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Targeting FcRn for therapy: From live cell imaging to *in vivo* studies in mice

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ABSTRACT

The role of FcRn in regulating antibody levels and transport in the body is well documented. The use of fluorescence microscopy to investigate the subcellular trafficking behavior of FcRn and its IgG ligand has led to insight into the function of this receptor, including the identification of new intracellular pathways. The inhibition of FcRn using engineered antibodies that bind to this receptor with increased affinity through their Fc region can be exploited to treat antibody mediated autoimmunity. The efficacy of this approach in mouse models of arthritis and multiple sclerosis has been demonstrated. Finally, the cross-species difference between mouse and man for FcRn–IgG interactions needs to be considered when engineering antibodies for improved activities in FcRn-mediated functions.

1. Introduction

The function of MHC Class I-related receptor, FcRn, as a recycling/transcytotic receptor to regulate IgG transport and levels in the body is well established [1,2]. The transporting activity of FcRn not only impacts multiple aspects of humoral immunity, but can also be exploited by antibody engineering to modulate the levels of either therapeutic or endogenous IgG levels in the body [3–6]. For example, FcRn inhibition or deficiency results in accelerated clearance of antibodies [6–15], whereas FcRn overexpression in transgenic animals results in abnormally high serum IgG concentrations [16,17]. The current review will include a discussion of the use of microscopy and cell biological studies to improve our understanding of the intracellular trafficking of FcRn and its IgG ligand. In addition, how subcellular trafficking analyses can be used to understand mechanistic aspects of FcRn inhibition for the treatment of autoimmunity will be presented.

2. The interaction site for FcRn on IgG

FcRn interacts with IgG residues, including several histidines, located at the CH2–CH3 domain interface [18–20]. These histidines interact with acidic residues on FcRn [20] and are important for the pH dependence of complex formation [18–20]. The IgG amino acids that are involved in FcRn binding are relatively well conserved across species [21] and do not overlap with the interaction site for the classical FcγRs or complement [22–24]. Thus, in general, engineering antibodies for alteration in FcRn function does not impact FcγR or complement binding or vice versa, although there are exceptions to this that most likely arise due to long range perturbations [4]. Ablation of binding of an IgG to FcRn can be readily achieved by mutation of several key interaction residues on IgG [18,19]. Consistent with the subcellular trafficking model for FcRn function (Fig. 1), this generates IgG molecules that are poorly transported across cellular barriers and have short *in vivo* persistence [18,19,25–29]. Conversely, antibodies that are engineered for increased binding to FcRn at acidic pH but with retention of low affinity at near neutral pH are recycled/transcytosed more efficiently and have longer *in vivo* half-lives [3–5].

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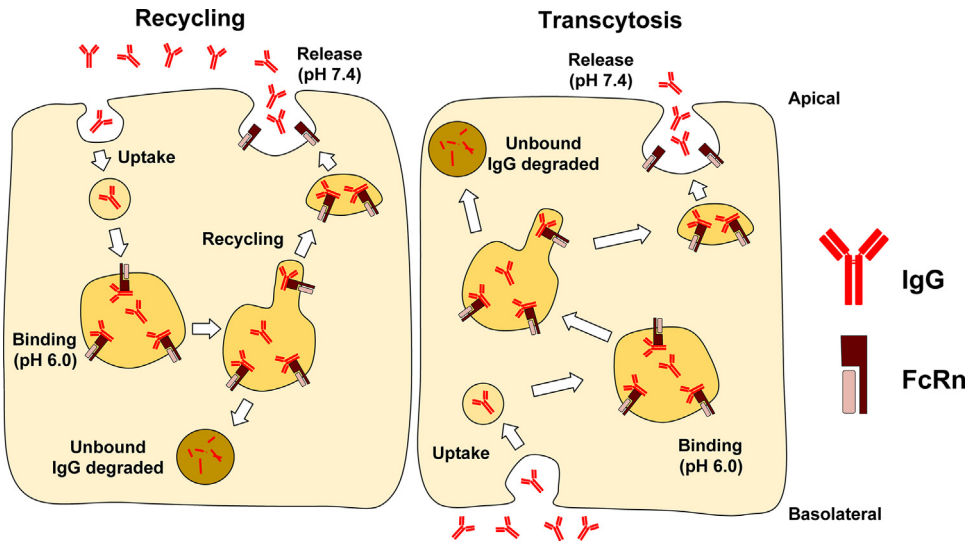

