Journal of Translational Autoimmunity 4 (2021) 100122

Contents lists available at ScienceDirect

Journal of Translational Autoimmunity

journal homepage: www.sciencedirect.com/journal/journal-of-translational-autoimmunity

"Ways in which the neonatal Fc-receptor is involved in autoimmunity"

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ARTICLE INFO

Keywords:
Neonatal Fc receptor
Autoimmunity
Autoimmune disease
Monoclonal therapeutic antibodies

ABSTRACT

Since the neonatal IgG Fc receptor (FcRn) was discovered, its role has evolved from immunoglobulin recycling and biodistribution to antigen presentation and immune complex routing, bringing it to the center of both humoral and cellular immune responses. FcRn is thus involved in the pathophysiology of immune-related diseases such as cancer, infection, and autoimmune disorders. This review focuses on the role of FcRn in autoimmunity, based on the available data from both animal models and human studies. The knowledge concerning ways in which FcRn is involved in autoimmune response has led to the development of inhibitors for the treatment of autoimmune diseases, also described here. Up to date, the literature remains scarce, shedding light on the need for further studies to fully understand the various pathophysiological roles of this unique receptor.

1. Introduction

Since the description of FcRn by Brambell in 1964 [1], its structure, ligands and functions have been reviewed in a wide range of publications. The topics have evolved, matching the successive discoveries on FcRn properties from recycling/transcytosis functions down to its role in humoral and cellular or innate *versus* adaptive immune responses [2,3]. During the last decade, several reviews also started discussing the various strategies aiming at improving both the pharmacokinetics and pharmacodynamics of monoclonal antibodies (mAbs), or at inhibiting FcRn, switching its role from coworker to therapeutic target [4–6]. The research on FcRn has shed light on its role in human pathophysiology such as in infectious diseases, cancer and autoimmune diseases [7,8]. The involvement of FcRn in both the triggering and/or natural course of these diseases is not always clearly defined but can be directly connected to some of its properties, autoimmune disorders being a neat example of this. Thus, FcRn inhibitors stand out as a logical perspective for the treatment of these pathologies, mainly aiming at decreasing circulating levels of autoreactive IgG by blocking FcRn-dependent recycling.

Autoimmune diseases are usually classified as either organ-specific or systemic diseases characterized by autoantibody production and/or self-reactive T and B lymphocytes leading ultimately to cell dysfunction and/or tissue destruction. The development of an autoimmune disease requires both a genetic predisposition and an immune response dysregulation triggered by environmental factors [9]. Despite their diversity, some of the pathogenic mechanisms are shared amongst autoimmune diseases, as for loss of self-tolerance leading to the emergence of either self-reactive antibodies or T-lymphocytes, accompanied by defective regulatory T-cell function, increased cell apoptosis, immune complex (IC) deposition and excessive pro-inflammatory cytokine secretion leading to chronic inflammation [10,11]. These features explain the wide and common use of immunosuppressive agents such as glucocorticoids, mycophenolate mofetil, methotrexate or azathioprine for the treatment of these disorders [12,13]. However, new approaches thrive in the treatment of autoimmunity, aiming at blocking specific inflammatory and/or effector immune pathways. The former is embodied by therapeutic monoclonal antibodies that block inflammatory pathways, historically TNF-α, [9]. Monoclonal antibodies, target a wide range of molecules involved at various stages of the pathophysiological processes that lead to autoimmunity. Recently, anti-FcRn mAbs have been developed for the treatment of autoimmune diseases. FcRn, through its functional properties is involved in the immune-related dysregulations

Abbreviations: mAbs, Monoclonal antibodies; FcRn, Neonatal Fc receptor; IC, Immune complexes.

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https://doi.org/10.1016/j.jtauto.2021.100122
Received 14 July 2021; Accepted 6 September 2021
Available online 11 September 2021

leading to some of these conditions. In this review, we describe the biological and clinical features of autoimmune diseases either thought or known to relate to FcRn.

This review was written thanks to orthogonal bibliographic techniques, namely manual and artificial-intelligence-based. A deep-learning text-mining algorithm was implemented to screen the usual databases and find relevant information inside papers that would have otherwise been missed, adding some very interesting findings to this extensive focused review [14].

