Review Article

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IAN R. MACKAY, M.D., AND FRED S. ROSEN, M.D.,
Editors

IMMUNOMODULATION OF AUTOIMMUNE AND INFLAMMATORY DISEASES WITH INTRAVENOUS IMMUNE GLOBULIN

MICHEL D. KAZATCHKINE, M.D.,
AND SRINI V. KAVERI, D.V.M., PH.D.

INTRAVENOUS immune globulin has been used in the treatment of primary and secondary antibody deficiencies for more than 25 years. It is a safe preparation with no long-term side effects. Intravenous immune globulin was first demonstrated to be effective in an autoimmune disorder — idiopathic thrombocytopenic purpura — two decades ago. Since then, it has been established to be efficacious in the treatment of the Guillain–Barré syndrome, chronic inflammatory demyelinating polyneuropathy, myasthenia gravis, corticosteroid-resistant dermatomyositis, and Kawasaki's syndrome and in the prevention of graft-versus-host disease in recipients of allogeneic bone marrow transplants. Benefits have been reported in many other autoimmune and systemic inflammatory conditions, but controlled trials are often lacking.

The mode of action of immune globulin is complex, involving modulation of the expression and function of Fc receptors, interference with the activation of complement and the cytokine network, provision of antiidiotypic antibodies, and effects on the activation, differentiation, and effector functions of T cells and B cells (Fig. 1). This broad range of activities reflects the importance of immunoglobulins in the immune homeostasis in healthy people.

COMPONENTS OF INTRAVENOUS IMMUNE GLOBULIN

All commercial preparations of immune globulin consist of intact IgG molecules with a distribution of IgG subclasses corresponding to that in normal human serum. Most preparations contain traces of IgA, which can sensitize IgA-deficient persons during long-term treatment. Immune globulin also contains trace amounts of soluble CD4, CD8, and HLA molecules and certain cytokines.[1,2] The half-life of infused immune globulin in immunocompetent persons is three weeks. The Fc region in IgG allows it to interact with and signal through Fcγ receptors on phagocytes, B cells, and other cells as well as with Fc-binding plasma proteins, such as components of the complement system (Fig. 2).

Immune globulin is prepared from pooled plasma from 3000 to 10,000 (and sometimes up to 100,000) healthy blood donors. It can thus be assumed to contain the entire array of variable (antigen-binding) regions of antibodies in normal serum. The large number of donors in the pool increases the number of individual antibody activities in the preparation but risks diluting any useful rare activity. Hence, immune globulin contains a broad range of immune antibodies against pathogens and foreign antigens. These antibodies are critical for replacement therapy in patients with humoral immune deficiencies.

NATURAL ANTIBODIES

Normal serum contains natural antibodies of the IgG, IgM, and IgA isotypes, which are believed to be essential for the immunoregulatory effects of immune globulin in immune-mediated disorders. The antibodies are called "natural" because they are generated in the absence of deliberate immunization and independently of exposure to foreign antigens.[3] Most natural antibodies in healthy people and hence in the immune globulin pool are autoantibodies. Recent evidence indicates that autoantigens stimulate autoreactive B cells to grow and produce natural autoantibodies.[4] The repertoire of natural autoantibodies remains invariable from early childhood through adult life.[5] Most natural autoantibodies in adult serum are of the IgG class, implying that autoreactive T cells contribute to the repertoire of autoreactive B cells under physiologic conditions.

Natural autoantibodies are more polyreactive than immune antibodies, in the sense that they can often bind to different antigens.[6] Natural autoantibodies can also recognize and be recognized by other autoantibodies in the same person. Since there is a high level of natural autoantibodies in immune globulin, a considerable fraction of immune globulin consists of antibodies capable of interacting with idiotypes (serologically defined constituents of the variable region) (Fig. 1) of other antibodies in the preparation to form dimers with complementary idiotypes. The content

From INSERM Unité 430, Hôpital Broussais and the Department of Clinical Immunology, Hôpital Européen Georges Pompidou and Université Pierre et Marie Curie — all in Paris. Address reprint requests to Dr. Kazatchkine at INSERM U430, Hôpital Broussais, 96 rue Didot, 75014 Paris, France, or at michel.kazatchkine@egp.ap-hop-paris.fr.