Fig. 1. Model for FcRn function as a transporter of IgGs. IgGs enter cells by fluid phase/pinocytic uptake. Following entry into acidic endosomes, the antibodies can bind to FcRn. FcRn binding results in sorting into tubulovesicular transport carriers (TCs) that recycle (left panel) or transcytose (right panel) bound cargo to the plasma membrane. FcRn positive compartments release their IgG cargo upon fusion with the plasma membrane and exposure to near neutral pH. IgGs that do not bind to FcRn within sorting endosomes traffick to lysosomes and are degraded.

3. Microscopy analyses of FcRn-mediated sorting and transport

Microscopy studies have given a dynamic view of how IgGs with different binding properties for FcRn are sorted within endosomes. Live cell imaging analyses of human endothelial cells (HMEC-1) transfected with FcRn-GFP enables the visualization of endosomal sorting events [30]. Following entry into cells, wild type IgG binds to FcRn in acidic endosomes and can be visualized on the limiting membrane. In HMEC-1 cells, these endosomes are 1–2 μm in diameter. Bound IgG is sorted into relatively small recycling, tubulovesicular transport carriers (TCs) which segregate from sorting endosomes and fuse with the plasma membrane to release their cargo during exocytosis [30–32]. IgG can also be transcytosed across polarized cells [27–29,33–35]. By contrast, IgGs containing His435 to alanine mutations (H435A) do not interact with FcRn following entry into cells and remain in the endosomal vacuole (Fig. 2). Mutated IgGs of this class are not sorted into TCs and enter the lysosomal pathway in which they are degraded [30]. Consistent with the intracellular trafficking behavior, IgGs with the H435A mutation, or other mutations that ablate FcRn binding, have short *in vivo* half-lives and are inefficiently transcytosed across FcRn-expressing cells [19,26–29].

The TCs that are sorted from endosomes can undergo fusion with the plasma membrane to release their exocytic cargo [31,36]. However, an understanding of the dynamic behavior of tubulovesicular TCs within cells has been limited by the high numbers of the intracellular compartments and their rapid movement. This has prompted the development and merging of several imaging modalities to overcome these limitations in defining the behavior of FcRn containing TCs within cells [37]. First, the implementation of multifocal plane microscopy (MUM) enables the tracking of highly dynamic subcellular trafficking processes across multiple planes [32,36]. Second, the combination of MUM with localized photoactivation [38] of photoactivatable fluorophores on individual sorting or early endosomes allows the destination of TCs that emanate from single endosomes to be defined, without the confounding effects of the vast numbers of other TCs within cells. These approaches have resulted in the identification of four distinct trafficking itineraries of FcRn+ TCs within cells [37] (Fig. 3).

TCs on different subcellular trafficking pathways can be distinguished by the presence of different combinations of Rab GTPases (Rab4 and Rab11), SNX4 and APPL1. A schematic representation of these pathways, and the identifiers that can be used for each type of event, is shown in Fig. 3. Specifically, a pre-endosomal sorting step involves the movement of APPL1+ TCs from the cell periphery to merge with sorting endosomes. The subsequent trafficking pathways can be classified as follows: TCs can migrate between two different sorting endosomes in interendosomal transfer events or, following separation from a sorting endosome, the TC can return to the same compartment in a looping pathway. Alternatively, TCs can separate from sorting endosomes and undergo exocytic processes at the plasma membrane. Unlike the other pathways that lead TCs to different destinations within cells, the function of the apparently futile looping pathway is unclear. However, by contrast with TCs on other pathways, looping TCs have associated Rab4, Rab11 and SNX4 rather than subsets of these proteins. This suggests that they might represent missorting events, or steps of an iterative process that could contribute to endosomal sorting [39]. Collectively, these pathways form a platform for further analyses of the recycling pathway using systems biology approaches.