2. FcRn in humoral autoimmunity: Autoantibody support

2.1. Autoantibody recycling

FcRn is composed of an α chain non-covalently associated with the β2-microglobulin. It belongs to the family of MHC class I proteins [15]. FcRn has a double-specificity and binds both IgG and albumin at acidic pH in endosomes, whilst releasing them at neutral pH [2]. It is the basis underlying its recycling and transcytosis properties. It is now well established that FcRn-mediated IgG recycling is responsible for their extended half-life. Whatever the origin (endogenous or recombinant) or the specificity (self- or xeno-reactive) of IgG, they undergo FcRn-mediated recycling. Autoantibodies can sometimes be IgM or IgA isotype [16,17] but mainly belong to IgG subtypes, and their FcRn-mediated extended half-life has been early evoked [18] (Fig. 1).

In 1997, it was described that β2-microglobulin-deficient mice exhibited attenuated bullous pemphigoid manifestations [19] as compared to wild type counterparts upon administration of specific pathogenic autoantibodies. The suspected pathophysiological mechanism was a decreased tissular exposure to autoantibodies due to β2-microglobulin-linked FcRn-α-chain functional abnormalities. A direct FcRn contribution to humoral autoimmune disease through pathogenic autoantibodies protection was later described in a murine, FcRn-knocked-out model of autoimmune arthritis [20] or bullosa acquisita epidermolysis [21]. As suggested by these studies, FcRn blockade efficiently reduced circulating pathogenic IgG levels, representing a promising perspective in antibody-mediated diseases. Based on this rationale, the inhibition of FcRn-dependent IgG recycling was applied to human patients with myasthenia gravis or with immune thrombocytopenia, two autoantibody-mediated autoimmune diseases [22,23]. Therapeutic blockade of FcRn-dependent-IgG-recycling by

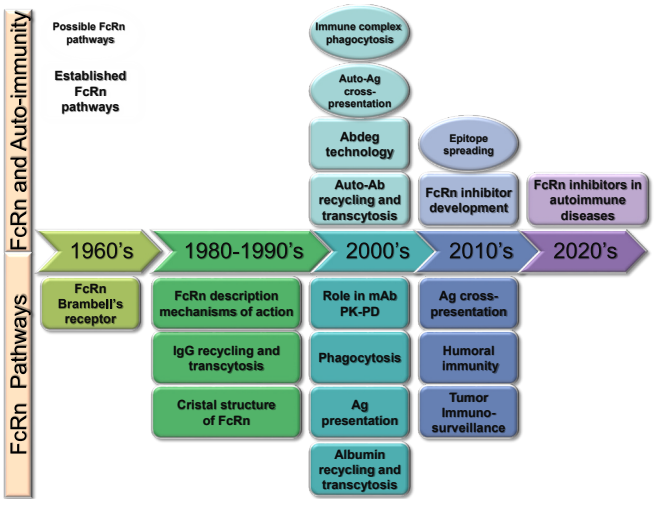

Fig. 1. FcRn pathways involved in autoimmunity, Above timeline, each box description represents FcRn pathways in autoimmunity through ages. Under the timeline, each box represents different FcRn pathways through ages. Rectangle box represent established FcRn pathways whereas oval box represent possible FcRn pathways. Colors represent different decades.

therapeutic mAbs or derived molecules is also discussed in this review. These molecules have demonstrated their potential in clinical trials [24,25].

However, targeting FcRn to reduce autoantibody circulation is not always sufficient to reduce pathogenicity, especially in lupus, a disease characterized by autoreactive T cells and uncontrolled production of autoantibodies against a variety of antigens such as nucleic acids, ribonucleoproteins, or phospholipids [26]. This point was stressed out by Singh et al. in a murine β2-microglobulin-deficient lupus model showing increased levels of specific anti-DNA autoantibodies despite low total IgG concentrations [27]. Conversely, FCGRT deficiency did not improve the overall survival towards lupus in knocked-out mice as compared to their wild-type counterparts [28]. The wide ranges of roles supported by the β2-microglobulin-associated MHC class I-proteins family may help explain the low impact of FcRn deficiency in related animal models [28].