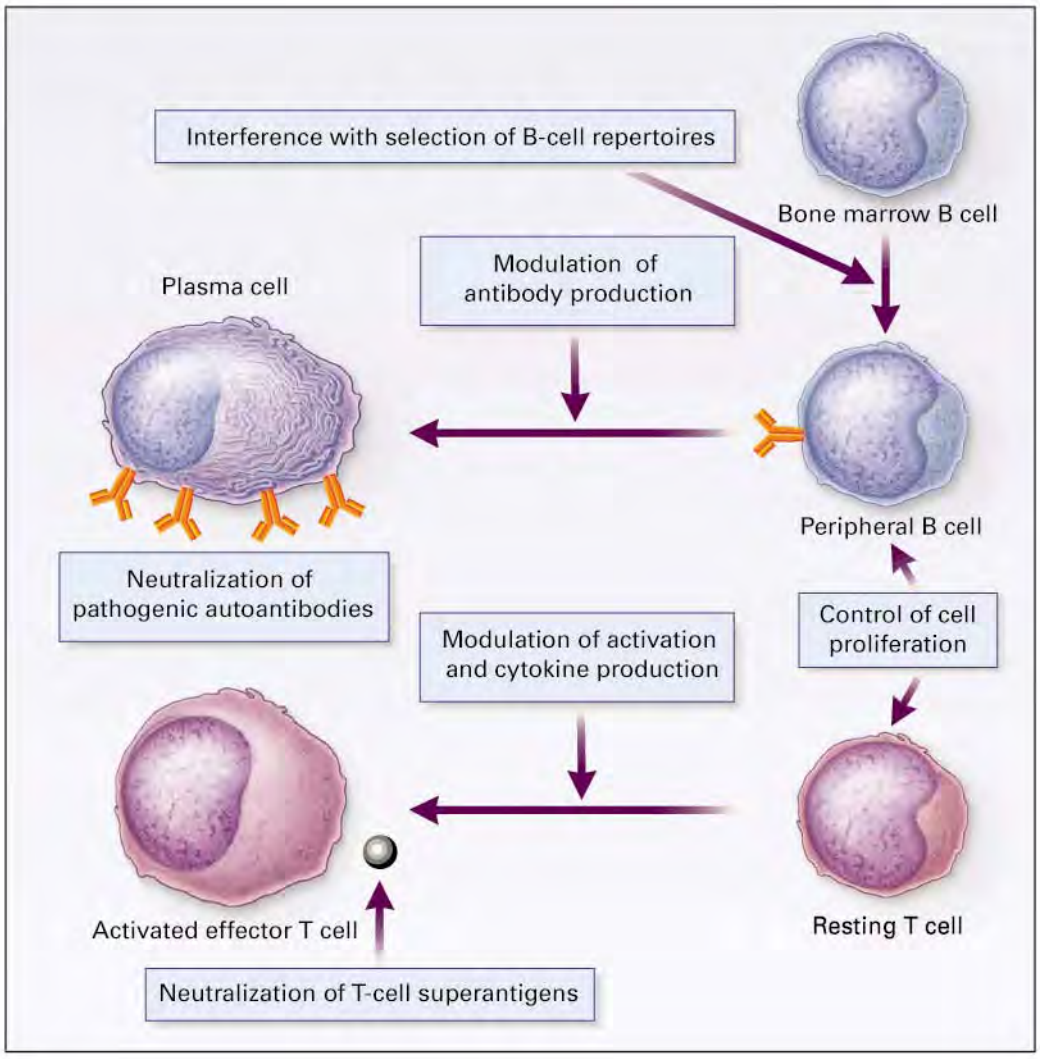

Figure 1. Immunomodulatory Effects of Immune Globulin on B Cells and T Cells.

