FcRn: the neonatal Fc receptor comes of age

Derry C. Roopenian and Shreeram Akilesh‡*

Abstract | The neonatal Fc receptor for IgG (FcRn) has been well characterized in the transfer of passive humoral immunity from a mother to her fetus. In addition, throughout life, FcRn protects IgG from degradation, thereby explaining the long half-life of this class of antibody in the serum. In recent years, it has become clear that FcRn is expressed in various sites in adults, where its potential function is now beginning to emerge. In addition, recent studies have examined the interaction between FcRn and the Fc portion of IgG with the aim of either improving the serum half-life of therapeutic monoclonal antibodies or reducing the half-life of pathogenic antibodies. This Review summarizes these two areas of FcRn biology.

Syncytiotrophoblast
The outermost multinucleated syncytial cell layer of the trophoblast, which covers the chorionic villi. It is formed by fusion of the underlying layer of mononuclear trophoblast cells, and forms a barrier between the fetus and the mother.

Transcytosis
The process of transport of material across a cell layer by uptake on one side of the cell into a coated vesicle. The vesicle might then be sorted through the *trans*-Golgi network and transported to the opposite side of the cell.

**The Jackson Laboratory, 600 Main Street, Bar Harbor, Maine 04,609, USA.*
‡Department of Pathology, Washington University School of Medicine, 660 S. Euclid Avenue, BOX 8118, St Louis, Missouri 63110, USA.
Correspondence to D.C.R.
e-mail: dcr@jax.org
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Antibodies are the hallmark components of humoral immunity that link specific antigen recognition to different effector mechanisms of the immune system. Antibodies have two functional domains, namely the Fab (fragment of antigen binding) and the Fc region. The Fab region is responsible for antigen recognition, whereas the Fc region couples the antibody to immune effector pathways. The process of antibody class switching enables B cells to vary their expression of the heavy-chain constant region, and thereby the Fc region, to produce antibody with different effector functions. Differing localization of B-cell blasts and plasma cells that express these different heavy chains confers different tissue localization and effector-cell recognition to the five classes of antibodies — IgA, IgD, IgE, IgG and IgM.

Of the five antibody classes, IgG is the most prevalent class in the serum and non-mucosal tissues. IgG antibodies have an important role in protective immunity against a wide range of pathogens and toxins. Attesting to its important role in protective immunity, IgG has long been known to be the only class of antibody that is actively transferred from mother to offspring to confer short-term passive immunity[1–3]. This specific transport of IgG is carried out by the neonatal Fc receptor (FcRn)[4,5].

FcRn transfers IgG from the mother to the fetus across the placenta and the proximal small intestine. These two sites of transport are of differing importance in rodents and humans (FIG. 1). In rodents, FcRn functions most efficiently in the neonatal period when it transports maternally derived IgG in ingested milk across the epithelial-cell layer of the proximal small intestine[6]. By contrast, in humans, FcRn transports maternal antibody to the fetus antenatally, across the placenta. FcRn is expressed by syncytiotrophoblasts, where it transports IgG from the maternal circulation to the fetal capillaries of the placental villi[7–9]. In both systems, FcRn transcytoses IgG across a polarized cell layer from the mother to the offspring.

How does FcRn carry out directional transport at these sites? Understanding the FcRn–IgG interaction sheds light on the mechanism of IgG transport. The Fc portion of IgG binds with high affinity to FcRn at an acidic pH (<6.5) but not at a physiological pH (7.4)[4,6,10]. Several pH-titratable residues at the FcRn–Fc interface are important for this binding to occur (see later)[11–13]. In the gut of neonatal rodents, after passing through the stomach, the slightly acidic stomach contents containing maternal IgG pass into the duodenum. Here, IgG can bind to FcRn on the apical surface of an epithelial cell (FIG. 1). FcRn then transcytoses bound IgG and releases it into the underlying extracellular space, which is at physiological pH. In humans, the syncytiotrophoblast internalizes fluid containing maternal IgG into endosomes; the IgG-containing endosome is then gradually acidified thereby allowing IgG to bind tightly to FcRn present in this compartment (FIG. 1). The vesicle then fuses with the membrane on the fetal side of the syncytiotrophoblast, where the physiological pH promotes the dissociation of IgG from FcRn. The FcRn molecule may then be recycled to the maternal membrane to perform additional rounds of transcytosis, as observed in other systems[14,15]. Therefore, the pH-dependent binding of IgG to FcRn allows for IgG transport through a cell layer and down a concentration gradient of IgG.

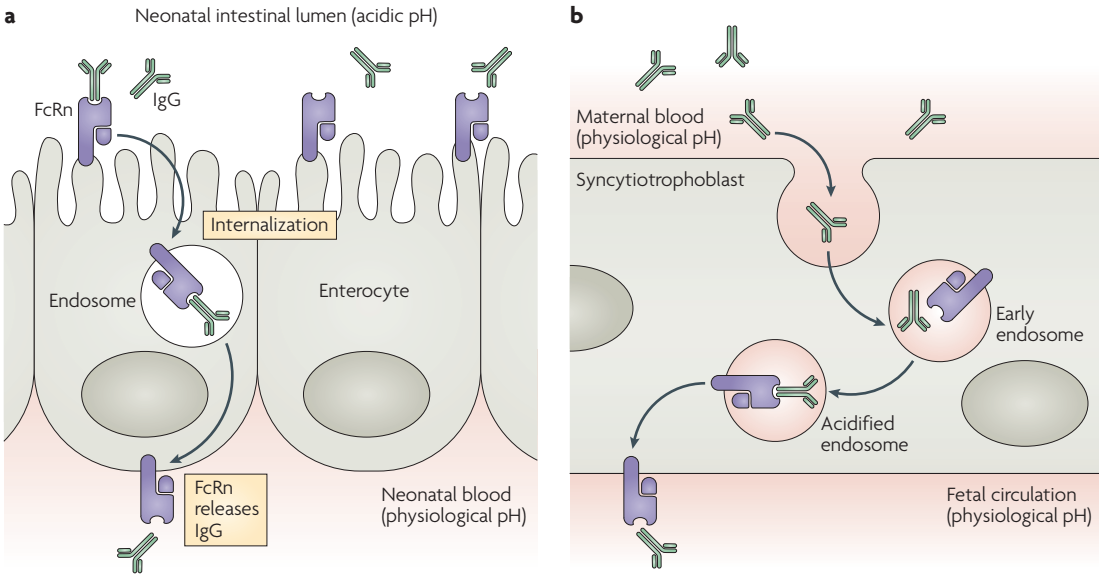

Figure 1 | **FcRn mediates the perinatal transfer of IgG.** In rodents and humans, the neonatal Fc receptor for IgG (FcRn) binds to maternal IgG in an acidic environment, transcytoses it across a polarized epithelial-cell barrier and releases it at physiological pH. **a** | In rodents, FcRn is expressed on the cell-surface brush border of enterocytes. Shortly after birth, rodent pups ingest maternal milk containing IgG, which binds FcRn on the brush border in the acidic milieu of the duodenum. Upon binding, FcRn transcytoses IgG and releases it at neutral pH on the neonatal side. **b** | In contrast to rodents, the bulk of materno fetal IgG transfer in humans occurs antenatally across the syncytiotrophoblast of the placenta. Syncytiotrophoblasts are bathed in maternal blood and internalize serum containing maternal IgG. FcRn is expressed in the internal vesicles of the syncytiotrophoblast. On acidification in the endosome, FcRn binds to maternal IgG and transcytoses it to the fetal circulation where it is released at physiological pH.