4. Engineering of IgG–FcRn interactions: therapeutic applications

The modulation of FcRn–IgG interactions using antibody engineering offers opportunities for not only tuning the pharmacokinetic behavior of an antibody [3–5], but also for altering the levels of endogenous antibodies in the body [6,40]. Increasing the affinity of an IgG–FcRn interaction at pH 6.0 with retention of low affinity at near neutral pH is known to increase the *in vivo* persistence of antibodies in rodents, non-human primates and man [3–5]. However, for an increase in half-life to be observed, it is essential that the antibody retain very low affinity at ~pH 7.4 to allow efficient release from cells during exocytic events involving FcRn+ TCs [41,42]. By contrast with half-life extension strategies, engineered antibodies that bind with high affinity at both near neutral and acidic pH compete very effectively with wild type IgGs for FcRn binding and as such, can be used to decrease endogenous levels of antibodies in

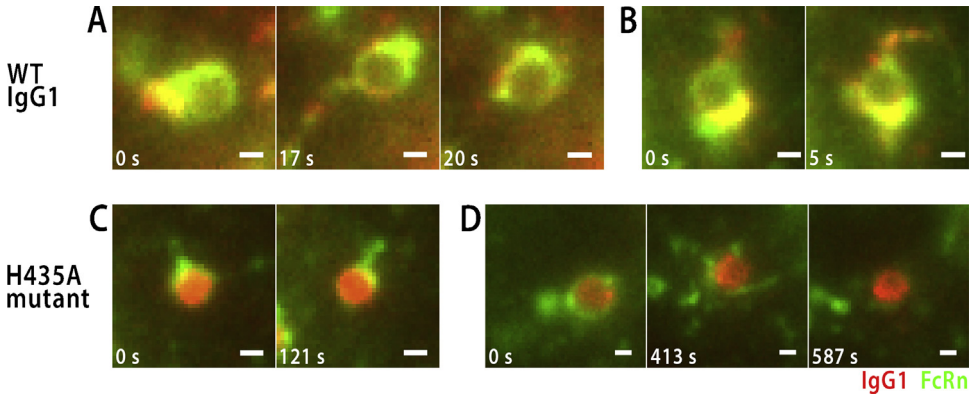

Fig. 2. Fluorescence microscopy analyses of the behavior of IgGs that have different binding affinities for FcRn within endosomes. A and B: wild type IgG binds to FcRn and remains associated with the limiting membrane of the sorting endosome. C and D: the mutated IgG, H435A, does not bind to FcRn and remains in the vacuole of the sorting endosome. HMEC-1 cells were transfected with FcRn-GFP and pulsed with Alexa 546-labeled wild type or mutated (H435A) IgG as described in [30]. The images represent individual frames of movies, with the time of the first frame arbitrarily set to 0 s. FcRn-GFP is pseudocolored green and IgG is pseudocolored red. Bars = 1 μm.

the body [6,43]. In the presence of these engineered antibodies, wild type IgGs are driven into lysosomes and are degraded [6].

The efficacy of engineered antibodies that competitively inhibit FcRn (Abdegs, for antibodies that enhance IgG degradation) as therapeutics in mouse models of antibody-mediated autoimmunity has been investigated [44]. The K/B × N serum transfer model of arthritis involves transfer of serum from mice that are transgenic for a T cell receptor specific for RNase residues 42–56 associated with I-A^{g7} into wild type recipient mice [45,46]. This T cell receptor cross-reacts with peptide residues 282–294 of glucose-6-phosphate isomerase (GPI), and loss of tolerance in the transgenic mice results in serum antibody responses against GPI that cause joint inflammation and arthritis [45]. Since disease is antibody-mediated, serum from the K/B × N transgenic mice can be used to induce arthritis in healthy, recipient mice [45,46]. The disease in the transfer model is self-limiting due to clearance of the pathogenic antibody. Treatment of recipient mice with Abdegs following the transfer of anti-GPI antibodies results in substantial reductions in joint swelling and decreased inflammatory infiltrates [44]. Amelioration of disease is accompanied by a rapid decrease in anti-GPI antibody levels in the serum. Further, treatment is not only effective several hours following anti-GPI antibody transfer, but can also be used to ameliorate disease three days post-serum transfer when joints are overtly swollen [44].