Arrows indicate the sites targeted for the effect of immune globulin. Immune globulin interferes with the selection of B-cell repertoires, down-regulates or up-regulates antibody production, neutralizes pathogenic autoantibodies and T-cell superantigens, modulates the activation and function of effector T cells and the production by CD4 T cells of cytokines mediated by type 1 and type 2 helper-T-cells, and controls cell growth.

in such dimers in the immune globulin pool increases with the number of donors in the pool.[7] The formation of idiotype–idiotype dimers may account for some of the clinical effects of immune globulin (see below).

Several functions have been proposed for natural autoantibodies.[8] They can bind to pathogens and may have a role in defending against infection. Natural autoantibodies help remove senescent or altered molecules, cells, and tumors. Their ability to induce remyelination may be pertinent to the effect of immune globulin in multiple sclerosis.[9,10] Of particular relevance for understanding the effects of immune globulin in autoantibody-mediated diseases is the ability of natural autoantibodies to inhibit the growth of autoreactive B-cell clones.

ANTIBODIES AGAINST SOLUBLE AND MEMBRANE MOLECULES INVOLVED IN IMMUNE REGULATION

A number of natural autoantibodies against soluble and membrane-associated self molecules involved in immune regulation are found in immune globulin.[11-21] Interactions between these natural autoantibodies

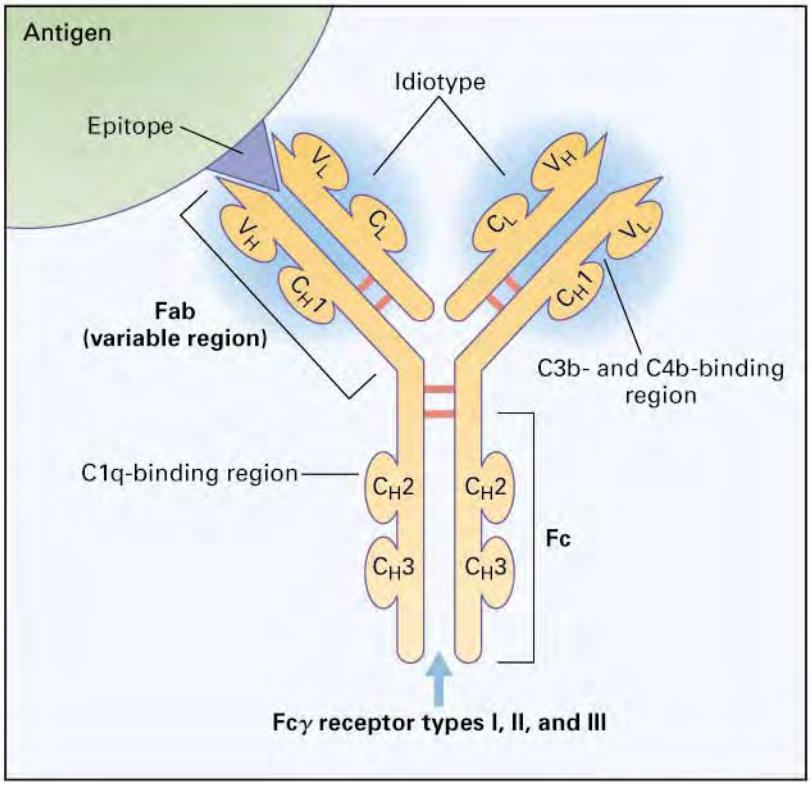

Figure 2. The IgG Molecule.