2.2. Autoantibody transcytosis

The first described role of FcRn is to mediate the transplacental transfer of maternal IgG to the fetus during gestation. This function provides passive immunity to the fetus and newborn [29,30]. FcRn-mediated transport from the mother to the fetus also concerns IgG autoantibodies and is part of the pathophysiological mechanisms of autoimmune fetal diseases. Neonatal lupus erythematosus comes from anti-Ro/SSa antibodies translocation from the mother to the fetus, responsible for the skin and importantly cardiac manifestations [31]. Other fetal diseases are also mediated by maternal IgG such as the hemolytic disease of the fetus and newborn or fetal thrombocytopenia, which have been detailed in a focused review [32].

Recent studies demonstrate that FcRn allows the transfer of other isotypes including IgE *via* IgG anti-IgE IC [33] promoting the development of allergies in mouse models suggesting a broader role of FcRn in the construction of the immune system and in tolerance regulation as suggested by Verhaselt et al. [34].

In the digestive tract the FcRn performs bidirectional transcytosis of IgG or ICs to mucosal dendritic cells [35] and participates in the maturation of the newborn immune system and immune tolerance induction through breastfeeding [36]. In a colitis model, FcRn has notably been suspected to participate in the immune-mediated development of digestive lesions by presenting self-anti-flagellin antibodies and ICs to dendritic cells [37].

In the central nervous system, the physiological role of FcRn is to send IgG back into the bloodstream. The precise role of FcRn in IgG transcytosis through the blood-brain barrier in the cerebral microvascular endothelium and the epithelium of choroid plexus remains to be established. Some studies make it a key player [38] especially when the barrier is broken such as in some autoimmune pathologies [39]. This concept recently challenged by *in vitro* mechanistical findings regarding FcRn-independent transcytosis at this level [40]. Besides, in neurological autoimmune diseases, some antibodies can act as biomarkers. Some are found in the bloodstream and/or in the cerebrospinal fluid [41] raising the question of their production site and trafficking, thus making it tricky to precisely determine the contribution of FcRn in these pathologies and the physiopathological relevance of its blockade.

In the kidney, FcRn is expressed by the brush border cells in the proximal tubule and in glomerular epithelial cells [42]. It allows for IgG to be transcytosed back in the general circulation, preventing their accumulation at the glomerular level, along with their passage through the proximal tubule to provide immune protection [43,44]. In some glomerulopathies, it may have a protective role. This was demonstrated in a murine model of glomerulopathy, in which an accumulation of autoantibodies resulting from lysosomal alkalinization (which hampers IgG and albumin ligation by FcRn) led to the development of a glomerular disease [45]. Whilst similar studies involving mice model of IC-mediated glomerulopathy give discrepant results, without resulting in either proteinuria or glomerular lesions upon FcRn knockout [46], the

contradiction might only be on the face of it. Indeed, the role of FcRn is to locally prevent the accumulation of IgG and ICs. At the body-level, the decrease of FcRn expression results in a decrease of pathological autoantibodies which are thus less likely to deposit at the glomerular level. Other explanations are provided by Dylewski et al. using *in vivo* and *in vitro* models of FcRn-knocked out podocytes revealing differential implications of FcRn depending on the model of glomerular impairment and the degree of disease course advancement [47]. Further studies on the pathophysiological contribution of FcRn-mediated IgG pharmacokinetics at the renal level appear necessary in order to find the right place for anti-FcRn therapies in antibody-mediated glomerulopathies.

3. FcRn in humoral autoimmunity: Immune complex (IC) support

ICs play a central role in the pathophysiology of autoimmune diseases. It has been objectified in systemic lupus [48], rheumatoid arthritis [49], two major systemic diseases [50], but their role was also ascertained in autoimmune thyroiditis [51], acute immune-mediated lung lesions [52], and upon direct deposition in the kidney [53]. ICs are composed of IgG-complexed-antigens and therefore are bound by FcRn [54]. Animal models overexpressing FcRn (3) and mouse model in which it was blocked resulted in a decrease of IC deposition at the glomerular level [46].

