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Review article

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The therapeutic age of the neonatal Fc receptor

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Abstract

IgGs are essential soluble components of the adaptive immune response that evolved to protect the body from infection. Compared with other immunoglobulins, the role of IgGs is distinguished and enhanced by their high circulating levels, long half-life and ability to transfer from mother to offspring, properties that are conferred by interactions with neonatal Fc receptor (FcRn). FcRn binds to the Fc portion of IgGs in a pH-dependent manner and protects them from intracellular degradation. It also allows their transport across polarized cells that separate tissue compartments, such as the endothelium and epithelium. Further, it is becoming apparent that FcRn functions to potentiate cellular immune responses when IgGs, bound to their antigens, form IgG immune complexes. Besides the protective role of IgG, IgG autoantibodies are associated with numerous pathological conditions. As such, FcRn blockade is a novel and effective strategy to reduce circulating levels of pathogenic IgG autoantibodies and curtail IgG-mediated diseases, with several FcRn-blocking strategies on the path to therapeutic use. Here, we describe the current state of knowledge of FcRn–IgG immunobiology, with an emphasis on the functional and pathological aspects, and an overview of FcRn-targeted therapy development.

Sections

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Introduction

Antibodies, or immunoglobulins, are an inherent part of vertebrate humoral immune responses. On the one hand, the extreme variability of the antigen-binding fragment (Fab) domain enables antibodies to specifically recognize an almost infinite number of epitopes. On the other hand, the "constant" crystallizable fragment (Fc) domain allows them to engage with various soluble and cellular molecules, such as components of the complement pathway or Fc receptors (FcRs), and to trigger highly tailored immune responses. In mammals, different Fc domains have evolved that correspond to specific immunoglobulin classes, namely IgA, IgD, IgE, IgG and IgM[1]. Similarly, numerous receptors also emerged that engage and provide specialized characteristics to each of these immunoglobulin classes. IgGs, the most prevalent antibody class, have unique features that are attributable to their interaction with neonatal Fc receptor (FcRn). FcRn is responsible for the transfer of IgGs from mother to offspring and across mucosal surfaces, in addition to maintaining high concentrations and a long half-life of this class of antibody in the circulation. Although Fc receptors for IgG (FcγRs) are crucial to IgG effector functions[2], the role of FcRn in responding to IgG immune complexes (IgG-ICs) has been gaining attention. FcRn is distinctively and directly involved in innate and adaptive immune responses to IgG-ICs, beyond its better-known role in the prevention of IgG catabolism. The important advances in the FcRn field over the past century (Supplementary Fig. 1) have allowed for the translation of these studies into the therapeutic age of FcRn. Here, we discuss the biology of FcRn in the immune response, in addition to its roles in protection against infectious diseases and cancer, and in the promotion of autoimmunity, with a focus on the advances in clinical trials for FcRn-blocking therapeutics. Although FcRn is also a receptor for albumin, we only discuss this briefly and refer the reader to other excellent reviews on this topic[3,4].

Basic concepts of FcRn biology

From *FCGRT* to FcRn

In humans, the FcRn heavy chain is encoded by the Fcγ receptor and transporter (*FCGRT*) gene, located on chromosome 19q13.3[5]. The gene contains seven exons and six introns, with exons 2–5 encoding the signal sequence and extracellular α1-α2-α3 domains, exon 6 encoding the transmembrane domain and exon 7 encoding the cytoplasmic tail[6]. *FCGRT* orthologues exist in most mammalian and marsupial species and the encoded proteins display high amino acid conservation with the human receptor, although in some species (ruminants, pigs, dogs, rabbits) deletions of 5–10 amino acids in the cytoplasmic tail have been described[7]. The α1-α2-α3 domains of FcRn share high structural homology with MHC class I molecules and non-covalently associate with β_2-microglobulin (β_2m), forming a heterodimer[8–11] (Fig. 1a). Unlike the high genetic variability observed in some FcγRs and MHC class I molecules, *FCGRT* is predominantly monomorphic with variability that is limited to its promoter in the form of variable number of tandem repeats (VNTRs)[12] (Box 1). Further, contrary to MHC class I molecules, the FcRn peptide binding groove is occluded, preventing it from presenting peptides[10,13]. Despite this, FcRn biogenesis involves the endoplasmic reticulum chaperones used by MHC class I molecules in its assembly and interactions with elements of the MHC class II pathway, such as the invariant chain, indicating the unique nature of FcRn function[14,15].

FcRn cellular distribution and regulation of expression

FcRn is expressed beyond the neonatal stage, in adult life, and is widely present throughout human body tissues, including parenchymal (epithelium, endothelium, hepatocytes and keratinocytes) and haematopoietic cell types[16–21]. The list of cells, tissues and organs that express FcRn is rapidly expanding (Supplementary Fig. 2), with gaps in our knowledge of FcRn's function in many cells and tissues remaining[20–22] (https://www.proteinatlas.org/ENSG00000104870-FCGRT/single+cell+type). Within the immune compartment, FcRn expression is especially high in myeloid cells such as monocytes, tissue-resident macrophages, dendritic cells (DCs) and neutrophils; in lymphocytes, low levels of FcRn are present in B cells but no FcRn expression has been detected in T cells or natural killer (NK) cells[20,21,23,24]. FcRn is mostly distributed intracellularly within vesicular networks, particularly in acidic endosomes, that allow for interactions with IgG and albumin; it is also present at the cell surface, especially in monocytes, macrophages, DCs and neutrophils[20,24]. The precise role of surface FcRn on these cell subsets is unclear.

