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Clinical Ramifications of the MHC Family Fc Receptor FcRn

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Abstract

Introduction—Knowledge that antibodies of the IgG isotype have remarkably extended persistence in circulation and are able to pass through cell barriers has substantial implications. While is well-established that so-called neonatal Fc receptor, FcRn, acts throughout life to confer these unusual properties, its ramifications on clinical medicine and therapeutic uses are not broadly appreciated.

Scope—Here we discuss basic principles and gaps in understanding of FcRn, including its management of IgG antibodies and along with albumin, its impact on use and design of antibody-based therapeutics, and its genetics.

Keywords

Neonatal Fc receptor; FcRn; Fcgrt; β_2 microglobulin; IgG; albumin; pharmokinetics; genetics; therapeutic antibodies

Novel properties of IgG antibodies

The humoral arm of adaptive immunity is comprised of IgA, IgD, IgE, IgM, and IgG antibodies. In all cases, the variable regions of the antibody (the Fab fragments), confer antigen specificity, while the Fc region of the heavy chain couples the Fabs to varying effector mechanisms, including complement fixation and cell-mediated mechanisms via Fc receptors. Among these antibody isotypes, IgG is regarded to play the most important role in protective long term humoral immunity against a wide range of pathogens and toxins.

Two properties of IgG maximize their effectiveness by increasing their bioavailability. The first is that they have a remarkably long half-life in circulation (~20d in humans) in comparison with a 1-2d for other antibodies classes [1]. This property, rather than more abundant plasma cells is why IgG is the most abundant antibody isotype in blood. The second is IgG's biodistribution. Under non-inflammatory conditions, only IgG can efficiently traffic from its major repository in the circulation across endothelial cell barriers to permeate tissues, including the fetus. IgG can additionally pass through mucosal epithelial cells [2,3]. These properties ensure that IgG antibodies equipped with potent effector domains are conserved and distributed for resolution of infections and are also made available to newborn animals for protective immunity. On the downside, these same properties can lead to deleterious effects by promoting the accumulation and distribution of pathological IgG antibodies that can cause a spectrum of humoral autoimmune disorders. Finally, both the extended persistence in circulation and the extravascular bioavailability of IgG afford substantial opportunities for treating a diversity of diseases utilizing therapeutic monoclonal antibodies (mAbs) and proteins fused to the Fc region of IgG.

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The FcRn management system

Both the conservation and bioavailability of IgG at all stages of mammalian life are attributed to FcRn (reviewed in [4,5]. The heavy chain of FcRn, also referred to as Fcgrt, is evolutionally distinct from all other Fc receptors [6] and is a novel member of the MHC class I protein family [7]. Like its prototypic family members, Fcgrt is a Type I membrane protein molecule comprised of 3 extracellular immunoglobulin superfamily domains (α1-3) and forms an obligate heterodimer with the β_2 microglobulin (β_2m) light chain [8-10] (Fig. 1a). Structurally, the FcRn heterodimer varies only subtly from conventional class I proteins by occlusion of the opposing α-helices that normally presents peptides to T cells and natural killer cells, and, most significantly, by the presence of localized glutamic and aspartic acid residues in the α2-3 domain junction [11] (Fig. 1b). These residues create an anionic pocket that allows easily protonated histidine residues unique to the hinge region of the CH2-CH3 IgG-Fc to engage in binding. However, binding only occurs in an acidic environment (pH ~6-6.5) with nanomolar affinity, and demonstrates a precipitous affinity drop at neutral pH [10-12]. These remarkable molecular adaptations are a prototypic illustration of how seemingly insignificant changes can give rise to novel, unpredicted protein functions that accommodate new physiological niches – control over the humoral arm of immunity in this case.

The functions of FcRn are facilitated by its intracellular transport behavior. The c-terminus of Fcgrt carries an endosomal targeting motif that directs FcRn to its steady state locatoin in the early acidic endosomes [13-15]. In this compartment, FcRn is thought to gain access to extracellular IgG mainly as the result of non-specific uptake of soluble extracellular material by processes, including fluid phase endocytosis. Fusion of the endocytic vesicles with the early endosomes exposes the cargo to the acidic environment, which permits the binding of FcRn to IgG [16,17] (Fig. 1D). This complex is then sequestered as microvesicles that exclude other proteins and is transported back to the cell membrane, whereupon fusion with the plasma membrane leads to exposure to a neutral pH and the release IgG to the extracellular environment [18-20]. In contrast, proteins that are not rescued by FcRn (or other possible protein-specific rescue receptors) are destined for catabolism through the lysosomal pathway.