The crystal structure of FcRn has revealed the geometry of its interaction with IgG and other insights. When FcRn was first cloned, it was predicted to be a heterodimer of an MHC-class-I-like heavy chain and the β_2-microglobulin (β_2m) light chain that is common to all MHC class I molecules[5]. This prediction was confirmed when the crystal structure of FcRn and the co-crystal structure of FcRn and the Fc portion of IgG were solved[11,16] (FIG. 2). Although FcRn has the versatile MHC class I fold, its peptide-binding groove is occluded and it does not present peptide antigens to T cells[11,16] (FIG. 2).

Despite its structural similarity to MHC class I molecules, the gene encoding FcRn is outside the MHC gene complex[17]. This raises the question of whether a primordial MHC class I molecule diverged to adopt IgG transport function or whether the MHC class I molecules evolved from FcRn. This evolutionary question was recently addressed by Bjorkman and colleagues[18]. Chickens transfer IgY antibody across the yolk-sac membranes into the developing egg to confer passive immunity to their young; the receptor that performs this function (known as FcRY) is structurally unrelated to mammalian FcRn and the MHC class I molecules present in chickens, which argues that IgG transport by FcRn is a recent adaptation of the remarkably versatile MHC class I protein family. Moreover, the convergent functional evolution of FcRY and FcRn illustrates the biological importance of not only IgG transport but also IgG homeostasis, as described below.

The study of FcRn-deficient animals established a dual contribution of FcRn to effective humoral immunity. Genetic proof of the function of FcRn in perinatal IgG transport was established when neonatal mice deficient in either β_2m or in the FcRn heavy chain proved unable to absorb IgG from maternal milk[19,20]. Importantly, as adults, these mice also had lower levels of IgG antibodies in their circulation and had diminished IgG responses after immunization owing to increased IgG catabolism[20–23]. Therefore, throughout life, FcRn prolongs the half-life of IgG antibodies in the serum, helping to maintain a high concentration of this protective class of antibody in the circulation.

Although a role for FcRn in IgG homeostasis is well accepted, it has recently been shown that FcRn also extends the serum half-life of albumin[24], as reviewed elsewhere[25]. In FcRn-deficient mice, the serum IgG level is ~20–30% of wild-type animals, whereas the serum albumin concentration is about 40% of the normal level[20,24]. It is important to note that IgG and albumin make up ~90% of the protein content of serum. In FcRn-deficient mice, the half-lives of IgG and albumin are reduced from about 6–8 days to about 1 day, which is the typical half-life of other serum proteins that are not freely filtered by the kidneys. This strongly suggests that normal turnover of these and presumably other extracellular proteins occurs in cells that express FcRn[26]. Therefore, through a surprisingly efficient process, FcRn intercepts IgG and albumin that are otherwise destined for degradation, and thereby selectively extends their half-lives in the circulation.

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Brush border
The surface layer of the normal small intestine that is comprised of small microvilli coated in a rich glycocalyx of mucus and other glycoproteins. The microvilli contain many of the digestive enzymes and transporter systems that are involved in the surface digestion and uptake of dietary materials. It provides a large surface area for absorption.

MHC class I fold
The prototypic structure of MHC class I molecules and the related MHC class Ib molecules. The heavy chain polypeptide forms an α-helical sandwich that sits on top of an immunoglobulin domain. The heavy chain polypeptide pairs non-covalently with β_2-microglobulin.

Recent years have witnessed an exploration of the function of FcRn beyond its well-characterized role in postnatal humoral immunity. In addition, it has become clear that the pharmacokinetics of monoclonal antibodies and Fc-coupled biological compounds can be modulated by modifying their interaction with FcRn. These advances have implications for the understanding and treatment of humoral autoimmunity and are discussed in this Review.

FcRn expression and function

In which organs and cell types does FcRn protect IgG from degradation? So far, there is no satisfactory answer to this important question *in vivo*. The issue is complicated by the fact that FcRn is expressed in several organs and tissues, in which it may have a role in IgG transport. Evidence for FcRn function at some of these sites is reviewed below.

Vascular endothelium. At present, most evidence points to the vascular endothelium as the main site at which FcRn protects IgG from catabolism[27,28]. Expression of FcRn is observed on the vascular endothelium of the large vascular beds of skeletal muscle and the skin in mice[28,101]. At these sites, FcRn has a large contact area with the blood. As endothelial cells efficiently internalize serum proteins, FcRn might intercept IgG and return it to the circulation, thereby prolonging the persistence of IgG in the serum (FIG. 3a). Alternatively, IgG may be protected from lysosomal catabolism if these polarized cells transcytose IgG into tissues, eventually returning it to the circulation through lymphatic drainage. In support of either model, FcRn has been shown to both recycle and transcytose IgG in cultured human endothelial cells[29]. However, the presence of FcRn in vascular beds and the results of these *in vitro* studies are insufficient to conclude that the main site of protection of IgG degradation *in vivo* is the vascular endothelium. To definitively test this hypothesis, FcRn would have to be conditionally deleted in the vascular endothelium.

Professional APCs. FcRn is also expressed by human myeloid-derived antigen-presenting cells (APCs; monocytes, macrophages and some dendritic cell (DCs) subsets), which are professional phagocytes that ingest significant quantities of proteinacious fluid[30]. We have detected FcRn expression in mouse APCs, and in irradiation chimaera studies, we have observed that bone-marrow-derived cells partially extended the serum half-life of IgG in an FcRn-dependent manner[101]. We interpreted this partial phenotype as a sum of the contributions of the radioresistant somatic cells and the transferred bone-marrow-derived cells. As B and T cells do not express FcRn[101], myeloid cells expressing FcRn are the most likely haematopoietic-cell candidates. It is therefore reasonable to propose that these cells use FcRn to recycle internalized IgG rather than to destroy it (FIG. 3a). This hypothesis does not preclude other functions for FcRn in professional APCs. Indeed, a recent report described the recycling of intact IgG immune complexes in DCs[31]. At the cell surface, FcγRIIb would bind to immune complexes, once internalized, the immune complexes could be transferred to FcRn in the endosomes and then returned to the cell surface, where they would be released at physiological pH. Further experiments will have to be performed to test the role of FcRn in antigen presentation.