The site of interactions between IgG and antigen (epitope) is shown, as are binding sites for C1q and activated C3b and C4b and sites of interaction between the heavy (H) chains of IgG and Fcγ receptor types I, II, and III. V denotes variable region, C constant region, and L light chain.

and their target molecules are directly relevant to the immunomodulatory effects of immune globulin. For example, because immune globulin can interact with idiotypes of autoantibodies[11,22,23] it can neutralize autoantibodies in certain autoantibody-mediated autoimmune diseases and down-regulate the synthesis of antibodies by B cells that express the relevant idiotype. Antibodies against the variable region of the T-cell receptor are also present in immune globulin and may regulate T-cell function in autoimmune disorders.[13]

Immune globulin contains antibodies against many cytokines.[16,17] The physiologic and therapeutic relevance of these antibodies is unclear. They may neutralize some cytokines or enhance the half-life of the cytokines.[16,17] Antibodies against granulocyte–macrophage colony-stimulating factor, interferon-α, interleukin-1α, and interleukin-6 in immune globulin have biologic activity in vivo.[17]

Natural autoantibodies in immune globulin can be purified by physical means and tested for biologic activity.[24] For example, purified antibodies against a nonpolymorphic region of HLA class I molecules inhibit the killing of autologous target cells containing influenza peptides by class I–restricted anti-influenza CD8 T cells.[18] Purified anti-CD4 antibodies can inhibit the proliferation of lymphocytes in a mixed-lymphocyte culture and prevent infection of a CD4 T-cell line by human immunodeficiency virus (HIV) type 1 in vitro.[15] Purified antibodies against the Arg-Gly-Asp (RGD) motif of integrins (the site of attachment of several adhesive matrix proteins) can block the aggregation of platelets induced by adenosine diphosphate, the binding of activated B cells to fibronectin, and the adhesion of platelets to von Willebrand factor.[21]

Immune globulin also contains both agonistic and blocking antibodies against Fas (CD95), the receptor for the Fas ligand, which transduces apoptotic signals into cells[25]; such antibodies can induce apoptosis of T cells and B cells in vitro.[19] Apoptosis mediated by normal IgG involves the activation of caspases and the

phosphorylation of serine residues of Bcl-2.[26] Most of the morphologic changes that occur during apoptosis are caused by caspases, a set of cysteine proteases that have a central role in the apoptotic pathway. Bcl-2 and related proteins act at the effector stage of apoptosis and may promote or prevent cell death by regulating the release of apoptotic factors (in particular, cytochrome *c*) from mitochondria into the cytosol.[27] In the early stages of immune globulin–induced apoptosis of T cells, mitochondria release cytochrome *c*.[26] Antagonistic antibodies against Fas may account for the therapeutic effect of immune globulin in toxic epidermal necrolysis (Lyell's syndrome),[20] a life-threatening condition characterized by generalized erythema, the formation of bullae, and exfoliation of the epidermis. The majority of cases of Lyell's syndrome are drug induced.

CLINICAL USE OF INTRAVENOUS IMMUNE GLOBULIN

The list of disorders that have reportedly responded to intravenous immune globulin[28-30] includes a wide spectrum of diseases mediated by autoantibodies or believed to depend primarily on autoaggressive T cells. However, the beneficial effect of intravenous immune globulin has been established by prospective randomized trials in only a few of these diseases (Table 1). In many other conditions, intravenous immune globulin has been shown to be an effective therapeutic option in uncontrolled studies and continues to be investigated; among these conditions are anti–factor VIII autoimmune disease, the antiphospholipid-antibody syndrome, polymyositis, systemic lupus erythematosus, and Crohn's disease. We still do not know enough about how intravenous immune globulin should be administered for optimal immunomodulation: should we keep plasma levels of immune globulin high for prolonged periods or spike the immune system intermittently with high doses of immune globulin?

TABLE 1. AUTOIMMUNE AND INFLAMMATORY DISEASES IN WHICH THE BENEFICIAL EFFECT OF IMMUNE GLOBULIN HAS BEEN ESTABLISHED IN CONTROLLED CLINICAL TRIALS.