The effects of Abdegs can also be compared with those induced by treatment with high dose intravenous gammaglobulin (IVIG). IVIG has multiple inflammatory effects, including the induction of regulatory T cells and the modulation of inhibitory FcγRIIb expression on innate immune cells [47–50]. In addition, high dose IVIG competes with endogenous IgGs for FcRn binding, resulting in FcRn inhibition [7,11]. However, the competitive activity for FcRn binding of the wild type IgGs in IVIG is lower than that for Abdegs [44], indicating that higher doses will be needed to achieve similar levels of inhibition. Consistently, 25–50 fold higher doses of IVIG are needed relative to the MST-HN Abdeg to achieve similar therapeutic effects in the K/B × N transfer model [44]. Given the current worldwide shortage of IVIG [51], combined with the heterogeneity and possible adverse side effects of this therapeutic [52,53], the use of Abdegs could therefore offer advantages.

Over the last decade or so, much interest has developed in the role of antibodies in multiple sclerosis [54,55]. Consistent with the involvement of antibodies in this neurodegenerative disease, about 50% of patients have antibody and complement deposits in the CNS [54,56]. Further, the transfer of MOG-specific antibodies into rodents can exacerbate experimental autoimmune encephalomyelitis (EAE), the animal model of MS [57–60]. This has prompted the testing of Abdegs in the treatment of demyelinating disease in an EAE model in which antibodies specific for myelin oligodendrocyte glycoprotein (MOG) play a clear role in pathogenesis [61]. The immunization of C57BL/6 mice with the human MOG peptide residues 35–55 results in mild EAE that can be exacerbated by the transfer of anti-MOG antibodies [59,60]. Transfer of anti-MOG antibody followed by treatment with Abdeg results in significant reductions in disease activity [61]. This reduction in disease activity correlates with lower levels of anti-MOG antibodies in the CNS following Abdeg treatment. These studies suggest that Abdegs might have use in the treatment of MS, particularly for patients in which there is evidence for antibody involvement

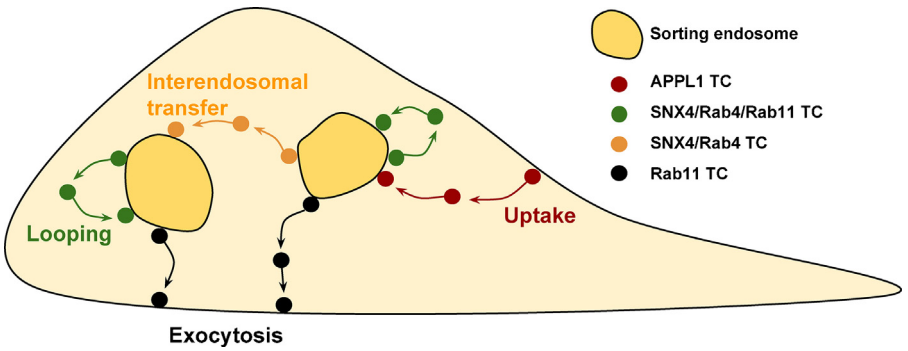

Fig. 3. Schematic representation of the different pathways taken by FcRn-positive tubulovesicular transport carriers (TCs) in endothelial cells [37]. The associated effectors (SNX4, Rab4, Rab11 and APPL1) that demarcate each pathway are indicated.