Albumin, the most abundant of all proteins in circulation is FcRn's second ligand. While not as well-characterized as is IgG/FcRn, a preponderance of evidence supports a model in which albumin undergoes pH-dependent binding to FcRn and is trafficked intracellularly in manner that is similar to IgG [21-25]. Mice deficient in FcRn demonstrate a ~40% reduction in serum albumin concentrations and an abbreviated half-life in blood [21]. In humans, FcRn-mediated management results in a plasma half-life of albumin that is equivalent to that of IgG [26]. Notably, IgG and albumin bind FcRn in a non-competitive manner [27]. Mutational analysis of human FcRn has identified a key conserved histidine residue at p166 that is necessary for binding to yet to be defined residues of albumin at an acid but not neutral pH [28]. The ability of FcRn to non-competitively protect and traffic IgG and albumin explains the extended persistence of both proteins in circulation, and further illustrates the adaptability of MHC class I protein family members.

Understanding the tissues and cell types that engage in IgG and albumin management is an issue of substantial importance. In polarized barrier cells, such as the vascular endothelium, FcRn that has acquired its cargo from the bloodstream can recycle its cargo apically, back to the bloodstream (Fig. 1D). It can also transport its cargo from the apical to basolateral surfaces; this transcytotic route is considered to be essential for the biodistribution of IgG from blood to extravascular sites. Furthermore, transcytosis can operate bidirectionally, as has been best documented in epithelial cell lines [2,29,30]. This bidirectional transport

system is thought operate in the mucosa to deliver IgG to luminal sites where it can bind and potentially incapacitate pathogenic microorganisms and then transport luminal antigen/antibody complexes to the lamina propria to reinforce the immune response [31-33]. Finally, IgG, and potentially albumin management by FcRn does not appear to be restricted to polarized cells, because bone marrow reconstitution experiments argue persuasively that monocyte lineage cells robustly express FcRn and extend the serum persistence of IgG and albumin ([34,35] and our unpublished data).

Are there tissues in which FcRn manages IgG and albumin differently? Most models note similarities in IgG and albumin homeostasis based the vascular endothelial cell paradigm. However, while maternal IgG is transferred efficiently to the fetus, albumin is excluded in both conventional mice and mice that transgenically express human FcRn (Al Kabbaz *et al*, manuscript in preparation). Differences in IgG and albumin management are also evidenced in the kidney, an organ that must filter an enormous volume of blood each day. In recent kidney transplantation studies, it was shown that the absence of renal FcRn rendered mice hypoalbulinemic through the loss of albumin in urine. However, the loss was limited to albumin since mice maintained comparatively normal serum concentrations of IgG [36]. At a minimum, these intriguing findings indicate that albumin and IgG are handled differently in the kidney and underscore the importance of gaining a greater understanding of the physiology of FcRn in that organ. Overall, as both of FcRn's ligands are increasingly being exploited for improving the efficacy of biotherapeutic proteins (reviewed in [25,37,38], there is a need to better understand the similarities and differences in pharmacokinetic behavior of these two ligands of FcRn.

Saturability of the FcRn protection pathway and implications for biological therapies

A principle of considerable clinical relevance is the fact that the FcRn salvage pathway is saturable, both in regards to IgG and albumin. This well-documented phenomenon, referred to as the concentration-catabolism effect [16,39], is caused by the fact that the pool of FcRn available in cells to recycle or transport its ligands can be limiting. Thus, when FcRn is fully occupied, the unbound ligand is cleared, primarily through lysosomal degradation. As modeled with the IgG ligand, at low to physiological serum IgG concentrations, there is a sufficient amount of FcRn to rescue IgG very efficiently. However, superphysiological IgG concentrations in circulation can overwhelm FcRn's recycling function. In such cases, the FcRn protection pathway can be sufficiently weakened as to negate its effect. This property can be exploited with benefit in treatment of autoimmune diseases with humoral involvement. Thus high dose intravenous IgG (IVIg) therapy is thought to act at least partially through FcRn saturation, flushing the body of intact, endogenous IgG, including that which is pathogenic [40]. However, the benefits of high dose IVIg acting through FcRn saturation are predicted to diminish in patients experiencing hypergammaglobulinemia because FcRn is already fully occupied.