FcRn expression is regulated by factors such as cytokines or infectious stimuli, with many transcription factor binding sites identified in *FCGRT*. FcRn expression is rapidly increased by tumour necrosis factor (TNF) stimulation of intestinal epithelial cell lines, human primary monocytes and the THP-1 monocytic cell line, and depends on NF-κB binding to *FCGRT* introns[25]. The Toll-like receptor agonists lipopolysaccharide and CpG oligodeoxynucleotides also increase FcRn expression in THP-1 cells, which is also probably due to NF-κB activation[25]. Transforming growth factor β1 (TGFβ1) promotes FcRn expression in porcine intestinal epithelial cells through JUN N-terminal kinase (JNK) activation and c-JUN transcription factor binding to the *FCGRT* promoter[26]. Similarly, transmissible gastroenteritis virus infection upregulates FcRn expression in porcine intestinal epithelial cells through NF-κB, which has four binding sites in the FcRn promoter, and Zika virus infection in pregnant mice upregulates FcRn expression in the placenta[27,28]. Conversely, FcRn expression can be downregulated by interferon-γ (IFNγ)-mediated JAK–STAT1 signalling in epithelial cells, THP-1 cells and human peripheral blood mononuclear cells, with multiple possible mechanisms of downregulation, including STAT1 binding to an IFNγ activation site in the *FCGRT* promoter region[29]. Overall, more investigation is needed to thoroughly explore the regulation of FcRn expression in the panoply of immune and non-immune cell subsets that express it.

FcRn–ligand interactions

FcRn engagement of the IgG Fc occurs at the CH_3 and CH_2 domain interface, with the Fab arms directed towards the membrane[10,11,30–32] (Fig. 1b,c). This binding involves Fc residues I253, T254, H310, H433 and H435, which mediate various hydrogen-bonded and salt bridge interactions with E115 and D130 on human FcRn[32,33] (Fig. 1b). The presence of imidazole side chains on histidine provides a pH-dependent switch whereby at pH 5–6 the group is positively charged, allowing for FcRn–IgG interaction, whereas at pH 7.4 it is neutral and the binding is lost[33–35]. In addition to the variability that exists within a given species at the level of IgG subclasses, allotypes, glycosylation or different Fab arms, mammalian FcRn and IgG orthologues have subtle amino acid differences that are the basis for the range of binding affinities observed within and between different species[36–38]. Notable examples are the lower binding affinity of human FcRn to human IgG3 (due to the presence of R435 instead of H435) and the inability of human FcRn to engage most mouse IgGs (except for weak binding to IgG2b)[36,39]. Adding further complexity is the fact that IgGs also bind antigens and interact with other receptors: for instance, the FcRn binding site for IgGs and the cytoplasmic Fc receptor tripartite motif containing 21 (TRIM21) overlap with each other[40]. In contrast, classical FcγRs bind to IgG at a distinct site[41], such that IgG can potentially engage both FcRn and FcγRs

