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Role of Fc Receptors as a Therapeutic Target

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Abstract

It has been forty years since the discovery of Fc Receptors and their function. Fc Receptors include the IgG receptors (FcγR), high-affinity IgE receptor (FcεRI), IgA and IgA/IgM receptors, and neonatal Fc receptor for IgG (FcRn). In particular, the FcγRs have been well known to play an important role in many biologic processes including those associated with the response to infection and cancer as well as in the pathogenesis of immune-mediated diseases. Both positive and negative regulatory function has ascribed to Fc receptors and FcγRs in particular which serve to establish a threshold for immune cell activation. In other cases, Fc receptors such as FcRn possess a novel structure and function by playing a major role in the transport of IgG across polarized epithelial barriers at mucosal surfaces and in the regulation of IgG half-life. These diverse functions highlight the potential effectiveness of targeting Fc receptors for therapeutic purposes. This review summarizes new information available in the therapeutic applications of this biology.

Keywords

Fc receptors; FcRn; IgG; FcγR

INTRODUCTION

Fc receptors, the receptors for the Fc portion of immunoglobulins, play an essential role in antibody-dependent immune responses [1]. Fc receptors are detected on many types of hematopoietic cells including macrophages, neutrophils, dendritic cells, eosinophils, basophils, mast cells, and NK cells [2]. Plasma cells produce five classes of antibodies, IgA,

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IgD, IgE, IgG and IgM. Fc receptors with an Ig superfamily related structure exist that correspond to each of these classes of immunoglobulins. They include the IgG receptors (FcγR), high-affinity IgE receptor (FcεRI), IgA receptor and polymeric immunoglobulin receptor for IgA and IgM. The second category of Fc receptors is the neonatal Fc receptor for IgG (FcRn), which is a unique FcR that has three major functions with respect to IgG; IgG transport across epithelial barriers, protection of IgG from catabolism and antigen presentation. This review focuses on the functions of the common Fc receptors (FcγRs) and FcRn and summarizes the application of this information to the therapy of human diseases.

THE FAMILY OF FCγ RECEPTORS AND THEIR FUNCTION

Fcγ receptors include four different classes of receptors in mice that are known as FcγRI, FcγRIIB, FcγRIII, FcγRIV. Functionally, these receptors are classified in two types of Fc receptors; those that are activating as opposed to those that are inhibitory. These receptors transmit their signals *via* immunoreceptor tyrosine-based activation motifs (ITAMs) or immunoreceptor tyrosine-based inhibitory motifs (ITIMs), respectively [3]. Activating FcγRs that possess ITAMs include FcγRI, FcγRIII and FcγRIV. Ligation of these receptors leads to activation of downsteam-signalling pathways. In contrast, the inhibitory FcγR, FcγRIIB, is a unique FcγR that directs an inhibitory program *via* ITIMs. The composite expression of activating and inhibitory FcγRs regulates the immune response by establishing a threshold for immune cell activation. In many murine models, the aberrant expression of FcγRs can result in uncontrolled immune responses and the initiation of autoimmune diseases [4–6]. Mice which are deficient in the Fcγ-chain, a subunit that is common to the FcγRI, FcγRIII, FcγRIV, FcεRI and FcαRI receptors exhibit an inability to activate all such FcRs. This results in abrogated or heavily impaired immune complex (IC)-mediated immune responses, such as antibody-dependent cell mediated cytotoxicity (ADCC), release of inflammatory mediators and cytokines, and phagocytosis of ICs [7, 8]. The inhibitory receptor FcγRIIB is the most broadly expressed FcγR, and is present on all leukocytes with the exception of NK cells and T cells. There are two different isoforms of FcγRIIb that are named FcγRIIB-1 and FcγRIIB-2. FcγRIIB-1 is specifically expressed on B cells and negatively regulates B cell activation. In comparison, FcγRIIB-2 is widely expressed on cell types that express FcγRIIB and functions in the inhibition of dendritic cells (DC) and macrophages as manifest by diminished antigen uptake, antigen presentation and cellular activation. Mice deficient in FcγRIIB exhibit spontaneous glomerulonephritis and an enhancement of many types of autoimmune responses. It is believed that the lack of FcγRIIB leads to a breakdown in immunologic tolerance. In humans, the FcγR system is more complex, as exemplified by the existence of the high-affinity IgG receptor FcγRI (FcγRIA, FcγRIB, FcγRIC) and low-affinity IgG receptors FcγRII (FcγRIIA, FcγRIIB and FcγRIIC) and FcγRIII (FcγRIIIA and FcγRIIIB) and the presence of several allelic FcγR variants [9]. FcγRI and FcγRIIB are structurally and functionally similar between human and mice. With the exception of human FcγRIIA and FcγRIIC, activating FcγR's typically consist of a ligand-binding FcγR α-chain and a signal-transducing γ-chain dimer, which carries immunoreceptor tyrosine based activating motifs (ITAMs). In addition, humans have a glycosylphosphatidylinositol (GPI)-linked receptor that is exclusively expressed by neutrophils, called FcγRIIIB. Moreover, a variety of human FcγR alleles with

