Dr. Ralph and Sallie Weaver Professor of Research Medicine; postdoctoral fellow **Zhuoer Lin, PhD**, and their collaborators from Ulm University in Germany and the University of Naples in Italy, have confirmed that protein tags on the surface of PNH erythrocytes bind with a complement receptor called CR3 after the complement system is activated and mark these blood cells for recycling. This erroneous marking for red blood cell recycling adds to the anemia associated with PNH. Their work was published recently in *Blood*.

Because eculizumab only affects the complement protein C5, the upstream complement protein C3 can still be activated. From this, PNH erythrocytes become increasingly coated with C3 fragments, turning them into tasty meals for cell-engulfing phagocytes, a specialized cell in the body's recycling system.

"The novelty of our study is that the final state of this C3 coating, called C3dg, which has sometimes been described as a 'safe harbor' against phagocytosis, can still mediate recycling of C3dg-laden cells," Ricklin says.

The team analyzed red blood cells from PNH patients for C3 fragments and examined how C3-derived opsonins (molecules that bind to foreign microorganisms or cells making them more susceptible to phagocytosis) interacted with CR3 receptors. They found that the interaction of the C3dg fragments on affected erythrocytes and the binding domain for CR3 on immune cells can lead to phagocytosis and the rupturing of red blood cells in PNH patients.

Ricklin explains that the team's findings, "further support the concept that complement inhibition at the level of C3 rather than C5 will hopefully confer better therapeutic benefits for PNH patients because it will prevent destruction of red blood cells both inside and outside of vessels."

One promising therapeutic possibility is compstatin, a C3 inhibitor drug discovered by the Lambris lab in 1996. It is being developed by the Lambris and Ricklin group and was recently licensed by Amyndas Pharmaceuticals. The resulting drug candidate is planned for clinical trials in 2015 and 2016.

The work "adds an important new facet to the housekeeping functions of complement," Ricklin says. "The destruction of red blood cells outside of vessels by immune cells in PNH has long been speculative due to limited experimental evidence." This new data corroborates such a mechanism, at least in a laboratory setting.

A next step that Ricklin and his colleagues are particularly interested in is how the presence of densely C3-populated cells affects clearance of PNH erythrocytes under anti-C5 treatment and immune cell modulation (the binding of C3 fragments to immune cell receptors such as CR3 to activate those immune cells). Because other cells under complement attack, such as during solid organ transplantation, also accumulate C3-

populated cells, the interaction with CR3 may have important implications beyond PNH.

"The truly interesting point will be to assess the clinical benefit of C3-targeted therapies for PNH patients, and we are therefore looking forward to the upcoming clinical trials of novel complement inhibitors," Ricklin notes.

Mark Wolverton contributed to this blog post.