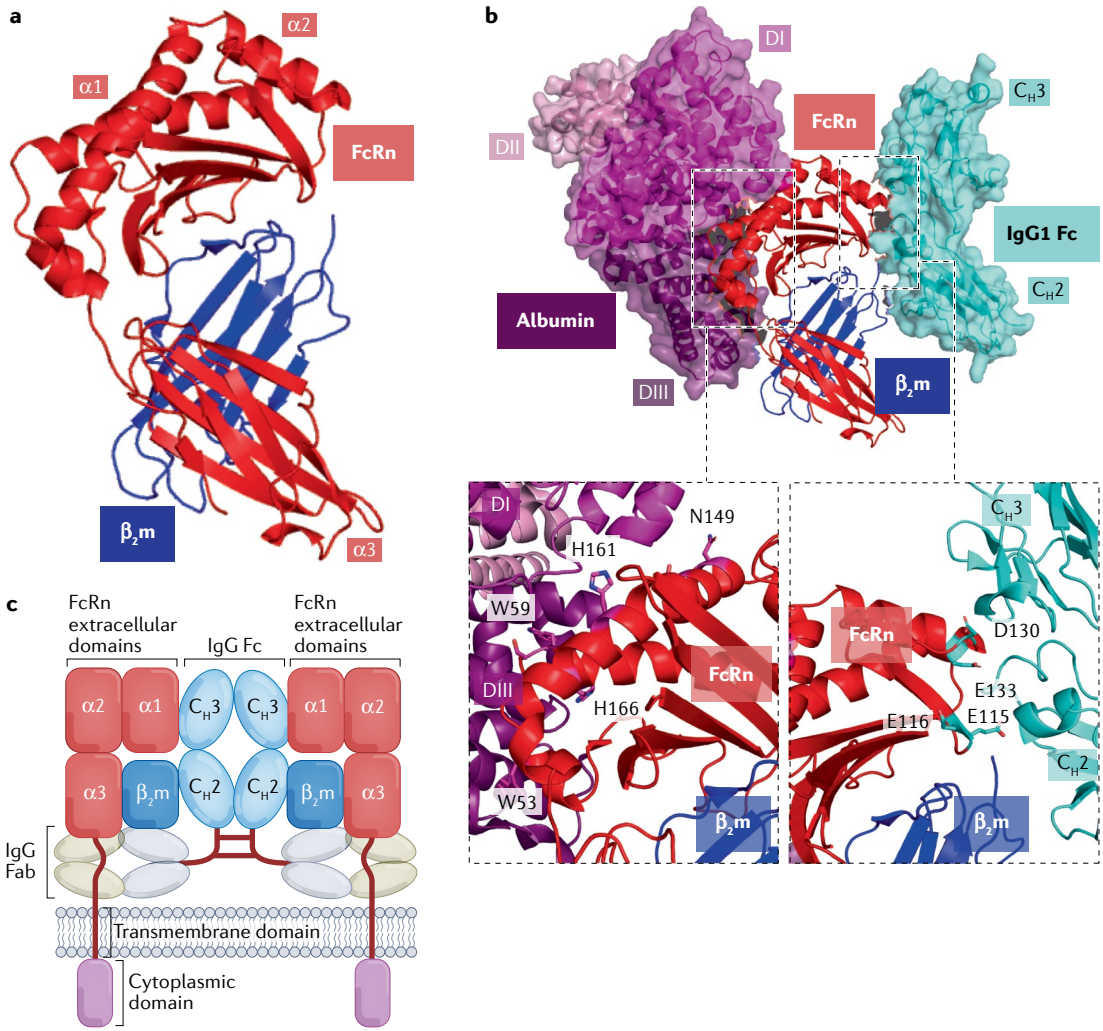


Fig. 1 | Structure of FcRn and its ligands. a, Ribbon diagram of the human neonatal Fc receptor (FcRn) heavy chain (red) with indicated α1, α2 and α3 domains, and β_2-microglobulin (β_2m; blue) light chain (Protein Data Bank (PDB) ID 1EXU). **b**, Ternary complex between human FcRn, human albumin (purple) and portion of human IgG1 Fc fragment (cyan) (PDB ID 4N0U). Albumin and half of the IgG1 Fc in ribbon and surface diagrams are shown with the indicated domains: albumin domains I (DI, purple), II (DII, light purple) and III (DIII, dark purple), and IgG1 Fc domains C_H2 and C_H3. Bottom-right inset box shows FcRn residues E115, E116, D130 and E133 binding with Fc residues H310 and H435 (not shown). Bottom-left inset box shows that, at acidic pH, the presence of H166 leads to intramolecular hydrogen bonding, which facilitates optimal binding of human FcRn residues W53 and W59 with albumin. Human FcRn residues S58 (not shown), N149 and H161 make various hydrogen-bonded interactions with albumin DI whereas FcRn residues W53 and W59 engage albumin DIII. **c**, Cartoon representation of two FcRn–β_2m heterodimers engaging monomeric IgG (in a T conformation), which presumably occurs on the membrane of acidified recycling endosomes. A short stalk, the transmembrane domain and the cytoplasmic domain are also depicted. Fab, antigen-binding fragment.

simultaneously[42,43]. Guided by this knowledge, IgG Fc engineering has allowed the development of IgG variants with different binding affinities to FcRn at acidic or neutral pH to enhance FcRn binding for extending IgG half-life (Box 2 and reviewed in[44]) or forcing the degradation of IgG antibodies; the best example is the IgG1$^{MST\text{-}HN}$ variant, also known as IgG1$^{YTE\text{-}KF}$ (M252Y/S254T/T256E/H433K/N434F), which has substantially higher binding to FcRn at acidic pH and retains binding at neutral pH[45], and is also known as an antibody that enhances IgG degradation (Abdeg). Indeed, the Fc fragment derived from this Abdeg, known as efgartigimod, is the first FcRn antagonist approved by the US Food and Drug Administration (FDA) (see below).

As IgG is a heterotetramer, two FcRn molecules can engage a single IgG[46,47], and physiological FcRn–IgG interactions are believed to occur at a 2:1 ratio[48,49] (Fig. 1c). Recently, through the use of negative stain electron microscopy, 2:1 receptor–ligand complexes were observed in which the Fab arms had a T-shaped or a mixed Y/T-shaped conformation (relative to FcRn)[50]. Whether the Fab arms can come in direct contact with FcRn has not been shown, although they certainly affect FcRn binding[51–56]. The evidence for such influences arose from observations that monoclonal antibodies possessing identical Fc domains yet distinct Fab domains exhibit different affinities for FcRn, resulting in modifications of their half-life[51,52]. Explanations for these "long-distance

Box 1

Genetic regulation of FcRn expression

The *FCGRT* promoter region contains up to five different repeats of 37-bp motifs that were designated as variable number of tandem repeats (VNTRs) 1–5[12]. Importantly, these VNTRs impact neonatal Fc receptor (FcRn) expression in human monocytes, with homozygous VNTR3/VNTR3 promoting 1.66-fold more FcRn mRNA than VNTR2/VNTR3 and increased IgG binding at acidic pH[12]. VNTR3/VNTR3 is the dominant variant found in ~84% of the human population, VNTR2/VNTR3 is the second most frequent, found in ~13% of the human population, and the remaining VNTRs (1,4 and 5) have ~3% prevalence[12,187–189]. In a later study of 476 patients with ovarian cancer, two additional VNTRs were identified (VNTR6 and VNTR8), in addition to a few rare single-nucleotide variations[189]. MicroRNA-3181, which was found in human liver samples, downregulates human FcRn mRNA and protein expression in A549, HEK293 and HepG2 cell lines[190]. Differential DNA methylation patterns at CpG sites of the regulatory regions of the *FCGRT* gene could explain variations in FcRn expression within the liver and myocardium[191].

perturbations" are still emerging, with studies indicating that these effects may be mediated by differences in the distribution of the positive charges in the Fab domains[53,54,56,57] and/or allosteric effects[50,55].