altered functionality exist. Specifically, FcγRIIA^{131H} and the FcγRIIIA^{158V} have a higher affinity for certain IgG subclasses compared to their allelic counterparts. The FcγRIIB^{232T} variant is unable to associate with lipid rafts and is therefore strongly impaired in its negative regulatory activity. There are many differences between the Fcγ receptors of mice and those of humans. However, observations in mouse have in general mirrored those of human systems.

FC RECEPTORS AND INFECTION

There are many reports describing the role of activating Fc receptors in defending against infection [10–12]. We recently reported, for example, on the role of FcγRs in the colonic inflammation induced by infection with *Citrobacter rodentium* [13]. *C. rodentium*, a murine model pathogen for enteropathogenic *Escherichia coli*, specifically colonizes the epithelium of the colon utilizing attaching and effacement structures to adhere to the luminal surface of intestinal epithelial cells and as such cause mucosal inflammation. CD4$^+$ T cells, B cells and IgG, but not secretory IgA or IgM, have been shown to play a critical role in eradicating this pathogen. Therefore, *C. rodentium* has served as an appropriate model to assess the role of IgG and FcγRs in defending against infections. FcRγ-chain deficient mice, which disables activating FcγRs, are more susceptible to *C. rodentium* induced colitis. This occurs through a decrease in the efficiency of FcγR-mediated endocytosis and associated maturation of DCs. As a consequence, in the absence of the FcRγ chain, the activation of antigen specific T cells is significantly diminished. Moreover, in the absence of FcγRs, phagocytosis by macrophages is significantly impaired. Therefore, activating FcγRs play an important role in defending against *C. rodentium* infection supporting a critical role for IgG and the importance of FcγRs in the control of this model of infection. Consistent with this, mice that are deficient in the inhibitory receptor, FcγRIIB, exhibit significantly less inflammation of the distal colon during *C. rodentium* infection (MY and AM, unpublished observations). Macrophages from FcγRIIB deficient mice display increased phagocytic function in comparison to those obtained from wild type mice. These observations with FcγRIIB mice suggest that targeting this receptor can be envisioned as a means to enhance the function of activating FcγR in the treatment of infectious diseases.

FC RECEPTORS AND CANCER

FcγRs play an important role in determining the therapeutic activity of monoclonal IgG antibodies (mAbs) by their ability to activate the cytotoxic activity of FcγR-positive cells such as NK cells, monocytes, macrophages and neutrophils and by increasing antigen presentation by DC when ligated by the Fc portion of therapeutic antibodies [14–17]. Recent studies in Fc receptor-deficient nude mice show that the anti-tumor effects of mAbs such as those directed at-CD20 (Rituximab) and HER2 (Herceptin) require the presence of the signal transducing Fcγ chain that is involved in the activation of FcγRI and FcγRIII receptors that are expressed on monocytes, macrophages, and NK cells [18]. In the B16 metastatic tumor model, FcγR [19] and FcγRIV in particular [20] have been shown to play a significant role in the therapeutic activity of the TA99 antibody specific for the gp75 tumor antigen.