The involvement of FcRn in the management of ICs in human autoimmune diseases is more recent. It has been described by using one of the inhibitory, anti-FcRn mAb (see section 5). By rapidly decreasing the level of circulating ICs, the systemic inflammatory response by hematopoietic cells was also contained [55]. The role of ICs has been established in thrombotic or hematological manifestations in warm autoimmune hemolytic anemia [49–52,56] and heparin-induced thrombocytopenia [57]. Cines et al. showed that FcRn blockade inhibits the IC-mediated activation of clotting pathways potentially responsible for thrombotic phenomenon in antiphospholipid syndrome, warm autoimmune hemolytic anemia, and heparin-induced thrombocytopenia [58]. Fc-gamma receptor IIA (FcγRIIA/CD32) engagement is one of the suspected pathophysiological initiation mechanisms of IC-mediated thrombotic events, and in tissue factor activation [59]. As recently described, FcγRIIA binds ICs and cooperates with FcRn for the induction of innate and adaptive immune responses [60]. FcRn therefore seems to play a role in hematological autoimmune pathologies, especially in IC-induced thrombotic events, notably through its interaction with FcγRIIA. This new pathway further extends the range of non-canonical roles of FcRn in immune responses.

4. Generating an autoimmune response: Possible pathways involving FcRn

4.1. Epitope spreading

Autoimmune diseases are initiated by the development of specific autoreactive T and/or B lymphocytes against self-proteins. The molecular targets can include several epitopes of a single protein or epitopes from different proteins of the same tissue. After a primary inflammatory response involving tissue damage, cryptic antigens are released, potentially leading to a secondary response against them. This process of immune response against endogenous epitope results in epitope spreading and contributes to diversification of the epitope repertoire recognized by the immune system. Epitope spreading has a significant role in both the pathophysiology and duration of autoimmune diseases [61,62]. It is implicated in multiple autoimmune diseases like systemic lupus erythematosus [63,64], bullous pemphigoid [65] or rheumatoid arthritis [66].

Although FcRn has yet not been directly involved in epitope spreading, there are clues towards such a role. For example, mice bearing 4/5 copies of bovine *FCGRT* gene (encoding the α-chain of FcRn) show an enhanced humoral response characterized by higher number of Ag-specific B cells and increased levels of Ag specific antibodies recognizing a wider panel of epitopes compared to wild type mice after specific immunization [67–70]. Studies in rabbits that overexpress FcRn showed similar enhanced humoral immune responses [71]. FcRn thus has both a qualitative and quantitative role in immune repertoire diversity, raising the hypothesis of its contribution in epitope spreading such as observed in autoimmune diseases.

4.2. FcRn expression level, inflammation and autoimmune response

In the context of inflammatory diseases, studying FcRn overexpression could prove to be informative, allowing to predict on the reinforcement of the immune response. In the literature, genetic variations inside the *FCGRT* gene and cytokines are known to modulate FcRn expression. Variable number tandem repeat (VNTR) polymorphisms in intron1 of the *FCGRT* gene modulate its transcription as demonstrated by Sachs et al. [72]. Indeed, VNTR3 homozygous individuals express significantly more FcRn transcripts than VNTR2/VNTR3 heterozygous individuals [73]. VNTR has a quantitative impact on therapeutic mAbs recycling and intravenous immunoglobulin (IVIg) pharmacokinetics in patients [74,75]. A recent study in patients with Myasthenia Gravis showed that the VNTR2/3 genotype (low FcRn transcripts) may be considered as a predictor of non-response to IVIg treatment [76]. In common variable immunodeficiency which is not an autoimmune disease, FcRn expression related to VNTR polymorphism is associated with the development of lung structural abnormalities [77]. Nonetheless, no association has been reported in Chinese patients suffering from lupus nephritis [78] nor in Guillain–Barré syndrome between the VNTR polymorphism and IVIg pharmacokinetics, or patient clinical course and outcome [79].