Idiopathic thrombocytopenic purpura[31,32]
Guillain–Barré syndrome[33,34]
Chronic inflammatory demyelinating polyradiculoneuropathy[35]
Myasthenia gravis[36]
Multifocal motor neuropathy[37,38]
Corticosteroid-resistant dermatomyositis[39]
Kawasaki's disease[40]
Prevention of graft-versus-host disease[41]
Antineutrophil cytoplasmic-autoantibody–positive vasculitis[42,43]*
Autoimmune uveitis[44]*
Multiple sclerosis[45-47]

*The results of preliminary trials have been published, and major controlled trials are under way.

SAFETY OF INTRAVENOUS IMMUNE GLOBULIN

Adverse reactions to intravenous immune globulin occur in less than 5 percent of patients.[48] Undesirable effects include headache, chills, nausea, fatigue, myalgia, arthralgia, back pain, and increased blood pressure in patients at risk for hypertension.[49,50] Patients with primary immunoglobulin deficiency who have never received intravenous immune globulin have a higher frequency of adverse effects than those who have been receiving regular therapy. Mild reactions to immune globulin occur within the first 30 minutes after infusion and may be relieved by reducing the infusion rate or temporarily stopping the infusion.[49] Acute aseptic meningitis with pleocytosis of the cerebrospinal fluid may occur within 48 to 72 hours after the administration of immune globulin. The symptoms resolve spontaneously[49] and can be prevented with nonsteroidal antiinflammatory drugs. The syndrome does not occur with further infusions of the same immune globulin and may not occur with use of an immune globulin from a different manufacturer. Very rarely, serious anaphylactoid reactions occur within the first hour after the administration of immune globulin. Anaphylaxis associated with sensitization to IgA in patients with IgA deficiency[51] can be prevented by using IgA-depleted immune globulin.[51,52] The presence of IgG anti-IgA antibodies is not, however, always associated with severe adverse reactions to immune globulin.[53,54]

Elderly patients and patients with diabetes or impaired renal function are at risk for acute renal failure, which is usually limited to a transient increase in creatinine levels within two to five days after the infusion of immune globulin.[55] Renal failure is related to tubular damage induced by sucrose in the immune globulin preparation.[55] Close follow-up of renal function is recommended in such patients.

The potential transmission of blood-borne agents by intravenous immune globulin has recently been reviewed.[56] Ensuring the safety of immune globulin begins with donor selection and screening of plasma donations for hepatitis C virus, hepatitis B virus, HIV, and hepatitis B surface antigen. Polymerase-chain-reaction testing of samples of individual plasma donations or pooled plasma has recently been introduced. There has been no report of the transmission of HIV by intravenous immune globulin. There were several outbreaks of hepatitis C associated with the administration of intravenous immune globulin in the mid-1990s,[56] but the risk of transmitting this virus should be substantially reduced by improvements in

the manufacturing process that are now required by regulatory authorities in the United States and Europe. There is no evidence that intravenous immune globulin has transmitted Creutzfeldt–Jakob disease.

MECHANISMS OF ACTION OF IMMUNE GLOBULIN

Each mechanism listed in Table 2 may be involved to some extent in the beneficial effects of intravenous immune globulin in different diseases. Some mechanisms depend on the interaction between the Fc portion of infused immune globulin and Fcγ receptors on target cells. Others hinge on the variable regions of antibodies in the preparation. The distinction between Fc-dependent and variable-region–dependent mechanisms is, however, artificial because several effects of immune globulin are amplified or, indeed, made possible by the binding of Fc to cells targeted by variable regions (Fig. 3). In addition, the integrity of the IgG molecule is important to the stability and half-life of infused immune globulin in vivo.

TABLE 2. IMMUNOREGULATORY EFFECTS OF IMMUNE GLOBULIN.