Adult gut. The pattern of FcRn expression in the human intestine differs markedly from that observed in rodents. In humans, FcRn is expressed by intestinal epithelial cells in both the fetus and adult[32,33]. Cultured human intestinal epithelial-cell lines express FcRn and can transcytose IgG across cell monolayers[34]. In addition to epithelial cells, human lamina-propria macrophages also

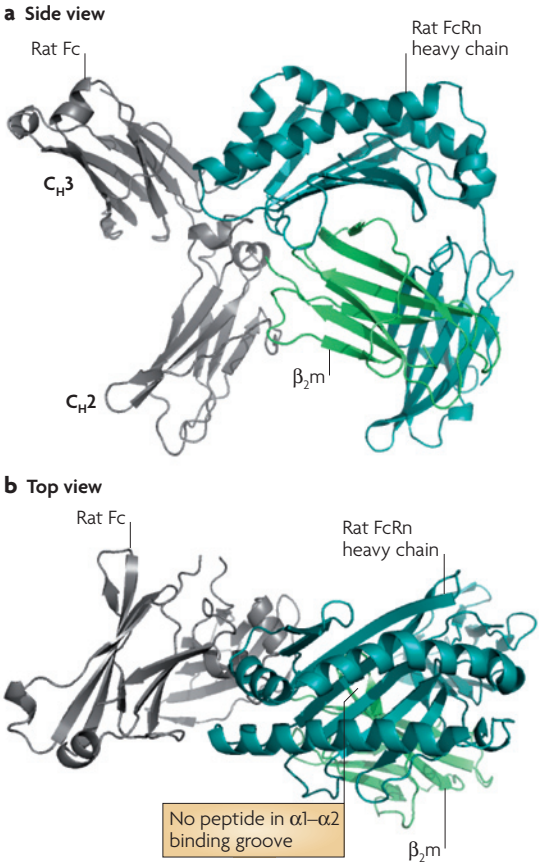
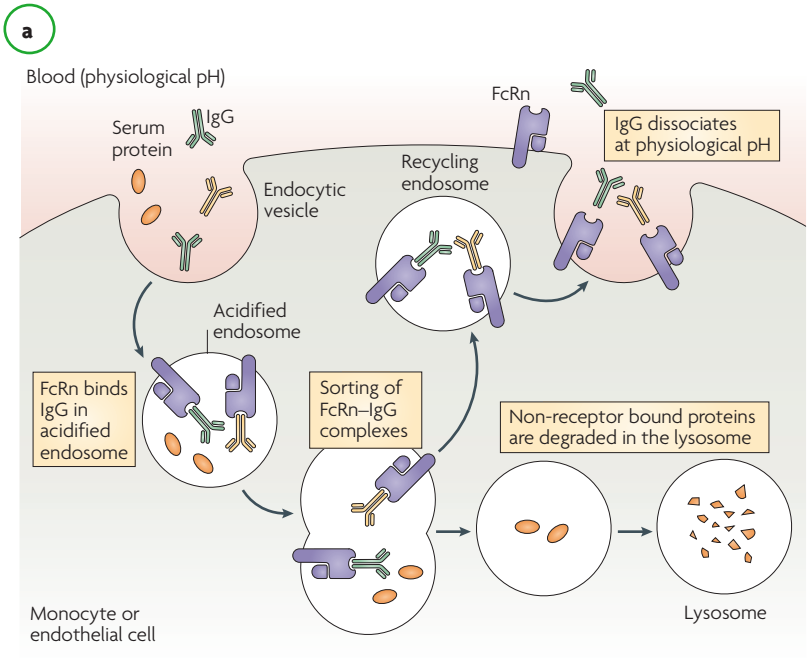
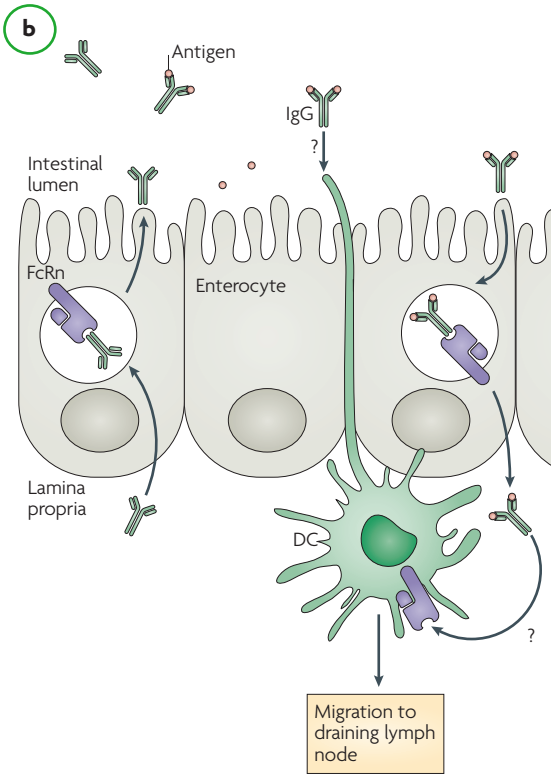
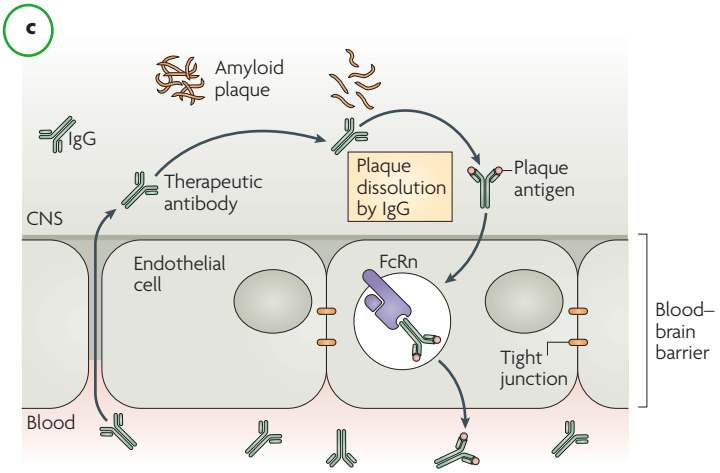
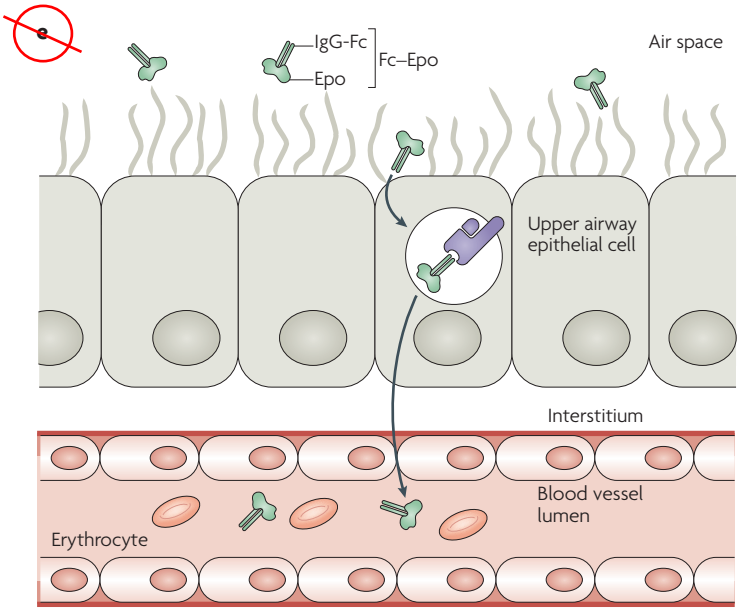