FcRn also engages albumin in a pH-dependent manner[58] (Box 3) and more recently has been described as a pH-independent receptor for two members of the Enterovirus B family: echoviruses and coxsackievirus A9[59–61] (Box 4).

Physiological functions of FcRn

The pH-dependent ligand binding is crucial for FcRn's passive and active immune functions. The passive functions involve recycling and transcytosis, which allow FcRn to salvage monomeric IgG from intracellular degradation and to transport it across cell layers; the active functions involve IgG-IC engagement and enhancement of innate and adaptive immunity.

Passive immune functions

FcRn as a recycling receptor. IgGs have a remarkably long half-life compared to other antibody isotypes. Although β_2m-deficient mice (*B2m*$^{-/-}$) were initially used to illustrate the role of FcRn as an IgG recycling receptor[62–64], the first direct evidence for FcRn's involvement in the recycling of IgGs and prevention of catabolism was described in 2003, upon generation of FcRn-deficient mice (*Fcgrt*$^{-/-}$)[65]. FcRn ablation resulted in significantly lower levels of serum IgG1, IgG2a, IgG2b and IgG3 (mice notably lack IgG4, which is specific to humans), with no differences in the levels of IgA and IgM[65]. The half-life of IgG1 is 9 days in wild type mice, whereas in FcRn-deficient mice it is dramatically lower at only ~1.4 days[65]. In humans, the half-life of serum IgG, but not of IgA or IgM, is similarly long at 20–23 days (except for R435 IgG3-carrying allotypes)[39,66], partly based on observations of a rare human disorder with β_2m deficiency called familial hypercatabolic hypoproteinemia[67]. Vascular endothelial cells, macrophages and monocytes, which are highly pinocytic, are responsible for the recycling of IgGs in mice, whereas B cells and DCs are not[17,68,69] (Fig. 2a). FcRn recycles IgGs by binding to the Fc region at acidic pH in the early endosome, and by releasing the IgG at neutral pH by exocytosis at the cell surface (Fig. 2b). This is a saturable process such that levels of IgG that exceed this protective activity are diverted to lysosomes for degradation[70,71].

Box 2

FcRn-based half-life extension of biologicals

As neonatal Fc receptor (FcRn) is responsible for the persistence of IgGs and albumin in the circulation, numerous therapeutic approaches have emerged over the past two decades to harness this FcRn-dependent function to extend the half-life of therapeutics via IgG Fc engineering, in addition to approaches using IgG Fc or albumin fusions. Although several factors influence IgG half-life, increasing the Fc fragment binding to FcRn at acidic pH, while maintaining its inability to interact at neutral pH, is essential[192,193]. This ensures proficient engagement within acidifying recycling endosomes and later proper release at the cell surface, where the pH is neutral[192,194–197]. For example, introducing YTE (also known as MST) or LS (M428L/N434S, also known as Xtend) mutations on an IgG1 scaffold have provided an up-to-fourfold increase in half-life in non-human primates and humans[194,196,198–200]. These alterations have been introduced into monoclonal antibodies targeting viral infections (respiratory syncytial virus, HIV-1 and SARS-CoV-2) or autoimmune diseases (psoriasis) and have reached clinical trials, or, because of the COVID-19 pandemic, have received Emergency Use Authorization by the US Food and Drug Administration (FDA). Another method to increase the persistence of short-lived proteins in the circulation is through fusion with albumin or the Fc region of IgG. This was originally done for Etanercept, the fusion of human IgG1 Fc with two TNF receptor II ectodomains, which received market approval from the FDA in 1998 for the treatment of rheumatoid arthritis[201]. Since then, ten more Fc fusion drugs have been approved by the FDA to treat a variety of diseases including autoimmunity (alefacept: LFA3–IgG1 Fc for psoriasis, which was discontinued; romiplostim: TPO–IgG1 Fc for immune thrombocytopenic purpura; abatacept: CTLA4–IgG1 Fc for rheumatoid arthritis; and rilonacept: IL-1R1/IL-1RAcp–IgG1 Fc for cryopyrin-associated periodic syndromes), anaemia (luspatercept: human ACTRII–IgG1 Fc), transplant rejection (belatacept: CTLA4–IgG1 Fc), haemophilia (eftrenonacog alfa: FIX–IgG1 Fc; efmoroctocog alfa: FVIII–IgG1 Fc), wet macular degeneration (aflibercept: VEGFR1–VEGFR2–IgG1 Fc) and colorectal cancer (ziv-aflibercept: VEGFR1–VEGFR2–IgG1 Fc).