Fc receptors
Blockade of Fc receptors on macrophages and effector cells
Induction of antibody-dependent cellular cytotoxicity
Induction of inhibitory Fcγ receptor IIB
Inflammation
Attenuation of complement-mediated damage
Decrease in immune-complex–mediated inflammation
Induction of antiinflammatory cytokines
Inhibition of activation of endothelial cells
Neutralization of microbial toxins
Reduction in corticosteroid requirements
B cells and antibodies
Control of emergent bone marrow B-cell repertoires
Negative signaling through Fcγ receptors
Selective down-regulation and up-regulation of antibody production
Neutralization of circulating autoantibodies by antiidiotypes
T cells
Regulation of the production of helper-T-cell cytokines
Neutralization of T-cell superantigens
Cell growth
Inhibition of lymphocyte proliferation
Regulation of apoptosis

Fc Receptor–Mediated Effects

There are specific Fc receptors for each class of immunoglobulin. IgG molecules bind through their Fc region to Fcγ receptors on hematopoietic cells (Fig. 3).[57]

The blockade of Fcγ receptors on macrophages is considered to underlie the mechanism of immune globulin in idiopathic thrombocytopenic purpura and other autoantibody-mediated cytopenias. Evidence in support of this interpretation includes the following: purified anti-D (Rh) IgG increases platelet counts in Rh-positive patients with idiopathic thrombocytopenic purpura[58]; in vitro, blood monocytes of patients with idiopathic thrombocytopenic purpura who receive immune globulin have a decreased ability to form rosettes with IgG-coated erythrocytes[59]; in vivo, intravenous immune globulin decreases the clearance of anti-D–coated autologous erythrocytes[60]; and the efficacy of antibodies against Fcγ receptor III or fragments containing the Fc region of IgG in patients with idiopathic thrombocytopenic purpura is similar to that of intravenous immune globulin.[61,62] Recent studies in an animal model of idiopathic thrombocytopenic purpura suggest that intravenous immune globulin increases the expression of the Fcγ receptor IIB, an inhibitory receptor that blocks the clearance of the opsonized platelets.[63]

Blockade of Fc receptors may also cause inhibition of antibody-dependent cell-mediated cytotoxicity. This mechanism could explain the protective effect of immune globulin against demyelination in inflammatory neurologic disorders.[64]

Antiinflammatory Effects

Immune globulin has potent antiinflammatory activity, as evidenced by its rapid effects on acute inflammation in Kawasaki's disease[40] and juvenile arthritis.[65] Kawasaki's disease is an idiopathic syndrome resembling toxic shock syndrome that usually affects infants and young children and is characterized by fever, conjunctival infection, redness of the lips and oral cavity, cervical lymphadenitis, and a maculoerythematous skin eruption in a glove-and-sock distribution. There are several ways in which immune globulin reduces inflammation. One is by preventing the generation of the membrane-attack complex (C5b–C9) and subsequent complement-mediated tissue damage by binding the activated components C3b and C4b, thus preventing the deposition of these fragments on target surfaces. The ability of immune globulin to bind C3b and C4b is relevant to the treatment of severe dermatomyositis. The effect of immune globulin in dermatomyositis is associated with decreased plasma levels of membrane-attack complex and a substantial decrease in the amounts of C3b and membrane-attack complex that are deposited in endomysial capillaries.[66]

Immune globulin also prevents damage mediated by immune complexes containing C3b by accelerating the decay of the C3b into an inactive form, iC3b.[67] By binding to free antigen or antibody in immune complexes, immune globulin can reduce the inflammatory activity of such complexes. In vitro, immune globulin decreases the amount of IgG deposited in renal-biopsy specimens from patients with immune complex glomerulonephritis.[68]

Modulation of the production of cytokines and cytokine antagonists is likely to be a major mechanism of the antiinflammatory effects of immune glob-

