this is most welcome, particularly for investigators working on strategies for cell replacement the United States, who must be feeling something of a déjà vu in face of yet another presidential moratorium, this time limiting the number of human stem cell lines that can be used for research and treatment. Ironically, this frustration recently led California voters to approve a $3 billion initiative to fund stem cell research, which some have predicted will lead to a "gold rush" on stem cell research (9). Regardless of whether or not this proves to be the case, it can be hoped that this new initiative will serve as a beacon of hope for scientists and patients alike as we press ahead in this challenging area of science that appears to promise so much for the treatment of human diseases.

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Immune complexes as therapy for autoimmunity

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For several decades, intravenous Ig has been used as treatment for a variety of immune-related diseases, including immune thrombocytopenic purpura (ITP), autoimmune neuropathies, systemic lupus erythematosus, myasthenia gravis, Guillain-Barré syndrome, skin blistering syndromes, and Kawasaki disease. Despite years of use, its mechanism of immunomodulation is still unclear. Recent studies using mouse models of ITP and arthritis, including one reported in this issue of the *JCI* (see the related article beginning on page 155), now provide some insights into this mechanism and the rationale for the development of Fcγ receptor–targeted therapeutics.

Fc receptors in the pathogenesis and treatment of ITP

Intravenous Ig (IVIg) is remarkably effective in the treatment of immune thrombocytopenic purpura (ITP), with improved platelet counts seen in 80% of treated patients. ITP occurs in patients as the result of the generation of autoantibodies that bind to platelet surface antigens. These opsonized platelets are phagocytosed by Fc receptor–bearing splenic and hepatic macrophages (1). In the mouse, macrophage-mediated clearance occurs via activating Fc receptors, with complement-mediated uptake playing little or no role (2, 3). Thus, blockade of activating Fcγ receptors (FcγRs) would be predicted to be an effective therapy in ITP. Indeed, this has proven to be a valid approach; antibodies that block FcγRIII have been shown to be effective in murine studies (2, 4) as well as in pilot clinical studies (5).

Although activating Fc receptor blockade is an appealing mechanism, a second, unexpected FcγR-related pathway is clearly relevant to the therapeutic action of IVIg. It was recently shown (4) that the protective effect of IVIg is associated with upregulation of the inhibitory receptor FcγRIIB on splenic macrophages and is abrogated in mice lacking *FcγRIIB*. Curiously, this effect is independent of SHIP and SHP-1 (6), the 2 downstream inhibitory phosphatases previously assumed to be responsible for the inhibitory signaling pathway. Redundant functions of SHIP and SHP-1 or other phosphatases downstream of FcγRIIB may be responsible (7), but as yet the FcγRIIB-mediated signal is unclear. Adding further to the mystery is the observation that 2 distinct macrophage populations are involved; IVIg protection requires CSF-1–dependent macrophages, whereas the macrophage responsible for FcγRIII-mediated platelet clearance is CSF-1 independent (8). Thus, while other targets may prove effective in the treatment of immune complex–related (IC-related) autoimmunity (9, 10), at least 2 distinct FcγR therapeutic approaches are tenable: direct blockade of the phagocytic Fc receptors and IVIg-triggered, FcγRIIB-mediated inhibition (Figure 1).

What is the active component of IVIg and intravenous anti-D?

A related therapeutic, intravenous anti-D, has also been highly effective in ITP, but only in Rh^+ patients. The active component is clearly anti-D antibodies that generate large particulate ICs, namely opsonized rbcs, in Rh^+ patients. In contrast, the active components in IVIg, a product obtained from sera pooled from thousands of donors, could conceivably include a variety of Fc receptor–binding ligands. In addition to the dominant species of monomeric IgG (which would bind FcRn and the high-affinity FcγRI), multiple types of ICs, which bind all Fc receptors, are likely to form in vivo after the administration of IVIg. These complexes of varying valencies include cell-associated and soluble host antigens bound by donor natural antibodies as well as dimers and aggregated Igs formed in the IVIg product itself. Using mimetic modeling studies, Siragam et al. (11) suggest that the 2 therapeutics IVIg and anti-D have

Nonstandard abbreviations used: FcγR, Fcγ receptor; IC, immune complex; ITP, immune thrombocytopenic purpura; IVIg, intravenous Ig.