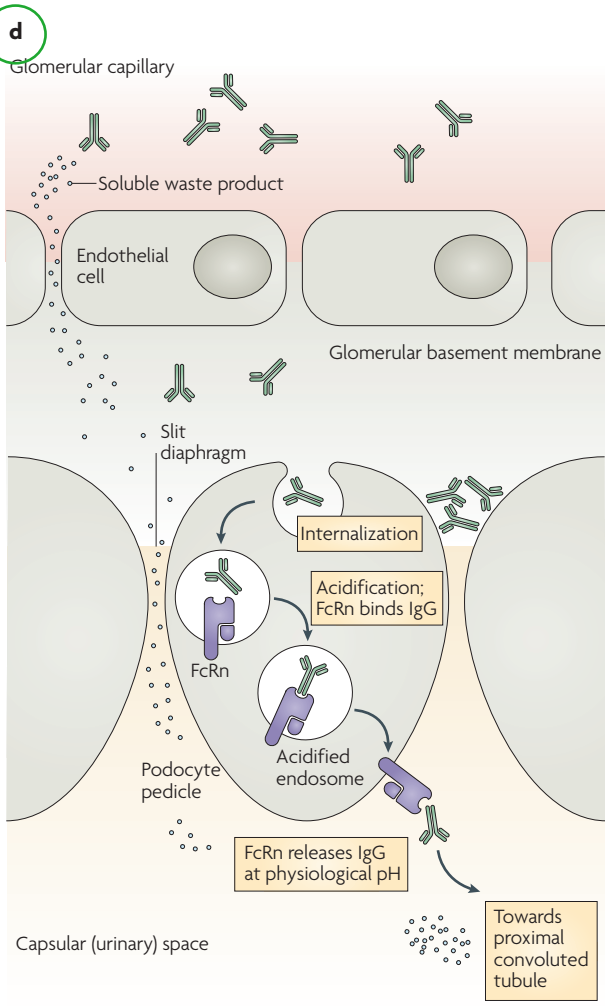
Figure 2 | **FcRn has a MHC-class-I-like structure and binds the C_H2–C_H3 hinge region of IgG.** The neonatal Fc receptor for IgG (FcRn) is a heterodimer consisting of an MHC-class-I-like heavy chain (shown in turquoise) and a β_2-microglobulin (β_2m) light chain (shown in green), which is the obligate light chain for all MHC class I molecules. Although MHC class I molecules present peptide antigen to T cells in their α1–α2 groove, FcRn does not bind peptides and the analogous groove is occluded (**b**). Instead, FcRn binds to the C_H2–C_H3 hinge regions in the constant region (Fc) of IgG antibodies (shown in grey). FcRn does not bind IgA, IgM, IgE or avian IgY. FcRn binds to Fc with nanomolar affinity at pH <6.5 but does not bind IgG measurably at physiological pH. The crystal structure is of rat FcRn complexed with the Fc fragment of rat IgG (protein data bank (PDB) ID: 1FRT[11]). The figure was generated using MacPyMol (DeLano Scientific).











express FcRn[30]. By contrast, FcRn is not highly expressed in the intestine of adult rodents[22,35]. Intestinal expression of rodent FcRn is highest on the epithelial cells of the proximal small intestine during the neonatal period, but levels in the gut decline rapidly after weaning[36]. As the promoters of the genes encoding human and mouse FcRn are structurally dissimilar[37,38], this differential pattern of expression is not surprising.

Although FcRn may not be functional in the adult mouse gut, Blumberg and colleagues have studied the potential role of FcRn in the adult human gut using a transgenic approach[39]. Using a human FcRn transgenic construct under the control of its endogenous promoter, they generated adult mice that expressed human FcRn in the intestinal epithelial cells[39]. Remarkably, epithelial-cell-expressed FcRn in the transgenic mice transcytosed IgG from the basolateral surface to the gut lumen where IgG could bind to antigens. The IgG–antigen complexes were then transcytosed across the epithelium and delivered back to lamina-propria DCs, which were then able to prime antigen-specific T-cell responses in the draining lymph node (FIG. 3b). Recently, these authors extended their original findings to a mouse model of infectious colitis[40]. These studies shed light on the previously underappreciated role of IgG and FcRn in the control of mucosal pathogens.

4

Blood–brain barrier. The central nervous system (CNS) is a site of immune privilege. The blood–brain barrier excludes serum IgG from the CNS interstitium and circulating cerebrospinal fluid. Unlike the endothelium in other organs, the cerebral vascular endothelial cells are joined by tight junctions that prevent the passive diffusion of macromolecules across the blood–brain barrier in the absence of specific transporters. It is therefore surprising that FcRn is highly expressed in the CNS endothelium and choroid plexus[41]. However, FcRn may have an important role in limiting CNS inflammation in pathological situations such as bacteraemia. The blood–brain barrier can open transiently in response to a variety of inflammatory mediators, such as tumour-necrosis factor (TNF), which is produced during bacteraemia[42]. In these situations, IgG would flood into the CNS down its steep concentration gradient. Therefore, rather than transporting IgG into the CNS, FcRn probably mediates reverse transcytosis of IgG from the CNS back into the circulation. For example, IgG molecules injected into the brain parenchyma are rapidly transported back into the circulation in an Fc-dependent manner[43]. In a recent report, this efficient export mechanism was used to reduce amyloid plaque burden in the CNS in a mouse model of Alzheimer's disease[44]. Systemic or cerebral injection of plaque-specific IgG resulted in an efflux of plaque protein into the peripheral circulation in wild-type mice but not in FcRn-deficient mice (FIG. 3c). These results provide a potential mechanism for the therapeutic efficacy of plaque-specific antibodies in the treatment of Alzheimer's disease.

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Kidneys. The kidneys filter plasma and excrete soluble waste products of metabolism. To prevent the loss of serum proteins in the urine, the kidneys have a size-selective barrier at the level of the glomeruli, the proximal portion of nephrons. The epithelial cells (podocytes) of the glomerulus have processes (pedicles) that interdigitate to form a comb-like structure through which serum is filtered and which excludes macromolecules of 70 kDa and larger. Therefore, the two most abundant serum proteins, albumin and IgG, are excluded from the primary urine. After glomerular filtration, the primary urine flows downstream to the tubular portions of the nephron. The proximal convoluted tubule (PCT), located immediately distal to the glomerulus, is responsible for the reabsorption of most of the glucose, amino acids and water from the glomerular filtrate back into the bloodstream, thereby beginning the concentration and processing of urine.