FcγRIIB has been examined in lymphoid tissues and B cell lymphomas suggesting an important role in these contexts. FcγRIIB expression has been described in reactive lymphoid follicles. Mantle cells of secondary follicles exhibit strong plasma membrane expression of FcγRIIB in contrast to the absence of detectable expression in germinal centers and specifically on follicular dendritic cells, tingible bodies macrophages or lymphoid cells. In the interfollicular region of lymph nodes, immunoblasts are negative for FcγRIIB expression in comparison to plasma cells which commonly exhibit strong membrane expression of this receptor [21]. A number of lymphomas however express FcγRIIB [21]. A recent study in mice examined an anti-human FcγRIIB antibody (2B6) in a xenograft model of FcγRIIB expressing lymphomas. The activity of this antibody is Fc-dependent and triggers ADCC. Despite its inhibitory properties, the expression of FcγRIIB on lymphomas led to eradication of the Daudi cell line as a human lymphoma tumor model in a manner that was as effective as targeting CD20 [22]. The outcome of 2B6 infusion in humans with lymphoma remains to be established. Therefore, the ectopic expression of FcγRIIB in human DLBCL (diffuse large cell lymphoma) and follicular lymphomas should be considered as a therapeutic opportunity.

FC RECEPTORS AND AUTOIMMUNE DISEASES

Autoimmune diseases are a complex group of diseases that depend on both genetic and environmental factors for their development. One group of environmental factors that are particularly important are those related to infections and the possibility that they may initiate abnormal immune responses [23, 24]. Consistent with a potential pathogenic origin of autoimmune diseases, recent studies have revealed links between innate immune responses to pathogens and auto-immunity in diseases such as systemic lupus erythematosus [25, 26]. Innate immune responses initiated by pathogens are moreover further linked to adaptive immune responses by a variety of mechanisms. For example, after the activation of innate immune cells such as macrophages, DC, B cells and NK cells by pathogens, the antigen presenting processes that are initiated are important to subsequent T cell activation and B cell maturation including class switching of B cells from IgM to IgG. IgG antibodies including those that are directed at autoantigens play a central pathogenic role in autoimmune diseases. Sequestration of antigen in immune complexes on the surface of follicular dendritic cells may promote class switching, selection of high affinity B cells and control of antibody responses *via* co-ligation of FcγRIIa and FcγRIIb [27]. Alternations of FcγRs may be linked to autoimmunity in three ways: 1. failure to clear immune complexes from the circulation and from specific sites such as synovial joints and kidneys, 2. hyper-responsiveness to circulating immune complexes through interaction with activating FcγRs and 3. lack of control of antibody production leading to immune complex formation [28].

Anti-inflammatory drugs that inhibit FcγRIIa function are a potentially novel means to block autoimmune disease development early on before the activation of the inflammatory cascade. It has recently shown for example that small molecules and antibody fragments that were designed to bind to the human FcγRIIa could inhibit collagen II induced arthritis in the FcγRIIa transgenic mice [29, 30]. These latter mice develop a spontaneous destructive arthritic disease that is characterized by erythema, swelling and joint ankylosis in up to 50% of animals over 25 weeks of age [31]. The FcγRIIa specific small molecules suppressed

disease in the FcγRIIa transgenic mice longer than that achieved with methotrexate, a treatment widely used for rheumatoid arthritis. Synthetic FcR mimetics have also been used to block the function of FcγRII *in vitro* [32] and the modulation of FcγRIIa and FcγRIIb function in humans [33]. Thus, FcγRII offers a valid target for the treatment of patients with auto-immune disease.

FCRN, THE NEONATAL FC RECEPTOR FOR IGG

FcRn was originally functionally identified in suckling rats as the receptor involved in the transport of IgG (derived from milk) across the intestinal epithelium into the bloodstream [34–36]. More recently, it has been shown that FcRn not only delivers IgG across the maternofetal barrier during gestation [37, 38] but is also responsible for the maintenance of serum IgG levels [39–42]. The gene encoding rat FcRn was first isolated by Simister and Mostov in 1989 [43]. FcRn is structurally related to MHC class I molecules and consists of a heterodimer that is composed of a glycosylated heavy (α) chain that is associated noncovalently with the β2-microglobulin (β2m) light chain [43]. The structural similarity to MHC class I molecules has been confirmed by solution of the X-ray crystallographic structure of the extracellular domains of FcRn together with IgG [44]. FcRn binding of IgG requires three critical amino acids within the CH3–CH2 domain interface of the Fc fragment (Ile253, His310, and His435) in humans and rodents [45]. FcRn homologues have been identified in rat [43], mouse [46], human [47], cow [48], pig [49], and sheep [50]. Although FcRn was originally described as being developmentally regulated in rodent intestine in that its functional expression at birth was notably downregulated within the intestinal epithelium at the time of weaning [39], it has recently been demonstrated that FcRn is also expressed in many human and non-human adult tissues and cell types including hepatocytes [51], endothelial cells [52], a variety of epithelial cell subtypes [53–58], monocytes, macrophages, and dendritic cells but not other hematopoetic cell lineages [59]. In various species, these findings have predicted that the functions of FcRn extend to adult mammalian (including human) life.