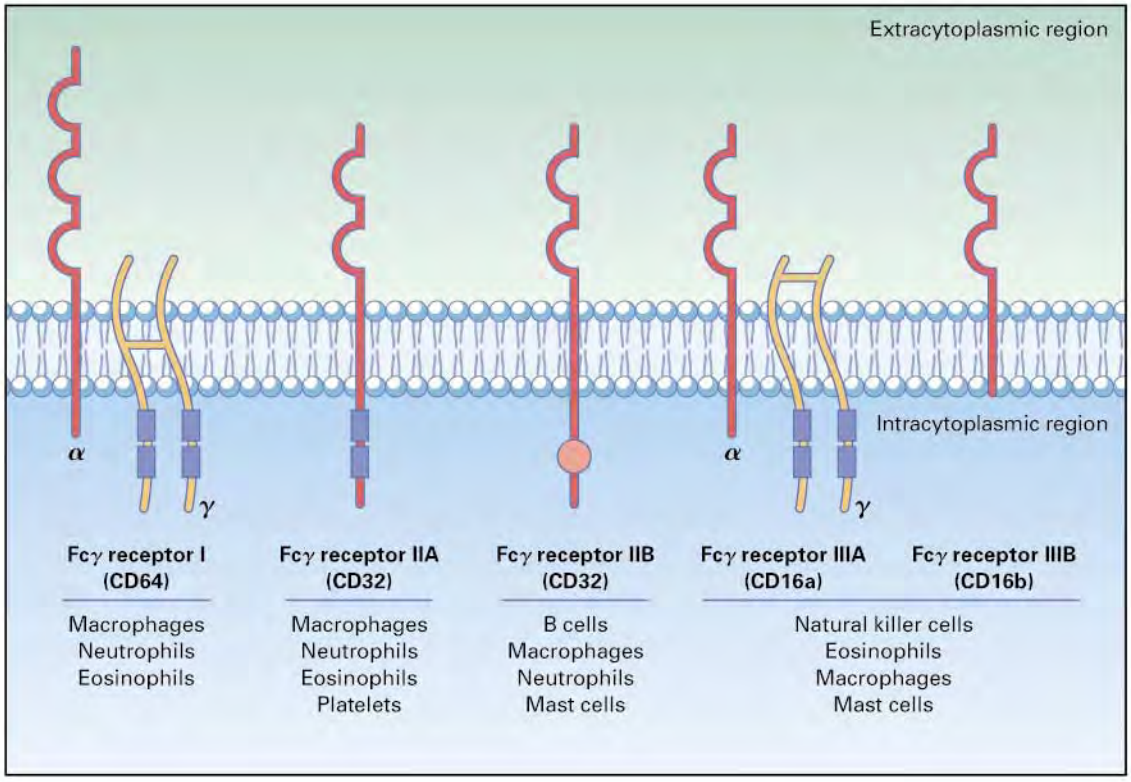

Figure 3. Members of the Family of Human Fcγ Receptors.

Listed below each receptor are the cells on which each receptor is expressed. Semicircular structures in the extracytoplasmic region represent immunoglobulin-like domains. Individual subunits of Fc receptors in the intracytoplasmic region are labeled α and γ. The immunoreceptor tyrosine-based activation motifs are depicted as blue bands, and the immunoreceptor tyrosine-based inhibition motif of Fcγ receptor RIIB is depicted by the pink circle. Fcγ RIII receptors on natural killer cells bear a ζ chain rather than an α chain.

ulin.[69-72] Decreased levels of the inflammatory cytokine interleukin-1 in Kawasaki's disease[73] and greatly increased plasma levels of interleukin-1–receptor antagonist (1000 times as great as those of interleukin-1β) have been reported after the administration of intravenous immune globulin.[74] Circulating levels of interleukin-1β decrease after treatment of the Guillain–Barré syndrome with intravenous immune globulin.[75]

Immune globulin inhibits the activation of endothelial cells in in vitro models of inflammation. Both tumor necrosis factor α and interleukin-1β induce transcription of genes for certain adhesion molecules and cytokines in cultured endothelial cells.[68] This process is blocked by adding immune globulin to the culture.[76,77]