If the glomerular filtration barrier excludes IgG, why then is FcRn expressed by podocytes and also by the epithelial cells of the PCT[45,46]? This remarkable pattern of expression suggests a reconsideration of the function of the kidney filter. One hypothesis predicts that IgG antibodies deposited in the vicinity of podocytes would clog the kidney filter if they were not efficiently removed. FcRn expressed by podocytes could transcytose deposited IgG from the basolateral surface of the podocyte into the urinary space of the glomerulus (FIG. 3d). Then, downstream, at the PCT, FcRn could transcytose IgG back into the systemic circulation[47]. Additionally, FcRn in the PCT may participate in the reabsorption of albumin that may enter the filtrate. In immune-complex diseases, such as post-streptococcal glomerulonephritis and systemic lupus erythematosus, large amounts of IgG may be deposited at the basolateral side of the podocyte. In these situations, the limited transcytotic capacity of the podocyte may be overwhelmed, resulting in IgG accumulation, complement activation and renal injury. Clearly, this proposed function for FcRn in the light of its localization in the kidney deserves further evaluation.

Immune privilege
Immune-privileged sites are areas in the body with a decreased immune response to foreign antigens, including tissue grafts. These sites include the brain, eye, testis and placenta.

Blood–brain barrier
A barrier formed by tight junctions between endothelial cells that markedly limits entry to the central nervous system by leukocytes and all large molecules, including to some extent immunoglobulins, cytokines and complement proteins.

Amyloid plaques
Sites of amyloid-β accumulation and dystrophic neurites in the brains of mouse models and patients with Alzheimer's disease.

◀ Figure 3 | **Proposed roles for FcRn at various anatomical sites in the adult.** **a** | The neonatal Fc receptor for IgG (FcRn) is expressed by endothelial cells and circulating monocytes. These cells internalize serum IgG, which binds to FcRn in an acidic endosomal compartment. FcRn then recycles IgG back into circulation, thus extending its serum half-life. Serum proteins without a recycling receptor are destined for lysosomal degradation. **b** | In the adult human gut, enterocytes and lamina propria antigen-presenting cells (APCs) express FcRn. Enterocytes transcytose IgG into the gut lumen where it binds to antigens. The IgG–antigen complex is then delivered to lamina propria dendritic cells (DCs) either directly or by reverse transcytosis across the epithelial-cell barrier. Antigen-loaded DCs then migrate to the draining lymph node to prime a T-cell response. **c** | FcRn is expressed in central nervous system (CNS) vascular endothelial cells. Therapeutic plaque-specific antibodies delivered systemically can enter the CNS through transient openings of the blood–brain barrier. Once in the CNS, these antibodies bind and dissolve plaque deposits. FcRn then mediates efficient transport of the plaque-bound antibodies across the blood–brain barrier back into systemic circulation, thereby reducing CNS plaque burden. **d** | FcRn is expressed in glomerular epithelial cells (podocytes), which form the main filtration barrier of the kidney. If IgG immune complexes deposit at the kidney filter, podocyte FcRn may transcytose trapped immune complexes to prevent the filter from clogging. Further downstream in the proximal convoluted tubule, FcRn may reclaim transcytosed IgG (not shown). **e** | In humans and non-human primates, FcRn is expressed by upper airway epithelial cells and can transport aerosolized Fc-coupled drugs, such as Fc-coupled erythropoietin (Fc–Epo), across the epithelium into the blood.

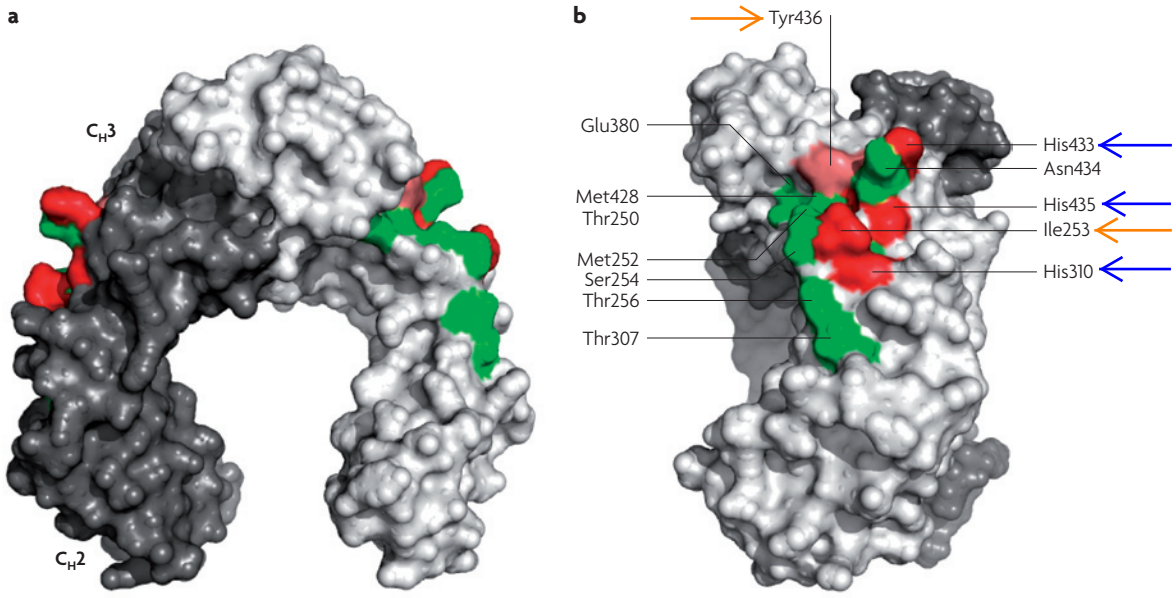

Figure 4 | **Structural basis of the FcRn–IgG interaction.** The neonatal Fc receptor for IgG (FcRn) binds to the C_H2–C_H3 hinge region of IgG. Staphylococcal protein A, streptococcal protein G and rheumatoid factor also bind to this region of IgG[59–61]. By contrast, C1q and the classical Fc receptors for IgG (FcγRs) bind to distinct portions of the Fc region[11,57,58]. Mutational analysis of IgG has identified several amino acids that when altered abrogate (shown in red) or reduce (shown in pink) the ability of IgG to bind to FcRn. Reducing the binding ability of IgG for FcRn reduces its serum persistence, which is desirable for acute imaging studies. Conversely, mutations of residues depicted in green can improve IgG binding to FcRn. A higher-affinity FcRn–IgG interaction prolongs the half-lives of IgG and Fc-coupled drugs in the serum. These improved pharmacokinetics would reduce the dosing frequency of monoclonal antibodies and reduce patient risk and discomfort. The crystal structure is of the Fc region of human IgG1 (Protein Data Bank (PDB) ID: 1DN2[97]) with the C_H2 domain carbohydrate omitted for clarity. The figure was generated using MacPyMol (DeLano Scientific).