Aside from the effect of VNTR polymorphism, FcRn expression is modulated by different cytokines. It is increased by TNF- and TGF-β *via* NF-kappaB and JNK/MAPK signaling pathways respectively [80,81], and decreased by IFN- through the JAK/STAT-1 signaling pathway [82]. Some of these cytokines are secreted in the context of autoimmune diseases and may modulate FcRn expression and thus the resulting functions, such as epitope spreading and recycling of pathogenic IgG. In Hashimoto's thyroiditis, characterized by anti-thyroperoxydase (an enzyme playing a role in the synthesis of thyroid hormones) antibodies, Zhao et al. have described a downregulation of FcRn in thyrocytes [83], alongside with a cytokine-dependent downregulation of FcRn in thymocytes suggesting an involvement of FcRn in the pathogenesis of this disease. This facet of FcRn regulation is probably underestimated and needs to be studied in other autoimmune diseases.

4.3. Phagocytosis and cross-presentation

FcRn is expressed in hematopoietic cell types endowed with phagocytic properties. It contributes to the enhancement of FcγR-mediated phagocytosis [84]. Then, by slowing down IC degradation in a pH-dependent manner in macrophages and dendritic cells [85,86], FcRn facilitates peptide loading onto MHC class I and II molecules. These mechanisms explain the role of FcRn in conjunction with FcγR in ICs presentation and cross-presentation, evidenced in animal models and in multimeric–IC–loaded dendritic cells [54]. This FcRn-dependent management of ICs at least partially explains the CD8 T lymphocyte cytotoxic response to a low dose of antigen [85]. Finally, the role of FcRn in IC cross-presentation was clearly established in cancer, allowing for the expansion of tumor-antigen-specific $CD8^+$ T lymphocytes [87].

Dendritic cells and autoreactive CD8 T lymphocytes [87,88] participate in the pathophysiology of rheumatoid arthritis by different mechanisms which lie beyond the scope of this review but involve both humoral and cellular pathological responses. CD8 T lymphocytes are also involved in the pathology of other autoimmune diseases such as Sjogren disease and human type 1 diabetes [89,90], allowing to suspect

a role for FcRn in IC management in these diseases.

FcRn blockade as a means of decreasing autoantibody concentrations is a therapeutic axis in autoimmune diseases (see section 5). In IC-mediated autoimmune diseases, targeting FcRn reduces the circulating IC concentration [55]. This phenomenon could also interrupt the IC-driven inflammatory response and could represent an interesting therapeutic effect.

5. FcRn targeting by therapeutic monoclonal antibodies in autoimmune diseases

As previously stated, autoantibodies are major contributors in the development of several autoimmune diseases. Reduction of autoantibody concentration may therefore be necessary to reduce clinical symptoms. Plasma exchange, immunoadsorption and IVIg injections are used to achieve this goal, with a broader immunomodulatory effect on the immune system in the case of IVIg [6,91]. New strategies aiming at modulating FcRn-mediated recycling were theorized as soon as 2005 [92] (Fig. 1). Currently, seven FcRn inhibitors, displaying different mechanisms are in clinical development. Their structures and characteristics allow to split them between three groups: Fc fragments, IgG, and affibody®.

5.1. FcRn inhibitor formats

The first category of FcRn inhibitors binds FcRn through an Fc portion. Efgartigimod (ARGX-113) is a human IgG1-based Fc fragment engineered to receive the "AbDeg" (antibodies that enhance IgG degradation) technology developed by Vaccaro et al. [92]. It consists in a set of five synergic point-mutations called MST-HN (M252Y/S254T/-T256E-H433K/N434F) increasing Fc affinity for FcRn at acidic (6.0) and neutral pH, thus blocking the receptor's recycling activity [92,93]. In a phase I carried out on healthy volunteers, a single administration of 50 mg/kg efgartigimod reduced IgG levels up to 50% [93]. Efgartigimod is currently in phase III clinical trials for the treatment of myasthenia gravis, pemphigus vulgaris, pemphigus foliaceus and immune thrombocytopenia [24,25] and in phase II in chronic inflammatory demyelinating polyneuropathy. CSL730, another Fc-based format consists in a human IgG1 Fc-multimer, which binds to both FcRs and FcRn, thus inhibiting immune-complex-mediated activation of immune cells, ADCC and phagocytosis. In preclinical studies, CSL730 proved to be efficacious in multiple disease models, such as immune thrombocytopenia, collagen antibody-induced arthritis and epidermolysis bullosa acquisita [94,95].