The sorting of monomeric IgGs into FcRn$^+$ recycling endosomes soon after pinocytic uptake and the dynamics of exocytosis have been visualized through advances in microscopy techniques, mainly in endothelial cell lines and more recently in primary macrophages[72–76]. Like IgGs, small, monomeric human IgG-ICs are recycled and protected via FcRn (Fig. 2b) in haematopoietic cells in mice, suggesting a similar mode of trafficking; large, multimeric human IgG-ICs, on the other hand, are not efficiently recycled yet are degraded more rapidly when FcRn is absent[77] (Fig. 2c). In human cell lines, large multimeric human IgG-ICs are excluded from recycling sorting tubules and are instead mainly directed to FcRn$^+$LAMP1$^+$ lysosomes, which may be important for the antigen presentation functions of FcRn[74,77,78] (Fig. 2c; see below). Blockade of the IgG interactions with FcRn via FcRn blockers in humans also reduces serum IgGs and IgG-ICs, showing the physiological relevance of these observations in model systems[20,79,80]. More studies are needed to understand how FcRn directs monomeric IgGs and small IgG-ICs to recycling endosomes for prevention of catabolism while directing relatively large IgG-ICs to antigen presentation compartments and lysosomes for regulated degradation, and how the size of IgG-ICs determines each of these outcomes (see below).

FcRn as a transport receptor. In addition to its recycling function, FcRn has a fundamental role in maintaining the tissue distribution of IgGs by their transcytosis, which is the movement of IgGs across polarized endothelial cells and numerous types of epithelial cells. This was first studied in neonatal rodents, in which passive acquisition of IgGs from ingested maternal milk occurs through transcytosis across the intestinal epithelium[81,82]. Later, it was shown that FcRn was also capable of bidirectional transfer of IgGs in intestinal epithelial cell lines[83] and between the lamina propria and gut lumen in human FcRn transgenic adult mice[84,85] as well as at other locations (reviewed in[86]). Still, FcRn might exhibit a dominant vectoral direction of transport[87,88]. For example, endothelial FcRn at the blood–brain barrier has been proposed to mediate the unidirectional transport of IgGs out of the brain and into the blood, which may maintain the immune-privileged status of the brain[89,90]. Although the precise role of FcRn at the blood–brain barrier and other tissue interfaces is still emerging[89,91–93], it is now well recognized that FcRn can thus mediate unidirectional or bidirectional IgG transfer, which has important implications for the delivery of therapeutics and potentially of vaccines[94,95]. Here, we focus on the most evident human example: the passive acquisition of immunity in the offspring from the mother.

FcRn and passive immunity. The passage of maternal antibodies to offspring is an important evolutionary mechanism of protection that operates in mammals and birds[96]. In humans, the acquisition of maternal IgG occurs in utero, whereby most antibodies are transferred during the third trimester of pregnancy[97,98]. IgG1 antibodies are transferred with the highest efficiency, followed by IgG4, with IgG2 and IgG3 subclasses having the lowest efficiency[39,99,100]. Several factors contribute to this Fc-dependent unidirectional transport, and their precise elucidation and effect on therapies, infections and vaccination during pregnancy is still ongoing (Box 5). In the human hemomonochorial placenta, as the gestation proceeds, the extensive invasiveness of trophoblasts into uterine tissues allows their direct contact with maternal blood, which is believed to facilitate IgG passage given that the antibody must traverse only three layers — syncytiotrophoblasts, embryonic connective tissue and embryonic capillary endothelium[101] (Fig. 3). Indeed, the presence of FcRn has been amply demonstrated in human term placental trophoblasts, placental cell lines, cultured human placental epithelial cells and more recently in placental fetal endothelium and macrophages (Hofbauer cells)[22,23,102–110]. Outside of the direct evidence from mouse models, the ex vivo human placental transfer model was essential to illustrate the dominant role of FcRn in this process[65,111,112]. Using the latter approach, it was illustrated that modified human IgG1 variants that lack FcRn binding were not transferred into the fetal circulation, whereas another IgG1 variant (H433K/N434F) with enhanced engagement to FcRn was transported more efficiently[108,113,114]. Importantly, FcRn antagonism with an anti-FcRn monoclonal antibody in this setting showed fast receptor blockade with almost complete inability to transfer a model IgG1 antibody[115].

Box 3

FcRn as an albumin receptor

Albumin is the main circulatory carrier and regulator of plasma oncotic pressure. The interaction of albumin with neonatal Fc receptor (FcRn) is responsible for its long half-life (~21–28 days) and high concentration (35–55 g/L) in the circulation[58,67]. FcRn engagement of albumin is also pH dependent, occurring in mildly acidic environments[58]. Binding of albumin to FcRn occurs in a 1:1 ratio at the FcRn interface that is distal from the IgG binding surface, such that both ligands can engage the receptor at the same time[33,202]. This interface involves two FcRn tryptophan residues (W53 and W59) that interact with two hydrophobic pockets in domain III of albumin, in addition to FcRn's H166 residue (see Fig. 1b), which forms an intramolecular hydrogen bond necessary to maintain optimal W53/W59 loop orientation at acidic pH[30,33,203,204]. Albumin histidine residues (H464, H510 and H535) also contribute to the pH-dependent binding[205]. Although initially considered to be of a slightly weaker affinity, FcRn–albumin interactions may display an equivalent binding strength to that of FcRn–IgG interactions[206]. The detailed physiological consequences of FcRn–albumin engagement is still emerging, through the use of mouse models[68,69,207,208]. Thus, expression of FcRn in proximal tubule epithelial cells of the kidney nephron is suggested to be involved in the reabsorption of albumin from the ultrafiltrate[88,207,209]. In the liver, where hepatocytes are the unique site of albumin synthesis, FcRn expression ensures albumin delivery into the circulation[208]. Further, FcRn expression in endothelial cells and monocytes is responsible for albumin recycling and maintenance of its high levels in the circulation[68,69,210]. As a novel therapeutic approach, engineered albumin and albumin-fusion proteins are increasingly becoming well-accepted alternatives to engineered Fc and Fc fusions, which use FcRn functions without having the risk of engaging FcγRs, with factor IX–albumin fusion (albutrepenonacog alfa)[211] being a prime example.

