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The biology and treatment of ITP: what's next?

Immune thrombocytopenic **purpura** (**ITP**) is the result of 2 pathologic processes: loss of tolerance to self-antigen accompanied by sustained autoantibody production, and antibody effector mechanisms that destroy platelets in excess of their production. There is a considerable challenge to hematologists treating the chronic, severe, refractory subset of patients. IVIG has many putative mechanisms of action in treating **ITP**. These include "blockade" of phagocytic Fc receptors, anti-idiotype effects, reduction of antibody production, reduced survival of the autoantibody in the circulation (Hansen and Balthasar, Blood. 2002;100:2087-2093), and, finally, stimulation of inhibitory FcγRIIb. In this issue, Crow and colleagues (page 558) follow up on the seminal observations of Samuelsson et al (Science. 2001;291:484-486) concerning how IVIG's efficacy in **ITP** depends on the inhibitory FcγRIIb on macrophages. FcγRIIb counters the phagocytic signal provided by the activating Fcγ receptors (I/γ and IIIa/γ in mice; I/γ, IIIa/γ, and IIA in humans) on splenic macrophages. Crow et al confirm that IVIG's effects in vivo depend on expression of FcγRIIb. They then explore the potential downstream signals of FcγRIIb used in B cells and mast cells that would explain IVIG's role in macrophages. Using germ line knockout of SHIP1, SHP1, or BTK in their **ITP** mouse model, Crow and colleagues found IVIG to be effective despite the absence of these individual signaling molecules. Functional redundancy among the known phosphatase families, or an as-yet undiscovered mechanism specific to macrophages, may explain their observations. The mechanism sought by Crow et al may yield new molecular targets for therapy. Equally of interest to the field is the mechanism by which IVIG increases FcγRIIb expression in the first place. Current data favor an indirect effect, in which IVIG causes a subset of splenic cells to secrete one or more substances— perhaps cytokines—that act on the phagocyte to increase the relative proportion of inhibitory FcγRIIb versus phagocytic Fcγ receptors. Elucidation of this pathway may also yield new molecular targets of therapy.

There are unanswered questions in the development of the **ITP** autoantibodies and in the antibody effector mechanisms. How is tolerance broken? Do dendritic cells, B cells, macrophages, or platelets themselves present antigen? Is there an intrinsic genetic predisposition for loss of tolerance and sustained autoantibody production? Are there genetic differences, for example in the Fcγ receptor endowment, that have an impact on disease course or response to

therapy? Now that Fcγ receptor crystal structures have been solved, will small molecule inhibitors of IgG ligand binding be useful? Can we block receptor signaling, as this family of activating receptors prefers lipid microdomains (rafts) in which to initiate signals via members of the src and syk protein tyrosine kinase families? Will additional ways be discovered to alter the balance of activating and inhibitory receptors to allow platelets to survive in circulation? The next step in the biology and therapy of **ITP** is more precise understanding of the origins of the disease and the promise of molecularly targeted therapy.

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IVIg-mediated amelioration of murine ITP via FcγRIIB is independent of SHIP1, SHP-1, and Btk activity

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