The second and most widely represented category is FcRn-specific, full IgG formats. These antibodies include S241P (hinge-stabilized) IgG4 mAbs, namely rozanolixizumab [96,97] and orilanolimab [98,99]; and IgG1 mAbs: nipocalimab [100] and batoclimab (also known as HBM9161, HL161, RVT-1401, or IMVT-1401) [101,102]. All these therapeutic mAbs bind to the human FcRn -chain with high affinity at both neutral (7.4) and acidic (6.0) pH without interfering with albumin binding. These FcRn inhibitors are currently in clinical trials in IgG-mediated autoimmune diseases like myasthenia gravis [103–105], immune thrombocytopenia [106], chronic inflammatory demyelinating polyneuropathy, pemphigus, hemolytic disease of fetus and newborn [107], warm autoimmune hemolytic anemia and Graves' ophthalmopathy.

The third category of FcRn inhibitors is quite different from molecules derived from IgG, and only contains ABY-039, which is a bivalent antibody-mimetic molecule called affibody® of 19 kDa, able to bind to FcRn at pH 6.0 only. This affibody® is in phase I of clinical trial and aims at several indications amongst B-cell driven autoimmune diseases [108,109].

5.2. Mechanisms of action of FcRn inhibitors

All FcRn inhibitors reduce circulating IgG including those involved in autoimmune diseases. Indeed, FcRn inhibitors either bind to FcRn *via* its Fc region, whilst IgG antibodies bind FcRn *via* their variable domains. After binding to FcRn with strong affinity at both neutral and acidic pH, the various inhibitors are internalized through a specific, FcRn-mediated process. Their binding competes with that of endogenous IgG in acidic endosomes, driving FcRn-unbound endogenous IgG towards lysosomal pathways and catabolism. The decrease in circulating IgG can reach 85% in a dose-dependent fashion, is reversible, and does not affect IgG production [110]. FcRn inhibitors, like Orilanolimab (SYNT001), also reduce circulating immune complexes within 5–6 days after one single dose. *Ex-vivo* studies also showed that blocking FcRn with SYNT001 inhibited the ability of IgG-containing ICs to induce innate inflammatory cytokine secretion by human peripheral blood leukocytes [99]. FcRn inhibitors have no effect on either FcRn expression. Furthermore, no clinically relevant changes were observed in circulating albumin, IgA, IgM and IgE levels [93,97,99,100]. Concerning Fc-mediated effector function involving C1q binding and FcR activation, Efgartigimod (MST-HN mutations) and Nipocalimab (aglycosylated IgG1) have no Fc effector potential [107,111,112].

Although these FcRn inhibitors reduce autoantibodies, they also decrease circulating IgG in a non-specific manner. This flaw encouraged the development of SelDegs (Selective depletion of antigen-specific antibodies) derived from the "AbDeg" technology that specifically remove autoantibodies. Comprising an Fc fragment with the MST-HN mutations fused to the targeted autoantigen, SelDegs allow for the selective degradation of IgG-isotype autoantibodies. Internalization of SelDeg-antibody complexes *via* FcRn leads to its lysosomal degradation without affecting overall IgG level [113]. Low SelDeg concentrations are required to reduce IgG autoantibodies in autoimmune diseases. Recently, this technology has been applied to myelin oligodendrocyte glycoprotein autoantigen, in order to target autoantibodies in demyelinating diseases [114].

6. Conclusion

FcRn is a receptor of ancient discovery, which has revealed many immunological properties over the years, making it an important subject of study due to its ubiquitous tissular expression. From an intracellular receptor allowing the recycling of IgG and albumin, it has become a central study subject due to its involvement in Fc- and albumin-based biopharmaceuticals pharmacokinetics, and a hub in IC-mediated immune response due to its role in the management of ICs and ability to collaborate with other FcγRs. With this review, we wish to highlight some of the leads to follow on the path of autoimmune diseases understanding, especially those that are mediated by pathogenic autoantibodies, and to broaden the spectrum of indications for FcRn-targeting therapies.

Funding

This work is supported by a public grant overseen by the French National Research Agency (ANR) as part of the "Investissements d'Avenir" program (reference: ANR-10-LABX -53-01).

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