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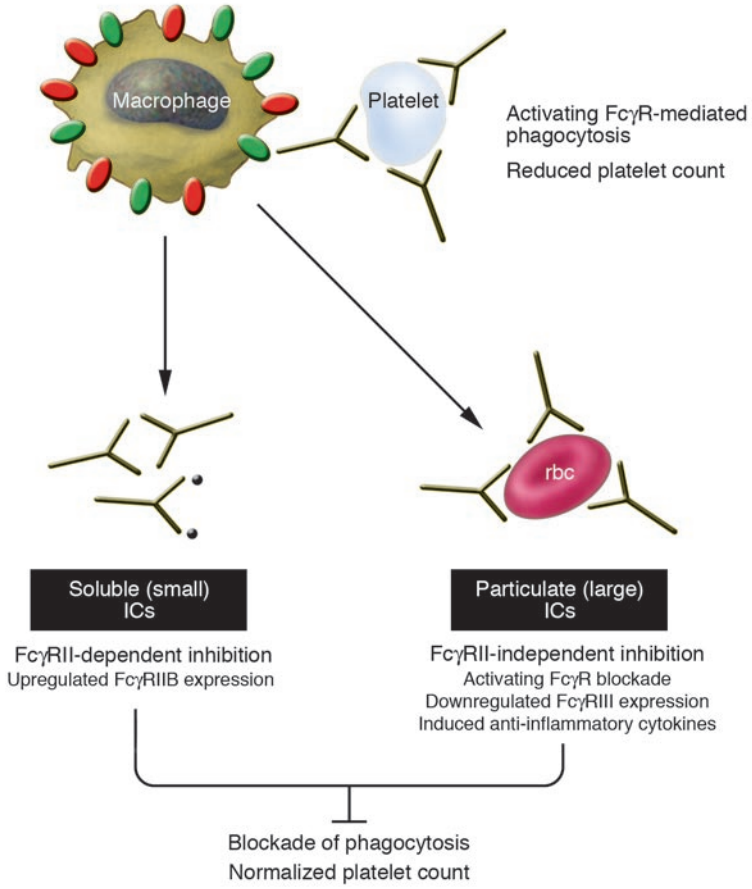

Figure 1
Inhibition of phagocytosis in vivo can be accomplished via IC-mediated inhibition of FcγR functional activity. These complexes, varying in size and valency, operate through distinct mechanistic pathways. IVIg leads to the formation of variably sized ICs, including small monomeric and dimeric complexes. The small ICs (Ig dimers or soluble antigen/donor Ig complexes) require CSF-1–dependent macrophages and FcγRII expression to mediate their as-yet-undefined anti-inflammatory effect. Intravenous anti-D generates large particulate ICs, namely opsonized rbcs. These large ICs induce a phagocytic block in vivo in a manner independent of FcγRII expression. Perhaps mimicking the situation directly, antibodies that specifically engage either the inhibitory FcγRII (4) or the activating FcγRIII (4, 5) can also induce platelet count recovery.

distinct mechanisms of action, either via small, soluble ICs or via large, particulate ICs.

The protective capacity of small ICs was found to be FcγRIIB dependent, which recapitulated results seen previously with the IVIg effect (4). This suggests that in contrast to anti-D, small ICs likely mediate IVIg protection. In contrast, as reported elsewhere (12), opsonized rbcs (anti-OVA/OVA-coupled rbcs) were capable of protecting against platelet clearance in both normal and FcγRIIB-deficient mice, which suggests that they interfere directly with activating FcγR–mediated phagocytosis. The FcγRIIB-independent anti-inflammatory mechanism of opsonized particulates might be assumed to be the straightforward result of activating FcγR blockade by antibody-coated rbcs. However, the fact that large increases in platelet counts are achieved with anti-D with little concomitant induction of anemia (13) suggests that there are other contributing mechanisms, including induction of cytokines and downregulation of activating FcγRIII (Figure 1) (12, 14–17).