This same principle may be even more relevant to the use and efficacy of therapeutic antibodies and related Fc-based biologics. Efficacy, both in terms of persistence in circulation and bioavailability at the target site is predicted to be greatest in patients with low to normal level of serum IgG (~12 mg/ml) (Fig. 2) while the therapeutic benefit will likely to diminish in relationship to their higher serum IgG concentrations. Patients with >20 mg/ml of IgG may therefore be less responsive to treatment. Routine consideration of this factor in the decision for use and dosing of antibody-based therapeutics may have value.

Therapeutic monoclonal antibodies and ways to improve them

Exploitation of the FcRn interaction is proving to be a generalized way to extend pharmacokinetics. Originally, fully mouse mAbs (*e.g.*, OKT3) tested in the clinic were found to have precipitous elimination kinetics making them only useful for short term therapy. It is now recognized that a primary the reason for this rapid clearance of mouse mAbs in humans was the failure of the Fc fragment of mouse IgG mAbs to interact efficiently with and be protected by human FcRn [41]. In the many cases where prolongation of the pharmacokinetics of therapeutic mAbs is desired, it has thus become standard to use the mouse Fc with human Fc, most commonly of the IgG1 subclass. Similarly, the incorporation of the human Fc into therapeutic proteins is becoming routine (*e.g.*, the TNF receptor fusion protein, Enbrel®) as the pharmacokinetics of such fusion proteins benefit from the human FcRn interaction.

Further improving therapeutic mAb and Fc-fusion protein pharmacokinetics by augmenting the Fc/FcRn interaction is gaining considerable traction. Owing both to crystallization and mutagenesis studies, the topology of the Fc/FcRn binding site and the critical amino acid residues involved is increasingly well understood [6,9,11,42-45] (Fig. 1B). This concept was pioneered by Sally Ward and her colleagues by their demonstration that certain amino acid substitutions in the CH2-CH3 Fc region of IgG increased mAb binding affinity at acidic pH and extended its serum persistence in standard mice [46]. Similarly, amino acid changes in the CH2-CH3 hinge of human IgG1 Fc improve the pH-dependent binding to human FcRn [43,45,47-51]. This gain in affinity may be explained by an increase in H-bonding and surface contact between Fc and FcRn [52]. However, such substitutions failed to increase their serum persistence in standard mice, raising questions regarding their utility for modeling of therapeutic mAbs [51,53]. This point of confusion is resolved by the knowledge that mouse FcRn promiscuously binds IgGs from many species, including human, with such high affinity as to mask their pharmacokinetic behavior in humans [41,53]. Analysis of mAbs modified in this manner showed much better correlations between IgG/FcRn affinity and serum half-lives in primates [47,49,50] and in mice expressing the human FcRn heavy chain [51,54,55]. This greatly strengthened the prospect that second “generation” mAbs that are engineered to enhance the FcRn interaction will improve their effectiveness beyond that observed with current mAb therapeutics. This key question was tackled recently by Zalevsky and colleagues at Xencor using substitutions in the CH2 CH3 Fc region (M428L/N434S) that were known to increase pH-dependent binding to human FcRn [55]. Substantially extended pharmokinetics and anti-tumor activity in immunodeficient human *FCGRT*-transgenic mice was realized when these amino acid substitutions were incorporated into the anti-VEGF mAb Cetuximab and the anti-EGFR mAb Bevacizumab. Therapeutic mAbs and fusion proteins engineered to enhance the FcRn interaction have multiple applications not only in treating cancer and autoimmune diseases but also for passive immunization, and are likely to assume widespread use in the future.

Is there functionally-relevant genetic variation in FcRn?

Monogenic Disorders

Given the key role for FcRn in IgG and albumin homeostasis and transcytosis, it is reasonable to consider the possibility that there are naturally occurring allelic variants of FcRn that have functional consequence. Identification of individuals with compromised FcRn function by routine clinical measures – low serum IgG and albumin and hyperlipidemia (as the result of hypoalbulinemia) – are confounded by the overlap of these abnormal parameters with numerous other disorders, especially those that compromise renal function. Evidence for a true monogenic disorder in FcRn, Familial Idiopathic Hypercatabolic Proteinemia, emanated from the remarkable early studies by Waldman and

