underlie the pathophysiology of this condition. Further investigation is underway.

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To the editor:

IVIg-mediated amelioration of murine ITP via FcγRIIb is not necessarily independent of SHIP-1 and SHP-1 activity

Crow et al[1] state that the protective effect of intravenous immunoglobulins (IVIg's) in murine idiopathic thrombocytopenia (ITP) requires FcγRIIb but not its signaling molecules Src homology 2 domain-containing inositol polyphosphate phosphatase-1 (SHIP-1), Src homology 2 domain-containing polyphosphate phosphatase-1 (SHP-1), or Bruton tyrosine kinase (Btk). However, SHIP-1 and SHP-1 can replace each other functionally. Thus, the study by Crow et al does not definitely rule out a role for these molecules in the effect of IVIg on murine ITP.

Treatment of ITP with IVIg's is nowadays well established. The mechanism of action of IVIg in ITP is considered to be blockade of Fcγ receptors (FcγRs). Indeed, in animal models there is evidence for such a mechanism.[2] However, studies in knockout mice have revealed that the mechanism of action of IVIg's in ITP may be more complicated, since mice deficient for the inhibiting Fc receptor, FcγRIIb, do not respond to IVIg's when suffering from experimental ITP.[3] This absolute requirement of FcγRIIb for the efficacy of IVIg's in murine ITP was confirmed in a study published by Crow et al[1] in the July 15, 2003, issue of *Blood*. In that interesting study the authors also report that mice with a single deficiency of molecules involved in signaling via FcγRIIb (ie, SHIP-1, SHP-1, and Btk), respond normally to IVIg's when suffering from experimental ITP. The authors concluded that the beneficial effect of IVIg's in this experimental ITP model is mediated via recruitment of as-yet-unknown signaling molecules by FcγRIIb. However, we would like to point to another possible explanation for the data of Crow et al. Huang et al[4] have published evidence that both SHIP-1 and SHP-1 bind to phosphorylated immunoreceptor tyrosine-based inhibition motifs (ITIMs) in FcγRIIb. Furthermore, these authors also show that SHIP-1 and SHP-1 carry out similar functions; as indeed is well known in literature, as summarized by Erneux et al.[5] In addition, SHP-1 and SHIP-1 share considerable homology, especially the N-terminal region, which harbors the SH2 domains. As a matter of fact, 24 of the first 107 amino acid residues are identical, yielding 22% identity. The homology of these domains, which have long been known to bind to phosphorylated tyrosine residues in so-called immunoreceptor tyrosine-based activation motifs (ITAMs) and ITIMs, is up to 56%. Thus, it is very well possible that signal transduction via FcγRIIb in the absence of SHIP-1 is mediated by SHP-1, and vice versa. Hence, the data in the report by Crow et al in our opinion do not definitely rule out a role of these signaling molecules in the FcγRIIb-dependent effects of IVIg's in experimental ITP. In addition, the role of SHIP-2, which has been shown to have inducible expression on monocytes,[6] is not taken into account in the study of Crow et al. Thus, it would be interesting to see whether IVIg's are capable of inducing SHIP-2 in cells of the reticulo-endothelial system and whether this has functional consequences for the protective mechanism of action of IVIg's.

In conclusion, the experiments by Crow et al do not allow definite conclusions regarding involvement of SHIP-1, SHP-1, SHP-2, and Btk in the intracellular signaling pathways triggered by IVIg's via FcγRIIb during ITP.

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Response:

SHP up or SHIP out

van Mirre and colleagues raise interesting questions in their interpretation of our recent paper.[1] Our work confirmed that intravenous immunoglobulin (IVIg)–mediated amelioration of murine immune thrombocytopenia (ITP) is absolutely dependent on the inhibitory receptor FcγRIIB.[2] Although van Mirre et al suggest that IVIg works by competitive blockade of activating FcγRs, IVIg had no noticeable effect whatsoever in FcγRIIB-deficient mice in our study, suggesting that a purely "competitive" reticuloendothelial system (RES) blockade per se may not significantly contribute to IVIg-mediated amelioration of murine ITP. We further demonstrated that this FcγRIIB-mediated reversal of ITP was independent of the individual activities of the phosphatases SHIP-1, SHP-1, and the kinase Btk. van Mirre et al suggest that SHIP-1 and SHP-1 can replace each other functionally and thus a redundancy pathway may exist. In point of fact, we clearly state in our paper that redundancy may exist in the SHIP/SHP families, although since the substrates for SHIP and SHP are markedly different, we would find it difficult to conclude that they can perform the same function. In addition, it has been demonstrated that FcγRIIB-mediated inhibitory signaling does not require SHP-1 in both B cells[3] and mast cells.[4] Experiments with SHIP-1/SHP-1 double knockouts also could not rule out other family members such as SHIP-2/SHP-2 or even another inositol phosphatase, PTEN, which can dramatically down-regulate phagocytosis through the activating receptor alone.[5]

We hypothesized in our paper that the FcγRIIB pathway utilized by IVIg may be different from that found in B cells. In the 2 cell types in which FcγRIIB has been extensively studied, namely B cells and mast cells, negative signaling through the immunoreceptor tyrosine-based inhibitory motif (ITIM) involves co-crosslinking with an activating receptor complex. Current data have not established that IVIg-dependent effects on the macrophage FcγRIIB require simultaneous interaction with an activating receptor. If co-ligation does occur, some likely candidates for the provision of an activating receptor in mice could be FcγRIIIA or FcγRI; we have, however, recently shown that IVIg can function independently of the activating receptor FcγRIIIA,[6] and that IVIg worked well in nonobese diabetic–severe combined immunodeficient mice,[7] which have a defective FcγRI.[8]

It is important to focus not only on SHIPs and SHPs, but to consider the contribution of other regions of FcγRIIB in terms of IVIg function. In particular, FcγRIIB-dependent inhibitory effects (promotion of apoptosis) have been demonstrated to occur independent of the entire FcγRIIB cytoplasmic tail and may therefore utilize the transmembrane region (or the extracellular portion) for initiating inhibitory effects.[9,10] We questioned whether IVIg might induce FcγRIIB to recruit the gamma chain, a signaling mediator which interacts with transmembrane regions and is required for function of both FcγRI and FcγRIII. However, we found that IVIg ameliorated murine ITP in mice expressing the human FcγRIIA in the absence of the gamma chain (A. R. C. and A. H. L., unpublished observations, October 2003). In conclusion, the mechanism underlying IVIg-mediated FcγRIIB-dependent amelioration of murine ITP remains elusive and may involve an as-yet-unappreciated biochemical mechanism distinct from that of B cells or mast cells.

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