Staphylococcal toxin superantigens, which are polyclonal activators of CD4 T cells, are targets of antibodies against superantigen in immune globulin.[78] In cultures of blood mononuclear cells, immune globulin blocks apoptosis of the blastic T cells that proliferate in the presence of superantigen.[79] Neutralization of the staphylococcal toxin is a probable mechanism of action of immune globulin in Kawasaki's disease.[80] Immune globulin also contains neutralizing antibodies against the Shiga toxin and the SLT-1 toxin of *Escherichia coli*. These toxins are candidate pathogens in the primary hemolytic–uremic syndrome.[81] It has been suggested that the toxin-neutralizing properties of immune globulin contribute to its effect in chronic relapsing colitis induced by *Clostridium difficile* in children.[82]

Effects on B Cells and Antibodies

The high content of antiidiotypes against autoantibodies in immune globulin probably accounts for its ability to neutralize autoantibodies, as shown in patients with autoimmune hemophilia due to autoantibodies against factor VIII.[83,84] Intravenous immune globulin also suppressed the level of antineutrophil cytoplasmic autoantibodies in patients with vasculitis to a degree that was related to its ability to

neutralize the activity of the autoantibodies in vitro.[85] Immune globulin also contains antiidiotypes against a number of other disease-associated autoantibodies, including those against thyroglobulin, DNA, intrinsic factor, peripheral-nerve gangliosides, platelet glycoprotein IIb/IIIa, and the acetylcholine receptor.[24] Antiidiotypes in immune globulin may be able to neutralize pathogenic autoantibodies with variable regions that resemble those of the corresponding natural autoantibodies. In this respect, immune globulin may be seen as a humoral regulatory element that controls the autoreactivity of antibodies in plasma, a function of normal IgG and IgM that has been well documented in healthy people.[86,87] The effects of normal immunoglobulin on B cells include the control of B-cell populations that migrate from the bone marrow to secondary lymphoid organs, as shown in experimental models in mice,[88] and down-regulation of specific autoreactive B cells, as shown with intravenous immune globulin in mice with severe combined immunodeficiency that were given lymphoid cells from patients with autoimmune disease.[89,90]

Effects on T Cells

In animal models, immune globulin prevents experimental autoimmune encephalitis (a model of multiple sclerosis) and autoimmune uveitis.[91,92] Refractoriness to experimental autoimmune encephalitis can be transferred by CD4 T cells from recipients of immune globulin to animals that have never received immune globulin. In the case of both experimental autoimmune encephalitis and autoimmune uveitis, infusion of immune globulin selectively decreases the ability of antigen-reactive T cells to produce interleukin-2 and interferon-γ, cytokines mediated by type 1 helper T cells (Th1), and in humans, immune globulin suppresses the production of interleukin-2 by stimulated T cells in vitro.

Data from in vivo experiments suggest that intravenous immune globulin helps to restore the balance between Th1 and type 2 helper T cells (Th2) in autoimmune diseases in which the population of self-reactive Th1 or Th2 clones is expanding. These results provide a strong rationale for the ongoing randomized trials of intravenous immune globulin in patients with multiple sclerosis. Evidence from earlier trials indicates that intravenous immune globulin decreases both the frequency and the severity of exacerbations in multiple sclerosis.[45-47]

CONCLUSIONS

Since it was first used in the treatment of idiopathic thrombocytopenic purpura, considerable progress has been made in understanding the mechanisms of the immunomodulatory functions of immune globulin. The mode of action is complex, involving modulation of the expression and function of Fc receptors, interference with the activation of complement and the cytokine network, provision of antiidiotypic antibodies, regulation of cell growth, and effects on the activation, differentiation, and effector functions of T cells and B cells. The therapeutic effects of immune globulin most likely reflect the functions of natural antibodies in maintaining immune homeostasis in healthy people. Over the past 20 years, immune globulin has become the preferred treatment for the Guillain–Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, and Kawasaki's syndrome. Since intravenous immune globulin is frequently used to treat autoimmune and inflammatory diseases for which evidence of its efficacy is insufficiently documented, controlled trials, particularly of some neurologic diseases in which immune globulin represents a promising but unproved treatment, are imperative.

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