FcRn has been linked to four major cell biologic pathways: IgG transcytosis across polarized epithelia such as epithelial cells of the placenta [47, 60, 61], intestine [53] and lung [62, 63]; the protection of IgG from catabolism in the circulation [64]; the protection of albumin from catabolism in the circulation as FcRn serves as the albumin receptor [65], and; immune complex mediated antigen presentation in dendritic cells [66]. These functions are driven by the characteristic binding features of IgG to FcRn, allowing for an “on–off” relationship between the receptor (FcRn) and cargo (IgG). IgG binding to FcRn is strongly pH dependent with high-affinity binding at acidic pH (pH<6.5) and weak to no binding at or above neutral pH (pH>7.0), which is consistent with the presence of histidine residues within IgG that are involved in FcRn binding [67]. Using β2m-deficient mice that lack FcRn function [41, 42, 68] and more recently FcRn-deficient mice [69], several groups have shown that FcRn expression is associated with all of these aforementioned functions. At the cellular level, it has been hypothesized that FcRn binds IgG either on the cell surface as driven by the acidic properties of certain cell surfaces (e.g., apical cell surface of epithelia due potentially to the presence of the Na+–H+ exchanger) [70] or in an acidic compartment such as early endosomes [55]. This binding between FcRn and IgG directs monomeric IgG away from

degradation in either late endosomes and/or lysosomes with either subsequent recycling into the extracellular milieu (protection function) [71] or to the opposite side of a polarized epithelial cell (transfer function) [72–74]. Such a process is important in protecting IgG from catabolism and shuttling IgG across polarized epithelial barriers in the process known as transcytosis. In contrast, binding of FcRn to polymeric IgG antigen-antibody complexes results in the mobilization of these to the lysosomes and enhancement of antigen presentation [66].

FCRN AND INFECTION

The bidirectional transport of IgG confers a unique ability upon FcRn to to be able to retrieve intestinal luminal antigens as a complex with IgG and to deposit these into the intestinal mucosa where the antigen/IgG complexes can be captured by DCs for subsequent presentation to $CD4^+$ T cells either locally or within regional lymphoid structures [75]. These properties of FcRn define a unique mechanism by which absorptive epithelia, which cover the majority of the surface of the intestines, can specifically acquire and transport antigens into the lamina propria and regional lymphoid structures. Consistent with this, recent studies have indicated that intestinal bacterial antigens are required to direct the maturation of immune responses [76] and that such immune responses are induced throughout the intestine rather than within restricted regions such as Peyer's patches [77,78]. Therefore, these recent observations have raised a potential possibility that epithelial cell-mediated sampling of luminal bacterial antigens throughout the intestinal surface contributes to the regulation of mucosal and systemic immune responses. It is interesting to note that $FcRn^{-/-}$ mice exhibit more body-weight loss and higher bacterial concentrations in the feces at 21 days after *C. rodentium* infection compared to $FcRn^{-/+}$ mice [79]. Consistent with these clinical changes, $FcRn^{-/-}$ C57BL/6 mice that were infected with *C. rodentium* exhibit increased cellular infiltration with mononuclear cells and neutrophils and significantly increased epithelial injury in comparison to that observed in $FcRn^{-/+}$ mice. These results indicate that $FcRn^{-/-}$ mice, which show an absence of transporting IgG and bacterial antigen/IgG complexes, are more susceptible to *C. rodentium*-induced colitis. Both innate and acquired immune responses are involved in the pathogenesis of infectious colitis [80, 81]. It has been hypothesized that FcRn also plays a role in infection-induced acquired immune responses by delivering bacteria-derived antigens coupled to specific IgG into mucosal immune cells in addition to potential local, immune protective effects of this receptor in the epithelium. To show this, a genetically engineered *C. rodentium* strain (*C. rodentium*-OVA) that constitutively expresses an OVA fragment containing the OT-II and DO11.10 peptides was examined in a transgenic animal expressing mouse FcRn and mouse β2m within the epithelium under the control of an IFABP. It was shown that FcRn-mediated delivery of IgG was required for the effective induction of immune responses to an epithelial pathogen *in vivo* by the ability to deliver epithelia-associated antigens to host immune cells in the mesenteric lymph nodes as defined by the detection of multiple cell divisions in CFSE-labeled transgenic, OVA-specific T cells [79]. These studies indicate that epithelial FcRn can induce effective $CD4^+$ T cell responses systemically to pathogen-derived antigens associated with the lumen and/or intestinal epithelium when they are retrieved as antigen/IgG complexes.