Hinge region
A sequence of amino acids, which is often rich in cysteine and proline residues, that is present in the constant region of immunoglobulin heavy chains. It provides increased molecular flexibility. This region might be involved in the disulphide bonds that link adjacent immunoglobulin heavy chains.

Staphylococcal protein A and streptococcal protein G
Proteins expressed on the cell surface of Staphylococcal or Streptococcal species. These proteins bind to the heavy chain of IgG antibodies from various species and therefore can be used in antibody isolation and purification.

Rheumatoid factor
An antibody (usually IgM) that binds to the Fc region of IgG thereby forming immune complexes. Rheumatoid factors are sometimes found in patients with rheumatoid arthritis and other autoimmune diseases such as systemic lupus erythematosus.

Lungs. The lungs are a prominent site of FcRn expression in several species studied to date. Consistent with its expression by professional APCs, FcRn is highly expressed by the alveolar macrophages of all species[48,49]. However, across species, there are differences in the sites of FcRn expression; in primates, FcRn is expressed predominantly in the upper airway epithelium, whereas in rats and cows, FcRn is expressed mainly in the bronchiolar and alveolar epithelium[48–51]. From our investigation in mice, we were unable to detect FcRn in the upper airways, and we detected very low levels of FcRn in mouse alveolar epithelial cells[101]. These results may reflect inter-species differences in FcRn expression or may be the result of different reagent affinities or specificities used in the studies.

Studies in primate systems suggest that delivery of Fc-fusion proteins to the upper airway results in an Fc-dependent, saturable uptake of these proteins into the systemic circulation[52–56]. However, given the much larger surface area of the alveolar epithelium compared with the upper airway epithelium and the fact that alveolar epithelial cells can transcytose IgG *in vitro*[51], a role for IgG absorption by the alveolar epithelium aswell cannot be discounted in these systems. In humans and primates, pulmonary administration of Fc-fusion proteins results in bioavailabilities that are comparable to standard routes of administration. A recent study showed that Fc-coupled erythropoietin (Fc–Epo) could be transported across the epithelium of the upper airway in humans[53] (FIG. 3e). So, FcRn-mediated transport across the lung epithelium may be a useful route to deliver Fc-coupled biological agents.

Analysis of the FcRn–IgG interaction

FcRn binds to the Fc portion of IgG at a site that is distinct from the binding sites of the classical FcγRs or the C1q component of complement, which initiates the classical pathway of complement activation[11,57,58]. The FcRn–Fc co-crystal structure revealed that FcRn binds to the C_H2–C_H3 hinge region of IgG antibodies — a versatile region of Fc that also binds staphylococcal protein A and streptococcal protein G, and rheumatoid factor[59–61] (FIGS 2, 4). In contrast to conventional Fc receptors for IgG (FcγRs) and other Fc-binding proteins, FcRn binds to the Fc region of IgG in a strictly pH-dependent manner. At physiological pH 7.4, FcRn does not bind IgG, but at the acidic pH of the endosome (pH 6–6.5), FcRn has a low micromolar to nanomolar affinity for the Fc region of IgG. FcRn does not undergo a dramatic conformational change when it binds IgG[62]. Instead, the sharp pH dependence of the FcRn–Fc interaction is mediated by the titration of histidine residues in the C_H2–C_H3 hinge region of IgG and their subsequent interaction with acidic residues on the surface of FcRn. Importantly, when the IgG histidine residues at positions 310 and 435 are mutated to alanine, IgG binding to FcRn is severely reduced or abrogated[12,13,63–67] (FIG. 4). The anionic residues Glu117, Glu132 and/or Glu135 and Asp137 on the

α_2-helix of FcRn form salt bridges with these protonated histidines of IgG at acidic pH[68]. The exact number of titratable residues on the Fc-hinge region varies among species and antibody isotypes[69]. Perhaps because of this, the histidine residue at position 433 and the tyrosine at position 436 in human IgG1 (mouse IgG1 has a histidine at this position) seem to have variable effects on FcRn binding affinity, depending on the methodology used[12,64,66]. In addition to these charge interactions, the hydrophobic isoleucine residue at position 253 of IgG interacts with Trp133 of FcRn, and both residues have been shown to be crucial for binding. Last, Ile1 of β_2m also participates in IgG binding, probably by interacting with a hydrophobic residue at position 309 of Fc. In summary, mutational and crystallographic studies indicate a hydrophobic interaction between FcRn and Fc that is only stabilized when salt bridges form between the two molecules at an acidic pH.

The stoichiometry of the FcRn–Fc interaction has been a matter of debate. When rodent FcRn is immobilized on the cell membrane or a solid surface, it binds to IgG with a 2:1 stoichiometry, with two receptor molecules binding to a single Fc fragment[70,71]. Studies of FcRn–Fc binding in solution show a 1:1 FcRn:Fc stoichiometry under non-equilibrium conditions[72] or a 2:1 stoichiometry at equilibrium[73]. The apparent discrepancies in the stoichiometry can be attributed to the different methods and conditions in which the binding studies were performed. Human FcRn also binds to IgG with a 2:1 stoichiometry in solution[74]. Therefore, the consensus of studies of the FcRn–Fc interaction across species points to a 2:1 FcRn:Fc stoichiometry.

Crystallographic analysis of rat FcRn complexed with Fc revealed that there are two structural conformations for the FcRn–Fc complex[11]. As the Fc fragment has two binding sites (being a homodimer of two heavy chains) for FcRn, one structure shows the two FcRn molecules on opposite sides of the Fc homodimer, with each receptor binding symmetrically to one Fc hinge region. The presence of only one FcRn binding site on the Fc fragment (as in a heterodimeric Fc molecule in which there is one FcRn-binding chain and one non-FcRn-binding chain) reduces the overall binding avidity for FcRn and decreases transcytosis and the *in vivo* half-life of the heterodimeric Fc molecule[13,75,76]. In the other structure, the two FcRn molecules contact IgG asymmetrically. One receptor dominates the asymmetric interaction with Fc, but the other FcRn molecule contributes to stabilize the complex. FcRn dimerization is not absolutely required for binding Fc in this manner, but it increases the affinity of the interaction. In support of this asymmetric binding mode, mutation of histidine residues 250 and 251 in the α_3-domain of FcRn, and mutation of Glu89 of β_2m, reduces but does not abrogate the binding of FcRn to Fc[12,68]. These residues mediate the formation of the FcRn homodimer that forms the high-affinity binding site for IgG. The dimerization of FcRn in crystal structures has only been observed for rodent FcRn and depends on the glycosylation of the FcRn heavy chain[62]. Although dimers of human FcRn have not been observed in crystals, the receptor still dimerizes when immobilized on a membrane[77]. So, two FcRn molecules bind asymmetrically to a single Fc-hinge region of an IgG molecule. However, both Fc-hinge regions on an IgG molecule must be competent to bind to FcRn for effective transport and recycling.

