changes in platelet counts follow seroconversions by approximately 2 days for the initial decline and approximately 4 days for a platelet count decline of more than 50%. Thrombotic complications, on the other hand, do not follow a particular pattern relative to development of thrombocytopenia; thromboses were shown to occur either before or after thrombocytopenia. The most intriguing finding in this study is the observation that PF4/heparin antibody responses are at or near maximal at the time of the fall in platelet count.

These studies offer new insights for clinicians and researchers alike. For clinicians, both studies provide a critical “timeline” of events related to PF4/heparin seroconversions. These studies show that IgG seroconversions can occur rapidly (within 4 days of heparin exposure), and the majority of immune responses occur within 14 days of exposure. It is also evident that seroconversions precede development of thrombocytopenia and/or thrombosis, and antibody levels are near maximal intensity by the time clinical complications develop in HIT. This latter observation necessarily implies that a platelet count decline and/or thrombosis preceding a seroconversion is unlikely to be “incipient” HIT. Finally, the observation that some patients with circulating platelet-activating PF4/heparin antibodies can be exposed to LMWH must be noted, but viewed with caution. Because circulating PF4/heparin antibodies are known to be associated with “rapid-onset” HIT, care must be exercised in knowingly exposing seropositive patients to heparin in the absence of additional studies or compelling clinical indications.

For researchers, these studies furnish new avenues for investigation. The finding that IgG seroconversions can occur rapidly and unambiguously without IgM precedence suggests that the immune response to PF4/heparin may be primed by prior exposure to PF4 and endogenous glycosaminoglycans. Alternatively, as suggested by the authors, lack of a “classic” pattern of isotype switching in HIT could also be explained by mechanisms, such as independent signaling pathways, induction of peripheral tolerance mechanisms, or unique immunostimulatory signals elicited by antigen binding to a particular class of antigen-presenting cells. The observation that the immune response “peaks” during sustained heparin therapy is also intriguing and suggests an active down-regulation of the immune response, further lending support for the role of peripheral tolerance mechanisms in HIT. Last and most importantly, both studies reinforce the notion that not all PF4/heparin antibodies act equally. The ultimate challenge to investigators in this field is to understand what additional serologic or host risk factors predispose PF4/heparin antibodies to be pathogenic in some patients but asymptomatic in others.

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

REFERENCES


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Blood group antigens can have critical functions beyond the red blood cell. In this issue of Blood, Lund and colleagues demonstrate a role for Pk in HIV entry, providing biologic insight, identifying potential therapeutic target motifs and expanding the intersections of hematology, transfusion medicine, and infectious disease.

It is said that there are more than 400 blood group antigens on the red blood cell and of these, about 40 have known clinical significance. Significance in this context refers to transfusion-related concerns, typically meaning the ability of an antibody, when in proximity to the cognate antigen, to cause hemolysis—intravascularly, extravascularly or in utero (as in transfusion reactions or hemolytic disease of the newborn). More recently using precise molecular methods, investigators have been able to ascertain and assign biologic functionality and thus clinical significance to a number of blood group antigens, now including Pk.

Pk or Gb3 is a member of the GLOB collection which includes P, Pk, and LKE. Pk is related to the P blood group system discovered by Landsteiner and Levine in 1927 and has its name “as it was the first letter following M, N and O, which had already been used.”1-2 Biochemically, Pk is Galα(1-4)Galβ(1-4)GlcCER (synthesized from lactosylceramide [or Galβ(1-4)Glc-CER] by the sequential addition of galactose via α(1-4) galactosyltransferase encoded in the Pk gene), which when acted upon by the enzyme encoded by the presence of the P gene becomes P.1 Alternatively, lactosylceramide can be modified to P1 via less understood reactions. In addition to the presence of Pk on erythrocytes, this antigen is also found on epithelial cells, monocytes, and B cells where it takes on the designation of CD77. Importantly, while P1 is found in approximately 80% of whites, Pk is found in only about 1 in a million.

Previously, this group has shown: (1) an accumulation of Pk, in patients with Fabry disease due to reduced α-galactosidase conferred resistance to RSV HIV-1,7 and (2) a soluble analog of Pk inhibits HIV infection in vitro.3 The current report also builds on the report of Fantini et al, demonstrating that HIV-infected mononuclear cells have increased Pk expression.4

It is upon this background that Lund et al assessed the susceptibility to HIV-1 of peripheral blood mononuclear cells (PBMCs) from blood donors high in Pk (the Pk1 phenotype) compared with those with essentially no Pk expression (the
p phenotype), and in HeLa and Jurkat cells modified to alter levels of Pk expression.5

The results were significant. P1k cells were protected from R5 and X4 HIV-1 infection and had increased CD4, coreceptor, and Pk expression, while PBMCs with the p phenotype had heightened susceptibility to R5 and X4 HIV-1 infection. Further supporting a role for Pk was that Pk-liposome fusion in Jurkat cells decreased susceptibility to HIV and cells transduced with Pk-synthase (augmenting Pk expression) showed decreased HIV-1 infectibility, while Pk depletion or Pk-synthase gene silencing promoted HIV infection.

Mechanistically, it may prove to be that the Pk effect is due to altered lipid raft formation and/or HIV receptor or coreceptor localization, function, or accessibility. Alternatively or perhaps additionally, Pk may be critical to viral internalization.

That Pk and indeed other blood groups have a more defined role in host-microbial infection is an important new finding. Other examples include Fya as the binding epitope for plasmodium6 and the P antigen as a receptor for the B19 parvovirus.7 With this discovery, Pk adds to our list of genetic polymorphisms that individually and/or in concert contribute to HIV resistance/susceptibility and potentially generates a site for possible future therapeutic use.8

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

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VASCULAR BIOLOGY

Comment on Bieker et al, page 5019

Flipping the wound that doesn’t heal: the upside of coagulation in cancer

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Two mechanisms for targeting tumor vasculature are well recognized: antiangiogenesis and vascular disruption. In this issue of Blood, Bieker and colleagues take therapeutic advantage of coagulation and add a third mechanism, vascular infarction, to this group by demonstrating the effect through first-in-man administration of tTF-NGR.

With the approval of several antiangiogenic agents including bevacizumab, sunitinib, and sorafenib, the usefulness of targeting tumor vasculature with inhibitors has been clinically established. Antiangiogenic agents may be described as drugs that block angiogenic signaling either by neutralizing secreted proangiogenic factors or by inhibiting intracellular signaling by their receptors resulting in regression of neovasculature in the tumor.1 A second approach to targeting the tumor vasculature therapeutically is vasculature disrupting agents. Vasculature disrupting agents are designed to produce rapid vascular collapse or shutdown in tumors.2,3 The resulting ischemia results in tumor cell killing, which causes extensive tumor necrosis. Although no vascular disrupting agents are approved as yet, several including combretastatin derivatives (CA4P and OXi4503), the dimethylxanthenone DMXAA, and the antiphosphatidylserine bavituximab are progressing through clinical trial. In preclinical in vivo models, decreased tumor blood flow can...
A new role for P<sup>k</sup>: finding the 1 in a million

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