New approaches to Fc receptor therapeutics

The implication is that IVIg is far from an optimized therapeutic. Thus, in addition to theoretical and practical concerns regarding safety, cost, and availability of this biologic, a better understanding of how the small IC component within IVIg exerts its therapeutic impact will drive development of an improved pharmaceutical product. Targeting FcγRIIB directly by cross-linking FcγRIIB-specific antibodies has been shown to be beneficial in the mouse model of ITP, and injection of small, preformed ICs is also protective (18). The current work provides another potential solution, namely injection of antibodies with specificities for serum proteins including albumin and transferrin, which provide FcγRII-dependent protection (11). Monoclonal antibodies recognizing a single epitope form monomeric ICs, implying that clustering of FcγRs by these small ICs is not required for their therapeutic effect. Even with polyclonal α-albumin or α-transferrin antibodies, the resultant ICs formed in vivo are still likely to be quite small, since the serum target proteins are present in such large molar excess. While this is an intriguing approach, an obvious concern is the potential for untoward IC-triggered hypersensitivity responses, which might complicate its clinical use.

Implications for other autoimmune states

Siragam et al. extend their observations beyond antibody-mediated thrombocytopenia in showing that both IVIg and its mimetic anti-murine albumin antibodies protect in the K/BxN serum–induced arthritis model (11). The clinical benefit of IVIg has been spotty in autoimmune conditions, such as rheumatoid arthritis (19–24), in which autoaggressive T cells are believed to be the culprits. Recent attention in these T cell–mediated diseases, however, has been redirected toward the role of humoral immunity in the activation of T cells (25). Further, deficiency of activating FcγRs has been shown to be protective in classical T cell–mediated diseases, including arthritis (20–24) and experimental autoimmune encephalomyelitis (26–29), which suggests that FcγR-based therapeutics might have as-yet-undiscovered clinical activity in T cell–mediated autoimmune conditions through regulatory effects on FcγR-bearing antigen-presenting cells. Identifying the critical FcγR mechanistic pathways hinted at by studies of IVIg may prove helpful in generating more effective pharmacologic agents and could widen the circle of patients possibly benefiting from FcγR-targeted therapeutics. Thus, other autoantibody-driven diseases, beyond ITP, may prove treatable with a little of what ails you.

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SDF-1 tells stem cells to mind their P's and Z's

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Stromal cell–derived factor–1 (SDF-1) is a chemokine with unique functions, including a role in the trafficking of primitive blood precursor cells. A better understanding at a molecular level of how the binding of SDF-1 to its cell surface receptor, CXCR4, elicits specific biological responses in these cells has now been achieved through the identification of PKC-ζ activation as a common downstream signal. This finding suggests that treatment of a variety of clinical conditions might benefit from the targeting of PKC-ζ (see the related article beginning on page 168).

Overview of the regulation of stem/progenitor cell trafficking

Throughout adult life, the production of blood cells is normally confined to particular sites within bone cavities where a relatively small number of self-renewing hematopoietic stem cells that turn over slowly are also concentrated (1). In contrast, most of the cells circulating in the blood are highly specialized cells with little or no proliferative potential and a limited lifespan. However, not all hematopoietic stem cells and their primitive progeny are fixed in bone marrow niches. A small proportion of these cells continuously enter the blood and then rapidly return to the marrow (2). The distribution of primitive hematopoietic cells between the blood and bone marrow can also vary as a result of many perturbations and disease states. These include a variety of inflammatory conditions, leukemias, myelosuppressive treatments, and the administration of pharmacologic doses of hematopoietic growth factors. All of these conditions involve many physiological changes whose complexity has made it difficult to elucidate the molecular events that regulate the trafficking of primitive hematopoietic cells into and out of the bone marrow.

One fruitful approach came from early analyses of the molecular interactions between marrow stromal cells and primitive hematopoietic cells. This led to the identification of 2 pairs of molecular interactions that are important to the retention of primitive hematopoietic cells in the bone marrow: VCAM-1 with very late antigen–4 (VLA-4) and membrane-bound Steel

Nonstandard abbreviations used: PDK-1, phosphoinositide-dependent kinase–1; SDF-1, stromal cell–derived factor–1.

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