Strober in their evaluations of immunoglobulin metabolism [56]. They identified 2 siblings from a consanguineous marriage that had abnormally low serum levels of IgG and albumin while maintaining normal concentrations of other antibody isotypes. These siblings showed no evidence for a defect in IgG synthesis or leakage through the renal or gastrointestinal routes. Most telling was a substantial increase in the fractional catabolic rate (FCR) of both proteins based on infusion of radiolabeled IgG and albumin. Trangulation of this disorder to FcRn dysfunction awaited the advent of molecular tools many years later that allowed Anderson and colleagues to identify a loss-of-function allele of β_2 microglobulin (*B2M*) as the probable cause of [56]. Given the fact that *B2M* encodes is the obligate light chain of numerous MHC class I family proteins, these individuals would likely have numerous immunological and non-immunological abnormalities. A Mendelian genetic disorder caused by a mutation in *FCGRT*, thus affecting only FcRn's functions, is yet to be described in humans.

Secondary effects by other monogenic disorders?

Another intriguing, but unexplained observation again originally made by Waldman and Strober concerns patients with the dominantly-acting neuromuscular wasting disorder, Myotonic Dystrophy (MD) [1,57]. The majority of patients with this disorder demonstrate a reduction in serum IgG concentrations while maintaining normal concentration of other antibody subclasses and albumin [57,58]. Attribution of this specific IgG reduction to increased catabolism was made by the finding of a substantially increased fractional catabolic rate (FCR) for IgG in these patients while maintaining normal FCRs for other antibody isotypes and albumin [57,59]. The failure to observe this defect in patients with other degenerative neuromuscular disorders lent credence to this increased catabolism being specific for MD. While no subsequent studies have evaluated FCRs, many other studies have confirmed the selective lowering of serum IgG in such patients [59,60]. Trinucleotide CTG expansions in the 3′ untranslated region of dystrophia myotonica-protein kinase gene *(DMPK)* on chromosome 19 are responsible for the more severe form (MD1) and accounts for the great majority of the cases. Such explanations can be massive (up to 4,000) and correlate with disease severity and age of onset [61]. Of note is that *FCGRT* maps ~ 4 Mb distal to *DMPK*. This fact and evidence that such repeats in *DMPK* can reduce the activity of the closely-linked homeobox gene, *SIX1* [62] and with possible effects on more distal 3′ genes [63] lead to the intriguing notion that DMPK RNA containing these repeats acts in *cis* to compromise the expression of *FCGRT* [64]. However, the predominance of current evidence supports *trans*-acting effects in which the transcribed repeats act dominantly by binding key nucleoproteins, CUG-binding protein 1 and muscleblind-like 1, which then affect alterations of mRNA splicing, translation, and stability of multiple gene products, and by doing so contribute to varied manifestations of MD syndromes [61,65]. Even under this scenario, *FCGRT* (or *B2M*) would have to be one of the target genes affected if this gene was directly involved in the hyper-IgG catabolic trait. While one study of Japanese MD1 patients reported a strong correlation between the number of *DMPK* CTG expansions and serum concentrations of IgG, analysis of substantially larger Swedish cohorts failed to confirm this finding and furthermore failed to find obvious correlations between numbers of *DMPK* trinucleotide repeats, serum IgG concentrations, and *FCGRT* transcription of muscle and lymphocytes as detected by quantitative PCR techniques [60]. Moreover, as noted by Pan-Hammarstrom *et al*, patients with the alternative form of MD (MD2), caused by tetranucleotide repeat expansions zinc finger 9 (*ZNF9*) (unlinked to *FCGRT*), also show a selective reduction in serum IgG [60]. The selectivity for IgG while not affecting FcRn's other ligand, albumin, would not be predicted by a global influence on *FCGRT* expression. However, as mentioned in a preceding section, selectivity for IgG could be explained by the tissue affected: if the kidney is most critical for albumin but not for IgG homeostasis and tissues more generally abnormal in MD (skeletal muscle and its microvasculature) are more

critical for IgG homeostasis, one would expect to observe changes in IgG but not albumin homeostasis. Thus, given the facts that the fractional catabolic rates of IgM and IgA are not altered in MD, it is still plausible that the IgG/FcRn recycling pathway is compromised by this disease in affected tissues. *Trans*-acting effects caused by either *DMPK* or *ZNF9* trinucleotide repeat expansions and acting through *CUGBP1* and *MBNL1* could interfere with *FCGRT* mRNA splicing and/or translation. Alternatively, these expansions could negatively impact the IgG/FcRn recycling pathway more generally by interfering with elements of endosomal trafficking that are needed for FcRn to perform its functions. A test of these possibilities could be through analysis of mice that carry a CTG expanded, expressed human *DMPK* transgenes that recapitulate MD1 pathophysiology (reviewed in [61]).

