tectable permanent magnetic field to transport solar wind electrons to the nightside and excited O_2 was expected to be much less abundant. Slanger *et al.*'s measurements indicate, however, that the green line volume emission rates from the Venus nightside are comparable to the ambient nightglow emission rates observed in Earth's oxygen-rich atmosphere (*4*).

The green line intensities measured by Slanger *et al.* are far too dim to account for the so-called "ashen light" observed by amateur and professional astronomers since well before the space age (*5*), but the new observations should help to unravel the unusual oxygen chemistry and dynamics of the upper atmosphere of Venus. In particular, they may provide additional insight into the processes responsible for the much more intense and variable infrared O_2 airglow (*6–8*) (see the figure). This airglow is produced as atomic oxygen recombines in the upper atmosphere of Venus, producing O_2 in a particular excited state, $^1\Delta_g$. These molecules then emit a photon at wavelengths near 1.27 μm as they relax to their ground state. As in the case of the green line emission, the observed O_2 emission rates indicate that despite much lower concentrations of ground state O_2 on Venus than on Earth, the two atmospheres appear to have similar concentrations of O_2 in this particular excited state. Surprisingly, however, the Venus atmosphere appears to produce only O_2 ($^1\Delta_g$), whereas atomic oxygen recombination in Earth's atmosphere produces O_2 molecules in a variety of excited states.

The physical and chemical processes responsible for the high spatial and temporal variability in the O_2 ($^1\Delta_g$) airglow (*6*) are not well understood, but this variability may help to explain a puzzling aspect of the green line emission discovered by Slanger *et al.* Spacecraft observations of the nightside of Venus at visible wavelengths in 1975 revealed no evidence of atomic oxygen green and red lines (*7*), but both the new measurements and the earlier spacecraft observations detected comparable airglow intensities from the O_2 Herzberg II bands. The latter occupy the same wavelength range as the atomic oxygen green line and have comparable intensities. These results suggest that the green line emission is spatially and/or temporally variable. Could these variations be associated with the O_2 ($^1\Delta_g$) variability? Unfortunately, even this simple question cannot yet be answered because there are no simultaneous measurements of the atomic oxygen green line and the O_2 ($^1\Delta_g$) airglow.

Oxygen green line emission from Earth's upper atmosphere has been studied extensively from the ground and from Earth-orbiting satellites. These observations have been analyzed to produce global maps of winds, temperatures, and atmospheric waves at altitudes between 90 and 120 km in Earth's upper mesosphere and lower thermosphere (*9–11*). The chemistry, thermal structure and dynamics of the atmosphere of Venus at levels within and above the clouds have puzzled planetary scientists for decades. Additional observations and analyses of the O green line and O_2 ($^1\Delta_g$) airglow from the nightside of Venus may help to identify some of the mysterious processes operating in the upper atmosphere of our closest planetary neighbor.

References and Notes

1. T. G. Slanger, P. C. Cosby, D. L. Huestis, T. A. Bida, *Science* **291**, 463 (2001).
2. Airglow is a general term covering all phenomena that cause the air to glow. Airglow can be excited by a broad range of processes, including energetic photochemical processes (photochemistry and chemiluminescence), absorption of sunlight (resonance and fluorescence) electrical discharges (lightening), high-energy electron impacts (aurora), and inelastic collisions between atoms and molecules that result in energy transfers.
3. J. T. Trauger, J. I. Lunine, *Icarus* **55**, 272 (1983).
4. For both planets, the green line volume emission rates are ~150 Rayleighs, where 1 Rayleigh is 10^6 photons per square centimeter per second.
5. J. L. Phillips, C. T. Russell, *Sky Telescope* **75**, 250 (1988).
6. V. A. Krasnopol'sky, A. A. Krysko, V. N. Rogachev, V. A. Parshev, *Cosmic Res.* **14**, 789 (1976).
7. P. Connes, J. F. Noxon, W. A. Traub, N. P. Carleton, *Astrophys. J.* **233**, L29 (1979).
8. D. Crisp *et al.*, *J. Geophys. Res.* **101**, 4577 (1996).
9. U. B. Makhlouf, R. H. Picard, M. J. Taylor, J. R. Winick, *Adv. Space Res.* **19**, 583 (1997).
10. D. Y. Wang, W. E. Ward, G. G. Sheperd, D. L. Wu, *J. Atmos. Sci.* **57**, 1906 (2000).
11. W. E. Ward, G. H. Solheim, G. G. Shepherd, *Geophys. Res. Lett.* **24**, 1127 (1997).

PERSPECTIVES: IMMUNOLOGY

Giving Inhibitory Receptors a Boost

Shih-Yao Lin and Jean-Pierre Kinet

For more than half a century, patients with antibody deficiencies have been treated with intravenous injections of immunoglobulin (IVIG). IVIG is prepared from pooled serum and its major component is immunoglobulin G (IgG), the most abundant class of antibody in serum (*1*). IVIG is similar to other replacement therapies involving, for example, administration of coagulation factors to hemophiliacs or red blood cells to patients with various forms of anemia. Because antibodies are one of the principal weapons that the immune system uses to combat microorganisms, IVIG is also given as a treatment for septic shock caused by certain bacteria.