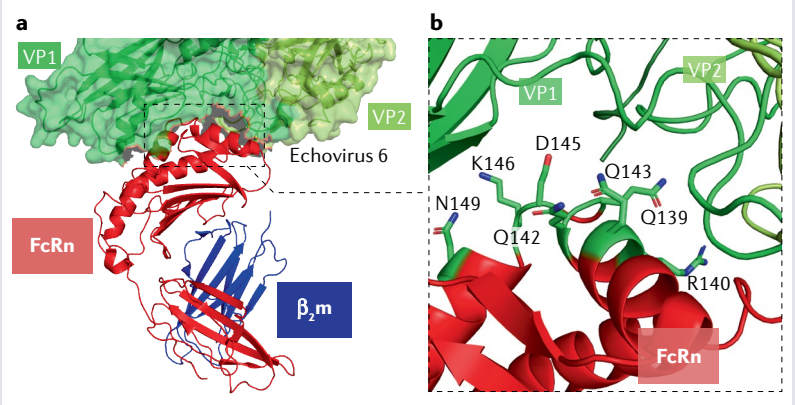
Active immune functions

Innate immunity. FcRn is expressed at high levels, along with FcγRs, at the cell surface and intracellularly in myeloid cells, where it participates directly in innate responses to IgG-ICs in a manner that is independent

Box 4

Pathogenic hijacking of FcRn

Echoviruses are single-stranded RNA viruses of the *Enterovirus* genus, which can cause viral hepatitis, meningitis, encephalitis and even death in neonates and infants[59]. In 2019, Morosky et al. discovered that human, but not mouse, neonatal Fc receptor (FcRn) is a pan-echovirus receptor[59]. They showed that echovirus (E11) infection occurs in neonatal mice expressing human FcRn, whereas wild type mice expressing endogenous mouse FcRn were protected[59]. Enterovirus B viruses, which include echoviruses, directly bind to FcRn at neutral pH, which may occur near the cell surface after a "hand-off" from the other viral receptor, CD55[60] (see the figure). Human cytomegalovirus (HCMV) can cause life-threatening infection in immunocompromised hosts through various immune evasion strategies such as via glycoprotein US11, which is known to hinder the expression of MHC class I molecules[212]. HCMV US11 has also been shown to target FcRn and cause its endoplasmic reticulum-associated degradation[213]. In this regard, FcRn-mediated antibody transcytosis was reduced, whereas IgG catabolism was increased in cell lines infected with HCMV or expressing FcRn and US11[213]. Interestingly, HIV may also "hijack" the immune response by using FcRn–IgG transcytosis, enabling the virus to be shed outside the body in genital secretions[214]. Although experiments were carried out in vitro, using human cell lines, IgGs from cervicovaginal or seminal fluids of people infected with HIV promoted transcytosis of clinical HIV isolates at acidic pH[214]. *Staphylococcus aureus* can potentially be a lethal opportunistic pathogen: staphylococcal protein A is a virulence factor that evades the humoral response by binding to the Fc region of IgGs, which coincides with the FcRn binding site, and thus prevents opsonophagocytic killing[42,215,216]. Similarly, streptococcal protein G binding to IgG overlaps with the FcRn binding site[217].



a, Cryogenic electron microscopy structures of human FcRn in complex with echovirus 6 nucleocapsid (Protein Data Bank IDs 6ILL, 6ILM). The icosahedral nucleocapsid consisting of viral protein 1 (VP1, green) and viral protein 2 (VP2, light green) are shown by surface and ribbon representation. Human FcRn α2 domain binds to echovirus 6 at a site between VP1 and VP2. **b**, FcRn α2 domain residues Q139, R140, Q142, Q143, D145, K146 and N149 mediate most of the interactions with VP1 residues.

of its roles in recycling and transcytosis[20,23] (Figs. 2 and 3). For example, the ability of IgG-ICs to promote pro-inflammatory cytokine production by innate immune cells involves FcRn (Fig. 4a). IL-12p35 mRNA production, phosphorylation of STAT1 and translocation of IRF1 and NF-κB subunit p65 to the nucleus in response to IgG-ICs depend on FcRn in mouse DCs and human monocyte-derived DCs[116]. Similarly, induction of IL-6 and TNF production by whole human blood exposed to IgG-ICs is FcRn dependent as it requires IgG binding to FcRn and can be pharmacologically blocked by an FcRn antagonist[20]. Further, FcRn cooperates with FcγRIIA, including its high-affinity (FcγRIIA^{H}) and low-affinity (FcγRIIA^{R}) allelic variants, in inducing these innate immune activities. Optimal responses necessitate the presence of both FcRn and FcγRIIA, which are presumed to function in a ternary complex that is bridged by an IgG-IC[43].