Box 1 | Why modulate the FcRn–IgG interaction?

To extend the pharmacokinetics of therapeutic antibodies

- To minimize adverse reactions caused by high doses
- To decrease frequency of injection
- To maximize transcytosis to specific tissue sites
- To enhance efficiency of trans-placental delivery
- To decrease production costs

To shorten the pharmacokinetics of antibodies

- To ensure rapid clearance of antibodies used for imaging and/or radioimmunotherapy
- To promote clearance of endogenous pathogenic antibodies as a treatment for autoimmune diseases
- To reduce the risk of adverse pregnancy outcome caused by trans-placental transport of maternal fetus-specific antibodies

Modulating the interaction of IgG with FcRn

As FcRn is responsible for the extended persistence of IgG and other Fc-conjugated proteins in the serum, it stands to reason that modulating the FcRn–IgG interaction will allow the deliberate control of the half-life of these agents in the circulation to various ends (BOX 1). Engineering therapeutic antibodies to have an extended serum half-life would improve their efficacy. Conversely, decreasing the serum levels of pathogenic antibodies by inhibiting FcRn function would alleviate symptoms of diseases in which IgG is the pathogenic aetiological agent.

Strengthening or weakening the FcRn–IgG interaction. Improving the affinity of the FcRn–IgG interaction can extend the half-life of a modified IgG. When residues around the FcRn–Fc binding interface are modified, the pharmacokinetics of the mutated IgG can be extended (FIG. 4). Various mutations at positions Thr250, Met252, Ser254, Thr256, Thr307, Glu380, Met428, His433 and Asn434 improve the pH-dependent binding of human IgG to FcRn[66,67,78–82]. Combinations of some of these mutations can synergize to further improve the binding affinity to FcRn. On the other hand, mutating the residues that are critical for FcRn–Fc interactions abolishes binding *in vitro* and also reduces the serum half-life of the mutated antibodies *in vivo*[12,64–67,79]. These short-lived antibodies may be desirable for situations in which an acute effect is required, such as the administration of toxin-conjugated therapeutic antibodies[83] or for the biological imaging of antibody distribution[84].

Although improving the binding of IgG to FcRn *in vitro* generally translates to an improved serum IgG half-life *in vivo*, this is not always the case. In fact, there

Table 1 | **Therapeutic approaches that involve FcRn**

Strategy	Effect	Reference
High-dose intravenous immunoglobulin	Increased IgG turnover by saturating FcRn function	91–93,100
Monoclonal antibody against β_2-microglobulin (obligate light chain of FcRn)	Increased IgG turnover by blocking IgG binding to FcRn	95
Monoclonal antibody against FcRn	Increased IgG turnover by blocking IgG binding to FcRn	96
Antibodies with increased binding affinity for FcRn via their Fc region ('Abdegs')	Increased IgG turnover by outcompeting endogenous IgG for binding to FcRn	67,80
Peptides that bind to the Fc region of IgG	Effect on IgG half-life not tested *in vivo*; predicted to increase IgG turnover by blocking interaction with FcRn	97,98
Humanized mouse monoclonal antibodies	Improved binding of recombinant IgG to human FcRn (mouse IgG binds poorly to human FcRn)	20,99
CTLA4–Fc	Increased serum half-life dependent on Fc region of IgG	20
Fc–Epo, Fc–FSH	Delivery across respiratory epithelium; enhanced serum half-life dependent on Fc region of IgG	49,52–55
Amyloid-β-specific antibody	FcRn mediated efflux of IgG–amyloid-β complexes from CNS with reduction of amyloid plaque burden	44

CNS, central nervous system; CTLA4, cytotoxic T-lymphocyte antigen 4; Epo, erythropoietin; FcRn, neonatal Fc receptor for IgG; FSH, follicle-stimulating hormone.

may be an upper limit for the improvement in serum half-life of IgG by mutating the FcRn–Fc interface. For example, the humanized IgG1 antibody hu4D5 (Herceptin; Genentech; an ERBB2-specific monoclonal antibody) variant Asn434Ala and the triply substituted variant Thr307Ala/Asn434Ala/Glu380Ala bind human FcRn with 3-fold and 12-fold higher affinity, respectively, than the wild-type hu4D5 antibody at pH 6.0 (REF. 66). Unexpectedly, in FcRn transgenic humanized mice, the half-lives of these two variant antibodies were essentially equivalent[67]. This discrepancy may be explained by the increased affinity of the triply substituted variant for FcRn at pH 7.4 (REF. 67). Fc mutations that improve the binding affinity at pH 7.4, as well as at pH 6.0, may actually accelerate the clearance of the antibody *in vivo* rather than prolong its half-life[85,86]. Efficient recycling of IgG by FcRn requires the release of IgG at physiological pH; however, IgG mutants that remain bound to FcRn at physiological pH seem to be degraded rapidly. Therefore, extending the serum persistence of IgG requires improved FcRn binding at acidic, but not at physiological pH. Still, additional mutational analysis of the FcRn–Fc interaction is warranted to test whether the maximum extent of IgG serum persistence has been achieved. However, as shown by these examples, it is crucial to validate the pharmacokinetic efficacy of all mutations discovered *in vitro* in suitable animal models (as discussed later).

Humanized mice
Mice lacking certain genes of interest but transgenically expressing the human equivalent. Such mice provide an easy model system to study the biology of human genes.

Strategies to interfere with FcRn function. Whereas the aforementioned modifications alter the serum persistence of administered exogenous antibody, it is sometimes advantageous to reduce endogenous serum IgG levels by interfering with FcRn function. This includes autoimmune diseases in which pathogenic or excess IgG antibodies are aetiological agents, such as myasthenia gravis, bullous pemphigoid, idiopathic thrombocytopenic purpura (ITP) and systemic lupus erythematosus (SLE).

One possible way to interfere with the function of FcRn is to overload it with 'innocuous' IgG. The half-life of IgG depends on its concentration in the circulation, a phenomenon known as the concentration–catabolism effect[87,88]. As FcRn functions as the IgG homeostatic receptor, the level of FcRn expression determines the serum concentration of IgG. Administering large quantities of exogenous IgG raises the serum concentration above this equilibrium set point and saturates FcRn[89]. As a result, the excess IgG that does not bind to FcRn enters the degradative pathway. This results in a shortening of the serum IgG half-life. High-dose intravenous immunoglobulin (IVIG) treatment is thought to exert an immunomodulatory effect by numerous mechanisms, including engagement of the inhibitory FcγRIIb receptor[90] and by FcRn saturation[89]. In mouse models of bullous pemphigoid, ITP and autoimmune arthritis, IVIG treatment results in the dilution of pathogenic antibodies to levels beneath the disease-causing threshold[91–93]. The fact that a therapeutic effect for IVIG is maintained in FcγRIIb-deficient mice and is attenuated in FcRn-deficient mice is strong evidence that an important mechanism of action of IVIG is its ability to compromise FcRn function[91,92].