More recently, some autoimmune disorders have been treated with high concentrations of IVIG and the results have been encouraging (*2*). These disorders are characterized by the presence of autoantibodies (antibodies against normal components of the human body) that cause inflammation and the consequent destruction of target cells or tissues. For example, autoantibodies that recognize antigens on platelets cause immune thrombocytopenia; anti-erythrocyte autoantibodies result in autoimmune hemolytic anemia; acute demyelinating polyneuropathy (Guillain-Barré syndrome) and myasthenia gravis are caused by autoantibodies that attack nerves and muscles, respectively. The ability of IVIG to reduce inflammation in patients with autoimmune disease remains unexplained.

According to Samuelsson *et al.* (*3*) on page 484 of this issue, the surprising key player that mediates the therapeutic benefits of IVIG is the Fc inhibitory receptor for IgG, FcγRIIB. In a murine model of immune thrombocytopenia—in which platelets bound by circulating anti-platelet antibodies are destroyed by macrophages (see the figure)—the authors showed that IVIG protected the mice from developing the disease. The protective effect of IVIG was unexpectedly abolished if the activity of FcγRIIB was blocked by antibody or if the receptor itself was deleted through genetic engineering. Treating mice with IVIG led to an increase in the number of macrophages expressing FcγRIIB, implying that this receptor could be responsible for the inhibition of platelet destruction.

How does IVIG induce macrophages to express more FcγRIIB? An increase in the surface expression of FcγRIIB does not seem to require that existing FcγRIIB receptors on macrophages are cross-linked by antibody. Administering the Fc fragment of antibody—the "stalk" without the antigen-binding portion (which is essential for cross-linking) that binds to the Fc receptor—is as effective as IVIG at prevent-

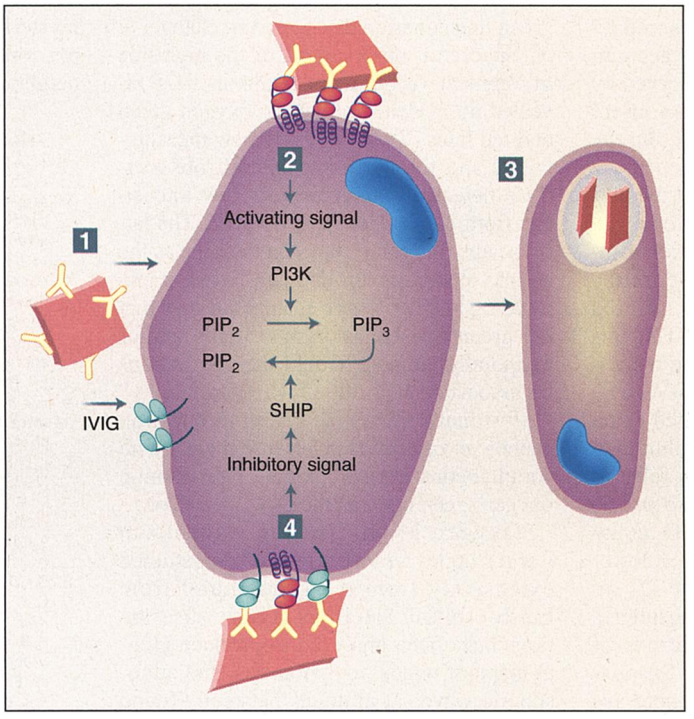
The authors are in the Division of Allergy and Immunology, Department of Pathology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston MA 02215, USA. E-mail: jkinet@caregroup.harvard.edu

ing immune thrombocytopenia. Furthermore, protection by IVIG is already apparent 1 hour after injection, and possibly even earlier; for this reason, protection is unlikely to depend on de novo transcription of the Fc inhibitory receptor gene.

The rapid up-regulation of existing FcγRIIB receptors from the cytoplasm to the surface of macrophages is reminiscent of the increased expression of FcεRI (the Fc receptor for IgE) by immune cells, which is induced by increased serum IgE (*4*, *5*). Injecting IgE-deficient mice that have low surface expression of FcεRI with IgE leads to rapid up-regulation of FcεRI. But direct up-regulation of Fc receptors by antibody is unlikely to be the mechanism at play here. First, there is no change in overall maximal expression of FcγRIIB by macrophages; rather, there is an increase in the numbers of macrophages that express high levels of FcγRIIB. In other words, macrophages that are apparently negative for FcγRIIB expression start to express FcγRIIB after IVIG administration. In addition, others have shown that the in vitro administration of IgG to cultured macrophages does not induce up-regulation of the corresponding Fc inhibitory receptor for IgG (FcγRIIB) (*5*) and that antibody-deficient mice express normal amounts of FcγRIIB (*6*).