Tissue factor production by monocytes is required for the initiation of coagulation and is involved in thromboembolic diseases that are associated with IgG-ICs in many IgG-mediated autoimmune diseases[117,118], such as warm autoimmune haemolytic anaemia[119]. Whereas FcγRIIA and Toll-like receptors are known to promote tissue factor production, the role played by FcRn in this process has only recently been discovered[120] (Fig. 4a). IgG-ICs, including those derived from clinically relevant pathogenic antibodies, can induce primary monocytes to produce tissue factor and tissue factor-dependent factor Xa; this activity is disabled if the IgG-IC is unable to bind FcRn or FcγR and if FcRn is blocked[120]. Similarly, blockade of FcRn prevents human platelet factor 4-mediated antibody induction of pathogenic fibrin (clot) accumulation in a mouse model of heparin-induced thrombocytopenia that depends upon FcγRIIA[120,121].

Traditionally, activating FcγRs are well known to facilitate endocytosis and phagocytosis of IgG-ICs. It is therefore of interest that FcRn promotes the phagocytic uptake of IgG-opsonized *Streptococcus pneumoniae*, as shown in mouse *Fcgrt*$^{-/-}$ neutrophils and using a human IgG1^{H435A} variant with diminished FcRn binding[24] (Fig. 4b). These observations, along with the cytokine and tissue factor induction studies, illustrate that FcRn can work in collaboration with FcγRs in conducting various innate immune-related activities.

Adaptive immune interactions. IgG-bound antigen that is diverted by FcRn to the lysosome for degradation also promotes MHC class II antigen presentation to CD4^{+} T cells, both in vitro and in vivo[77] (Fig. 4c). Macrophage-associated MHC class II presentation of a model antigen ovalbumin (OVA) as either soluble IgG-ICs or as larger latex bead–IgG-ICs to OVA-specific CD4^{+} T cells also depends on FcRn; this suggests that endocytic (soluble IgG-ICs) or phagocytic (latex bead–IgG-ICs)

uptake of antigen is regulated by FcRn[122]. Likewise, FcRn blockade with a therapeutic antibody can inhibit the presentation of OVA within IgG-ICs to CD4$^+$ T cells by mouse DCs expressing human FcRn, indicating that these pathways are amenable to pharmacological blockade[20]. This has clinical relevance, as the ability of human monocyte-derived DCs to present a disease-related antigen (gliadin) associated with coeliac disease as an IgG-IC also depends on FcRn[77]. Further, FcRn in monocytic cells also determines the ability of FcγRIIA to mediate antigen presentation, as the levels of CD4$^+$ T cell stimulation are significantly decreased if the IgG-IC is unable to bind FcRn irrespective of the FcγRIIA allelic variant, further indicating co-operation with FcRn, as observed with innate immune responses[43].

Some DC subsets are specialized in delivering extracellular antigens to CD8$^+$ T cells in a process called cross-presentation[123]. FcRn enhances the ability of specific types of mouse DCs to cross-present antigen contained within an IgG-IC to CD8$^+$ T cells relative to that observed with the soluble antigen alone[78] (Fig. 4c). This allows the DC to robustly respond to low amounts of antigen bound by IgGs. FcRn enables the IgG-associated antigen to enter endosomal compartments that possess the proper conditions for conducting cross-presentation, including optimal acidification and oxidation and the presence of distinct proteins participating in these processes such as transporter associated with antigen processing (TAP)[78]. Such activities also involve prolonged retention of IgG-ICs within these intracellular organelles.