Allelic variation

Even with the very rare case of Familial Idiopathic Hypercatabolic Proteinemia, there is minimal support for functionally relevant allelic variants of FcRn that segregate in the human population. Individuals with hypomorphic alleles that broadly compromise FcRn's function (either by regulatory or protein-coding changes) would be expected to show moderate hypergammaglobulinemia and hypoalbuminemia. It is less certain whether such individuals would be immune compromised to any substantial extent. Unfortunately, these symptoms overlap with gastrointestinal and renal disorders that leak IgG and albumin, and therefore, would only be distinguished by the absence of other clinical abnormalities. The efficiency of maternofetal transfer of IgG, as measured by the ratios of mother's IgG to newborn's IgG, is another possibility that would not be as confounded by such disorders.

Individuals with hypermorphic alleles of FcRn would be expected to support higher concentrations of IgG (and albumin) in circulation by raising FcRn's saturation threshold. This would potentially increase the severity of autoimmune diseases in which pathogenic IgG autoantibodies play an important role. However, while limited, our studies in mice, including those genetically prone to develop autoimmune disease, failed to identify functionally conspicuous allelic variants in FcRn that are indicated by abnormally shortened or increased serum half-lives of IgG [66]. There is evidence that FcRn-mediated transport in mammary glands of cattle contributes to the supply of IgG in colostrum [67]. While a limited study, single sequence polymorphisms (SNP) in bovine *FCGRT* were associated with concentrations of colostral IgG [68]**.** Studies in humans identified variable number of tandem repeat (VNTR) polymorphisms within the human *FCGRT* promotor that alter the transcriptional activity of this gene in monocytes [69]. Another study investigated whether such VNTR were associated with risk for glomerular nephritis in Chinese and found no such correlation [70]. Finally, a more recent study that evaluated whether these VNTRs influence maternofetal transfer of IgG and found no such effect [71]. Genome wide association studies provide an unbiased strategy to evaluate whether allelic variations contribute meaningfully to the disease studied. To the best of our knowledge, no associations with human *FCGRT* have been revealed with this approach to date and it seems unlikely that polymorphisms of substantial disease relevance will emerge. Overall, the possibility of functionally relevant allelic variants in the FcRn heavy chain remain to be firmly established.

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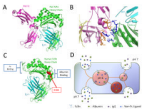

Figure 1. Structure features of FcRn and its binding partners and transcytotic pathways

(A) FcRn is a heterodimer consisting of the FcRn heavy chain (green) and b_2m (blue). FcRn binds at an acid pH to the C_H2–C_H3 hinge region of the Fc fragment of IgG antibodies. The structure is of rat FcRn complexed with the Fc fragment of rat IgG (PDB ID: 1I1A). (B) Close up view of the key human IgG1 and human FcRn amino acid residues that confer binding at an acid pH (PDB ID: 1I1A. (C) Structure of human FcRn (PDB ID: 3M17) indicating the histidine residue that is considered to engage in pH-dependent binding to human serum albumin. Depictions rendered in PyMol (DeLano, W.L. The PyMOL Molecular Graphics System (2002) DeLano Scientific). (D) Intracellular pathways by which FcRn rescues and transports IgG and albumin. In polarized cells, FcRn can recycle its cargo apically or transport it to the basolateral side, or from the basolateral to apical side (reverse transcytosis). In non-polarized cells, the directionality of transport is irrelevant; in such cells FcRn rescues its ligands from a catabolic fate.

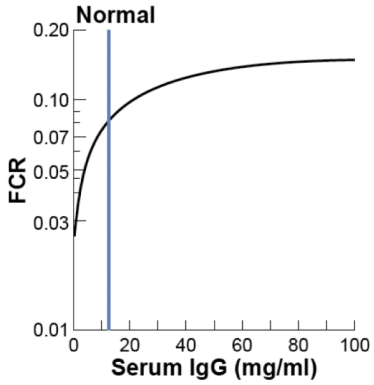

Figure 2. Relationship of serum IgG concentrations to clearance in humans

Representation of data from ref. [1]. FCR, fractional catabolic rate; the fraction of the serum IgG pool that disappears per day. The asymptote approaches that expected for complete loss of FcRn-mediated protection IgG and is expected to be similar to non-protected IgG isotypes.