There are at least two "indirect" models that could explain how IVIG induces surface expression of FcγRIIB by macrophages. Both models depend on an available intracellular pool of FcγRIIB in macrophages that could be deployed rapidly. In one model, the Fc fragment of antibodies (and IVIG) neutralizes circulating molecules that might participate in the negative control of FcγRIIB surface expression. As a consequence of this neutralization, the intracellular pool of FcγRIIB in macrophages is mobilized. Alternatively, Fc fragments and IVIG might bind, not to macrophages, but to other types of cells, perhaps lymphocytes or endothelial cells. Binding of Fc fragments or IVIG to these cells would result in the release of preformed factors, such as cytokines, that could then mobilize the intracellular FcγRIIB pool of the macrophage.

How does an increase in the surface expression of FcγRIIB abrogate platelet destruction by macrophages? In the case of immune thrombocytopenia, macrophages "see" platelets coated with anti-platelet antibodies as huge immune complexes and engulf them by phagocytosis. These autoantibody-platelet immune complexes bind to the Fc activating receptor (FcγRIII) on macrophages and cross-link them, resulting in activation of several signaling pathways (see the figure). One such pathway activates phosphatidylinositol 3-kinase (PI3K), which generates phosphatidylinositol 3,4,5-trisphosphate (PIP_3), an essential initiator of macrophage phagocytosis. For FcγRIIB to block macrophage phagocytosis, it must be located close to the Fc activating receptors that it inhibits (*7*). Cross-linking of inhibitory FcγRIIB and activating FcγRIII would ensure that the receptors are in close proximity. Because anti-platelet autoantibodies can bind to both FcγRIII and FcγRIIB, platelet-autoantibody immune complexes could induce cross-linking of both receptors. Such cross-linking is known to induce recruitment of the signaling molecule SHIP (*7*, *8*), an inositol phosphatase that breaks down PIP_3 (see the figure). This chemical reaction aborts one of the critical signaling pathways necessary for phagocytosis, thus halting the destruction of platelets. Both FcγRIII and FcγRIIB are low-affinity receptors that bind immune complexes but not free antibodies. Thus, it would not be possible for transfused IVIG (composed of free antibodies) to compete efficiently with immune complexes for binding to these receptors. Samuelsson and colleagues demonstrate, however, that blocking FcγRIII with high-affinity anti-receptor antibodies is as effective at preventing platelet destruction as increasing the number of macrophages expressing FcγRIIB. This suggests that what really regulates macrophage phagocytosis is the balance between inhibitory and activating Fc receptors.



IVIG and immune thrombocytopenia. (1) Circulating anti-platelet autoantibodies bind to platelets, forming platelet-antibody immune complexes. (2) Cross-linking of Fc activating receptors (FcγRIII) on macrophages by these immune complexes leads to the production of PIP_3 (mediated by PI3K) and macrophage activation. (3) Activated macrophages phagocytose the platelet-antibody immune complexes, leading to depletion of platelets. (4) Injected IVIG induces macrophages to increase expression of the inhibitory Fc receptor (FcγRIIB). Cross-linking of FcγRIIB and FcγRIII by platelet-antibody immune complexes abolishes the activating signal by recruitment of SHIP and breakdown of PIP_3, resulting in abrogation of phagocytosis and platelet depletion.

IVIG may prevent platelet destruction in the thrombocytopenic mouse and reduce inflammation in human autoimmune disease in the same way. Clinical administration of IVIG, however, is very different from the experimental setup of Samuelsson *et al.* These investigators injected IVIG before infusion of platelet autoantibodies; but in human patients IVIG is given after autoimmune disease has already developed. Other factors in human patients—such as the severity of autoimmune disease and the amount of circulating autoantibody and immune complexes, as well as the basal expression levels of FcγRIII relative to FcγRIIB—are likely to affect how efficiently IVIG modulates FcγRIIB expression and thus how therapeutically beneficial it will be.

The Samuelsson *et al.* study demonstrates that FcγRIIB is crucial for mediating the anti-inflammatory activity of IVIG and that modulating surface expression of FcγRIIB is a viable strategy for treating autoimmune disorders. The way is now clear to develop potent drugs that can mimic the effects of IVIG on FcγRIIB expression.

References

1. P. Quartier *et al.*, *J. Pediatr.* **134**, 589 (1999).
2. A. F. Hahn, *Curr. Opin. Neurol.* **13**, 575 (2000).
3. A. Samuelsson, T. L. Towers, J. V. Ravetch, *Science* **291**, 484 (2001).
4. J.-P. Kinet, *Annu. Rev. Immunol.* **17**, 931 (1999).
5. M. Yamaguchi *et al.*, *J. Exp. Med.* **185**, 663 (1997).
6. J. V. Ravetch, personal communication.
7. J. V. Ravetch, L. L. Lanier, *Science* **290**, 84 (2000).
8. A. M. Scharenberg, J.-P. Kinet, *Cell* **94**, 5 (1998).