tumors, and that Th17 cells may promote protective immunity in advanced human tumors. Interestingly, the authors have shown that IDO-specific CD8+ T cells tilt the balance between Treg and Th17 cells toward Th17 cells. IDO-specific CD8+ T cell target killing may impede the proliferation of Tregs while also allowing them exposure to IL-6, which aids in their conversion to Th17-like cells. In vivo, this phenomenon may be promoted by the inflammatory milieu that typically accompanies viral infection and certain instances of tumor development. However, although the presence of these IDO-specific CD8+ T cells has been established in humans, it will be essential to generate direct in vivo evidence of their biologic activity. These cells may indeed be physiologically and pathologically important. They may be induced during immune reactions and serve to fine-tune T-cell responses. Like many interesting works, this report raises more questions than it answers. Can IDO-specific CD8+ T cells in fact kill IDO+ tumor and DCs in a host? What is the functional relevance of this killing? In addition, do IDO-specific CD4+ T cells (or Treg cells) exist? If so, what are their support functions? It will be interesting to see whether future work from Sørensen et al and others can address these questions and establish IDO-specific T cells as an important regulatory component of immune responses.

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REFERENCES

Platelet Syk is a HIT target

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In his issue of Blood, Reilly and colleagues report a novel inhibitor (PRT-060318) of the tyrosine kinase Syk, expressed in platelets, as a new approach to the management of heparin-induced thrombocytopenia (HIT), using a mouse model of the disease.

Heparin-induced thrombocytopenia (HIT) is a common form of drug-induced immune reaction, with life-threatening potential, initiated by treatment of patients with unfractionated heparin or low molecular weight heparin. Heparin is widely used in the prevention and management of thromboembolic complications in surgery and trauma, in venous thrombotic disease, and in intravenous and intra-arterial lines to maintain patency. Although HIT is a product of immune reaction to the administered heparin, the immunogenicity is not heparin itself, but a complex of heparin bound to platelet factor 4 (PF4), an abundant platelet protein member of the CXC family of chemokines, alternatively known as CXCL4. PF4 is stored in platelet α-granules, and is released by exocytosis on platelet activation, whereupon it is rapidly bound to negatively charged glycosaminoglycans expressed on the surface of endothelial cells. Heparin, however, also highly negatively charged, binds

Role of Syk tyrosine kinase in the mechanism of platelet activation and thrombosis in heparin-induced thrombocytopenia (HIT). Platelet factor 4 (PF4) released from platelet α-granules binds with high affinity to heparin through a charge-charge interaction. The heparin-PF4 complex acts as an immunogen, and exposure to heparin after an initial sensitization will lead to the formation of immune complexes, in which the heparin-PF4 aggregates are coated with IgG. These circulating immune complexes activate blood cells expressing Fcγ receptors, including human platelets that express FcγRIIA. After binding to the immune complex, this receptor signals through Syk and activation of phospholipase C-γ2, leading to platelet shape change, aggregation and secretion of granule contents, including ADP. Platelet aggregates form thrombi, which lead to ischemic disease complications characteristic of HIT. (Professional illustration by Marie Dauenheimer.)
Syk pharmacologically may ablate platelet responses to stimulation of FcγRIIA. Because of the restricted expression of Syk, and its pivotal role in B-cell function and development, Syk has already been the subject of inhibitor development, and is currently successfully targeted in the treatment of B-cell lymphoma and immune-mediated disease such as immune thrombocytopenic purpura and rheumatoid arthritis. In the article by Reilly et al, the authors present evidence that their novel inhibitor of Syk, PRT-060318, is also highly effective in managing HIT in a mouse model system, both in vitro and in vivo. The mouse expresses a transgene for human FcγRIIA and also human PF4, to “humanize” the mouse platelets to allow them to respond to immune complexes. The data show clearly that PRT-060318 is highly selective for Syk and is substantially effective at selectively inhibiting Syk-dependent platelet function, such as aggregation in response to GPVI agonism or to a HIT-like antibody. This is the case whether the drug is administered to platelets in vitro or ex vivo after administration of PRT-060318 to mice orally. Importantly, in vivo administration of PRT-060318 was capable of preventing a thrombocytopenic episode in mice administered with a HIT-like antibody. The drug was also capable of blocking thrombotic events in vivo induced by the HIT-like antibody. This report is therefore potentially a major development in the management of HIT and also in understanding its biology. The major effect of Syk inhibition is likely to be on HIT immune complex–induced platelet activation, but because PF4 needs to be released by platelets in the first place, there may be an additional effect of PRT-060318 on early activation events leading to PF4 secretion. In addition, although the authors report no change in bleeding time with Syk inhibition, careful analysis of this, especially in the presence of residual heparin, will need to take place as one of the early steps in development of this approach in the treatment of HIT. Finally, although the effect is likely principally to be mediated by inhibition of platelet function, in the context of the control of thrombosis, it is possible that effects of Syk inhibition on immune cell function may also play a role in helping to dampen the response in HIT. These are points for further study and analysis, but in the first instance targeting platelet Syk would appear to be a promising novel way forward for management of this difficult clinical problem.

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Comment on Wootla et al, page 2257

Two-faced catalytic autoantibodies

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Factor IX (FIX)–activating catalytic antibodies in acquired hemophilia patients reported in this issue of Blood by Wootla et al1 reveal the potential of the immune system to influence life processes in unexpected ways.

Catalytic antibodies were originally described as pathogenic mediators in autoimmune disease, analogous to the traditional role of reversibly binding autoantibodies as mediators of Ehrlich’s horror autotoxicus theory of autointimunity. The FIX–activating antibodies, in contrast, are proposed to exert a beneficial procoagulant effect that compensates for the anticoagulant effect of conventional autoantibodies to Factor VIII (FVIII) found in acquired hemophilia patients. The authors present biochemical evidence for generation of activated FIX and improved blood coagulation occurring upon the enzyme-like
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