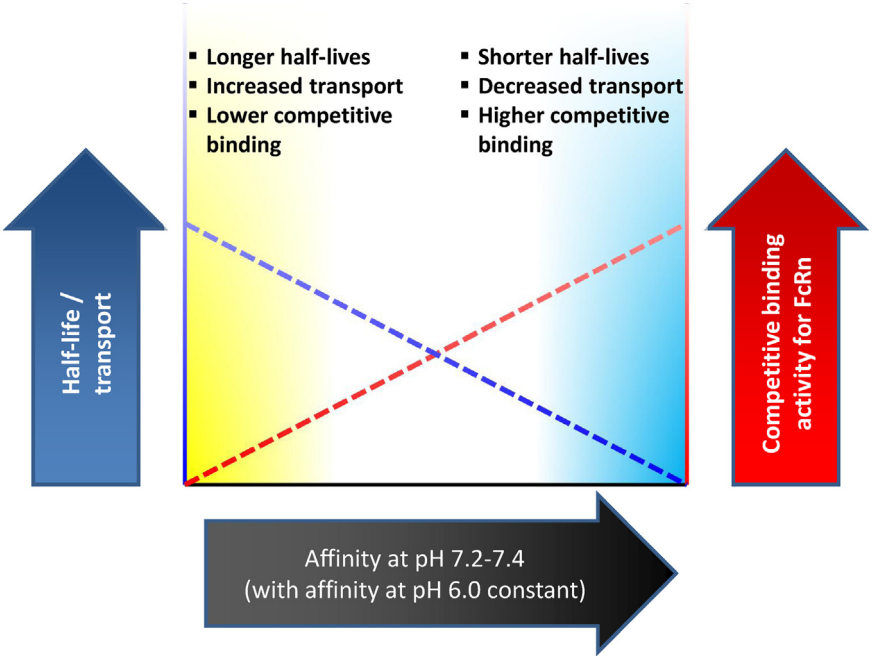

Fig. 4. Schematic representation of the effect of pH dependence on the activity of IgGs in FcRn-mediated functions. As the binding affinity of an IgG for FcRn at near neutral pH increases (with hypothetically constant affinity at pH 6.0), the ability of the IgG to compete for binding to FcRn increases. Conversely, increased binding affinity at near neutral pH results in decreased *in vivo* persistence.

in the disease process. Further, they also show that antibodies can be cleared from the CNS by Abdegs, suggesting that this approach might have applications in other neurological diseases.

The question arises as to how Abdegs traffick within cells? Microscopy analyses indicate that there are several fundamental differences between the trafficking behavior of Abdegs and wild type IgGs [6,42]. First, Abdegs can bind to FcRn at near neutral pH at the cell surface and therefore efficiently enter cells via receptor-mediated uptake pathways. Indeed, they have been used to track the endocytic pathways taken by FcRn [37]. Second, during exocytic processes involving FcRn, Abdegs are inefficiently released at the cell surface. Consequently, Abdegs are poorly recycled and become trapped inside cells, in which they ultimately follow the constitutive pathway of FcRn degradation and enter lysosomes [42]. The entry of Abdegs into lysosomes can be followed in live cell imaging experiments [42]. Consequently, Abdegs themselves have short *in vivo* half-lives which can be tuned based on their pH dependence for FcRn interactions [1,43]. However, modulation of the half-life of an Abdeg will also affect its competitive activity for FcRn binding, since these two properties are intertwined (Fig. 4). This suggests that for specific applications, the persistence and competitive activity will need to be optimized. For example, in situations where a rapid one-time clearance is needed, an Abdeg with high affinity at 7.4 (and 6.0) would be expected to be optimal.

5. Cross-species differences in FcRn binding

The pH dependence of the IgG–FcRn interaction complicates engineering approaches directed towards half-life extension [41]. This is exacerbated by cross-species differences that exist between rodent and human FcRn [62]. Specifically, the higher affinity of the majority of IgGs for mouse FcRn compared with human FcRn limits the use of mice as preclinical models when engineering antibodies for increased half-life [43]. The primary reason for this is that the threshold of binding at near neutral pH at which the antibody converts from being released during exocytosis to being re-endocytosed may be reached in mouse systems, whilst in humans the lower affinity of the interaction results in efficient exocytic release. Consequently a half-life extended antibody in assays for human FcRn function (or non-human primates) may have reduced persistence in mice [43]. The limitations of using mice as models for human FcRn function has prompted the generation of mice that transgenically express human FcRn without expressing endogenous mouse FcRn [40]. Such mice have been used, for example, to demonstrate that half-life extended antibodies are more potent anti-tumor agents [40,63].

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