FCRN AS A THERAPUTIC TARGET

These properties of FcRn have led to the concept of targeting FcRn for therapeutic purposes. Such opportunities would include extension of the serum half-life of therapeutic antibodies and Fc-fusion proteins to improve their efficacy or conversely decreasing the serum level of pathogenic antibodies by inhibiting FcRn function. The latter would be important in antibody mediated diseases such as myasthenia gravis, bullous pemphigoid, idiopathic thrombocytopenic purpura (ITP) and systemic lupus erythematosus (SLE). Alternatively, the transport functions of FcRn have lent themselves to enabling drug delivery across mucosal surfaces. Fc-fusion proteins of erythropoietin (EPO-Fc) have been shown to be able to be delivered across the epithelia of the lungs of mice [58], monkeys [63] and humans [62] in a pathway that is mediated specifically by FcRn since mutation of the critical isoleucine 252, histidine 433 and histidine 435 residues abrogates this transport. The clinical trials with EPO-Fc [62] in humans in particular proves that the FcRn is active at mucosal surfaces in adult human life.

The remainder of this discussion will focus on the manipulation of therapeutic and pathogenic antibodies within the circulation. The half-life of IgG depends on its concentration in the circulation in an inverse manner due to the saturability of the FcRn receptor [82, 83]. The level of FcRn expression controls the serum concentration of IgG such that excess IgG antibodies do not bind to FcRn and enter a degradative pathway. This leads to a shortening of the serum IgG half-life. High-dose intravenous immunoglobulin (IVIG) treatment [84, 85] is thought to exert an immunomodulatory effect by numerous mechanisms, including engagement of the inhibitory FcγRIIb receptor and by FcRn saturation. In mouse models such as bullous pemphigoid, ITP and auto-immune arthritis, IVIG treatment is effective because of the decrease of the pathogenic antibodies. The therapeutic effect for IVIG is maintained in FcγRIIb-deficient mice and its absence in FcRn deficient mice is strong evidence that an important mechanism of action of IVIG is its ability to compromise FcRn function [86, 87].

Another approach to reduce serum pathogenic antibodies is to block the FcRn–IgG interaction using FcRn-specific monoclonal antibodies. A monoclonal antibody against β2m has been reported to block the ability of FcRn to bind IgG *in vitro* [88] and *in vivo* [89]. β2m is the common light chain for all MHC class I and many MHC class Ib molecules besides FcRn. Therefore therapy using β2m specific monoclonal antibodies may incur unexpected side effects. Indeed, a monoclonal antibody directed against the FcRn heavy chain has been shown to reduce disease symptoms in rats with experimentally induced myasthenia gravis [90]. Such FcRn specific antibodies and other targeting modalities may be used as therapeutic agents in such contexts in the future. These alternative methods of targeting and inhibiting FcRn include the creation through genetic engineering of antibodies with increased binding to FcRn at both neutral and acidic pH (so-called “Abdegs”) [91, 92] or cyclic peptides with similar properties [93].

CONCLUSION

The FcγRs and FcRn are revealing themselves to be clinically useful targets in the treatment of infection, cancer and autoimmune diseases. These approaches include the blockade of inhibitory FcγRs for enhancing immune responses to infectious pathogens and cancer, blocking activating FcγRs for the treatment of autoimmune diseases and targeting the ectopic expression of particular FcγRs such as occurs in lymphomas for the elimination of tumors. The manipulation of FcRn interactions with antibodies allows for the development of designer antibodies that have particular pH dependent binding characteristics lends themselves to enhancing therapeutic antibody half-life or promoting the degradation of pathogenic antibodies. Finally, co-opting FcRn transport function is a means to enable the mucosal delivery of therapeutic proteins.

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