A more direct approach to reduce the serum titres of endogenous, pathogenic antibodies is to specifically block the FcRn–IgG interaction with FcRn-specific monoclonal antibodies. A monoclonal antibody directed against β_2m has been shown to block the ability of FcRn to bind IgG *in vitro*[94], and this results in a reduced titre of serum IgG antibodies *in vivo* in rats[95]. However, the therapeutic use of such an approach would risk unwanted immune side effects because β_2m is the common light chain for all MHC class I and many MHC class Ib molecules besides FcRn. Monoclonal antibodies directed specifically against the unique FcRn heavy chain would be a more promising approach. Indeed, recently, a monoclonal antibody directed against the FcRn heavy chain was shown to reduce disease symptoms in rats with experimentally induced myasthenia gravis[96].

A third approach to reduce the serum levels of pathogenic antibodies is to enhance their catabolism by the administration of recombinant IgG that can outcompete endogenous antibody binding to FcRn via their re-engineered Fc regions. Indeed, administration of humanized IgG monoclonal antibodies engineered to have Fc regions that bind to FcRn with an unusually high affinity results in the degradation of non-bound endogenous antibodies[80] and in the amelioration of arthritic lesions caused by pathogenic human immunoglobulin[67]. These so-called 'Abdegs' may be useful in forcing the rapid catabolism of pathogenic antibodies.

Last, small molecule or peptide inhibitors of the FcRn–Fc interaction could be attractive alternatives to the previously mentioned antibody-based approaches. Several groups have studied peptides that bind to the C_H2–C_H3 hinge region of IgG with high affinity[97,98]. It remains to be established whether these peptides or ones specifically designed to bind FcRn and block its interaction with the Fc of IgG would lead to enhanced clearance of IgG *in vivo*. Overall, the discovery and validation of inhibitors of FcRn promises to be an area of active research with applications in the treatment of various antibody-mediated autoimmune diseases (TABLE 1).

Model systems to test FcRn therapeutics. The design of novel human therapeutics to increase or decrease IgG persistence *in vivo* depends on their previous validation in appropriate model systems. Although primate systems are most likely to reproduce human pharmacokinetic parameters, it is desirable to initially test therapeutics in a higher throughput manner in a rodent model. Unfortunately, differences in the biology of rodent and human FcRn can influence the evaluation of FcRn therapeutics[86]. First, there are known variations in the pattern of FcRn expression between mice and humans (as discussed earlier). Second, human and mouse FcRn have different binding affinities for IgG antibodies from different species[99]. Human FcRn only binds human, guinea pig and rabbit IgG, whereas mouse FcRn binds IgGs from many different species with high affinity. Mice lacking endogenous FcRn but expressing a human FcRn transgene are currently proving to be the best 'translational' model for the assessment of FcRn-based therapeutics[20]. This mouse model is proving useful for studying the localization of human FcRn expression and the interaction of engineered therapeutics with human FcRn *in vivo*[20,39,67]. As β_2m also contacts Fc, an improvement to this model could be to introduce a transgene encoding human β_2m into the system[39]. However, such studies have failed to have an impact on the serum persistence of human IgG (T. Sproule and D.C.R., unpublished observations). Additionally, as human FcRn is unable to bind to endogenous mouse IgG, the serum IgG level in these mice is low, similar to that of the FcRn-deficient mice. As a result of the concentration–catabolism effect[87,88], FcRn receptor occupancy would be reduced and the half-lives of recombinant human IgG measured in these mice might be higher than those observed in the presence of normal serum IgG concentrations. Therefore, a further improvement to the model would be to introduce transgenes encoding human IgG to provide a normal serum IgG concentration in which to study the pharmacokinetic properties of recombinant IgG therapeutics[86]. Thus, despite these limitations, this human FcRn transgenic model still provides the best small mammalian system for the initial evaluation of FcRn therapeutics, including those directed at human FcRn blockade, before pharmacokinetic validation in primate or human systems.

Concluding remarks

FcRn is an unusual Fc receptor, the biological importance of which is only beginning to be fully appreciated. In addition to its critical role in the transfer of maternal IgG to the fetus or neonate, FcRn is the homeostatic receptor responsible for extending the serum half-life of IgG in adults. The exact site(s) of IgG protection from degradation has not been delineated *in vivo*, but both endothelial cells and bone-marrow-derived cells can extend the serum persistence of IgG. FcRn is also expressed in many other tissues in the adult animal, including barrier sites such as the blood–brain interface, the glomerular filter in the kidneys and the intestinal epithelium. FcRn expression at these sites merits further study with the goals of modulating specific IgG transport to promote host defence or to control immune-complex deposition. Exploitation of the FcRn–IgG interaction holds promise for the design of better therapeutics that have the desired pharmacokinetic properties combined with the appropriate antibody effector functions, such as complement fixation or anti-inflammatory potential. The next step involves tailoring the Fc region of IgG to suit such specific therapeutic goals. To fully exploit these next generation recombinant IgG therapeutics, we will need to develop the appropriate model systems to allow us to take full advantage of novel strategies to enhance or interfere with the FcRn–IgG interaction *in vivo*.

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This study indicates that FcRn extends the serum half-life of pathogenic autoantibodies, thereby contributing to humoral autoimmune disease.
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Competing interests statement
The authors declare competing financial interests: see web version for details.

DATABASES
Entrez Gene:
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene
β_2m | FcRn

FURTHER INFORMATION
Derry Roopenian's homepage:
http://www.jax.org/staff/derry_roopenian.html

ALL LINKS ARE ACTIVE IN THE ONLINE PDF.

1-1 Jan 9, 2013, 9:09 AM
Antibody introduction

1-2 Jan 9, 2013, 9:09 AM
pH dependence... The course topic focus that this paper was selected to explore...important!

1-3 Jan 9, 2013, 9:09 AM
Mechanism steps of FcRN transport

2-1 Jan 9, 2013, 9:09 AM
Third role of FcRN ... Recycling of IgG in the adult

3-1 Jan 9, 2013, 9:09 AM
Since FcRN is involved in prolonging the half life of IgG, drugs that modulate that interaction could help reduce the concentration, and therefore, the damage caused by autoantibodies in autoimmune diseases

3-2 Jan 9, 2013, 9:09 AM
The vascular endothelium lines the inside of blood vessels and so is in intimate contact with blood (and therefore IgG) that passes through the vessels

3-3 Jan 9, 2013, 9:09 AM
APC's engulf suspected pathogens and fluid like a sieve ... FcRN is thought to return the IgG to the blood/ lymph