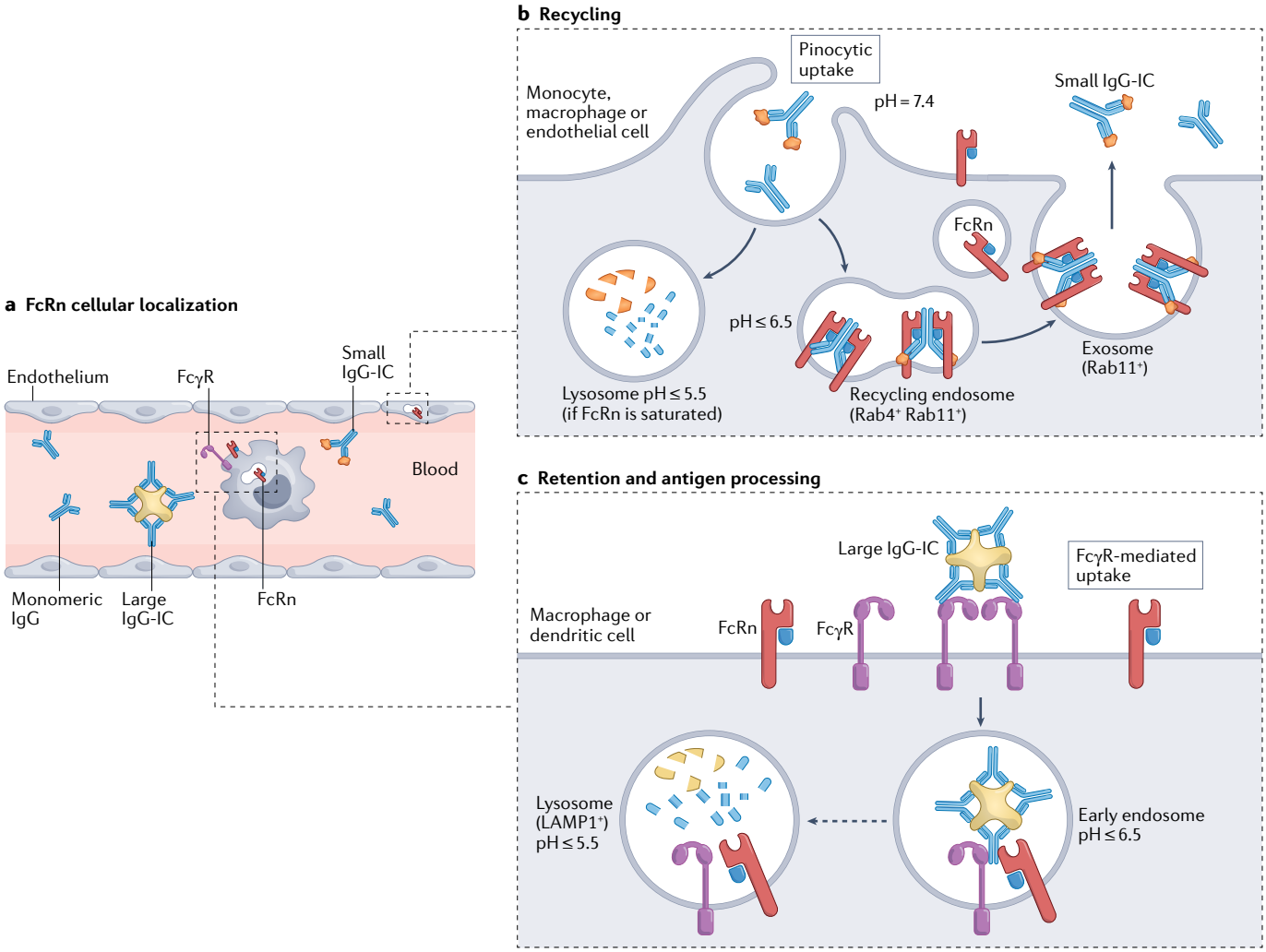


Fig. 2 | FcRn-mediated recycling provides a long half-life to monomeric IgG or small IgG immune complexes whereas multimeric IgG immune complexes are degraded. a, IgG recycling occurs within macrophages, monocytes and endothelial cells, based on mouse studies. **b**, Monomeric IgGs and small IgG immune complexes (IgG-ICs) consisting of a single antibody engaging two antigens are taken up by pinocytosis as they can not bind to neonatal Fc receptor (FcRn) at the neutral pH of the cell surface. Following the formation of an early endosome and its acidification, FcRn can bind to IgGs, which are diverted into recycling endosomes (Rab4$^+$Rab11$^+$) and exocytosed within Rab11$^+$ exosomes, where the IgGs or small IgG-ICs are released from FcRn at neutral pH, extending their half-life in the body, while FcRn is recovered for another round of recycling. When FcRn is saturated, the excess unbound antibody is degraded in the lysosome. **c**, FcRn retains and regulates the degradation of multimeric IgG-ICs. Multimeric IgG-ICs bind Fc receptors for IgG (FcγRs) on the cell surface (neutral pH), where they are taken up into endosomes by receptor-mediated endocytosis allowing for co-engagement with FcRn and FcγRs at acidic pH. The multimeric IgG-ICs are retained in a FcRn$^+$LAMP1$^+$ lysosomal compartment (pH ~5.5) enriched in antigen presentation machinery (dashed arrow). It is not well understood how FcRn differentiates between the recycling and retention pathways. LAMP1, lysosomal-associated membrane protein 1.

Box 5

Maternofetal transfer of IgGs: therapeutics, infections and vaccination

The role of neonatal Fc receptor (FcRn) in passive immunity has gained increased attention owing to the use of monoclonal antibody therapy before and during pregnancy, in addition to maternofetal vaccination and infections. However, current investigations that assess the contribution of FcRn specifically in this context are lagging mainly because FcRn-mediated transcytosis (occurring at the maternal–fetal interface) cannot be easily separated from FcRn-mediated recycling (occurring on the maternal and fetal sides) in addition to uncoupling the effects observed from FcRn-driven or FcγR-driven functions. Indeed, there is still considerable debate on the contribution of FcγRs to passive immunity, with data from different laboratories showing evidence for[218,219] and against[99,220,221] direct FcγR involvement in this process. In several autoimmune diseases that can affect gestation outcome, including inflammatory bowel disease, rheumatoid arthritis and psoriasis, medical treatment is often needed and its use in pregnancy is increasing[222]. In the case of anti-TNF therapy, some of the drugs administered to pregnant women were detectable in infants up to 1 year after birth[223]. Interestingly, data from mouse models indicate that antenatal or neonatal administration of antigen–Fc fusion proteins or antigens within an IgG immune complex can induce tolerance and protection from diseases via active and passive FcRn-mediated processes, as shown for asthma[224,225], type 1 diabetes[226], haemophilia[227] and food allergy[228]; in allergy, this involves FcRn-dependent induction of regulatory T cells. Vaccination (against tetanus, pertussis, influenza virus and SARS-CoV-2) during pregnancy serves to develop protection from serious disease not only in mothers, but also in the fetus and neonates, which has been exemplified by the SARS-CoV-2 pandemic[229,230]. Numerous studies have revealed several factors that can affect IgG transfer upon maternal vaccination or infection, such as (1) the timing between immunization or infection and delivery, (2) gestational age of the fetus, (3) total maternal IgG levels or those induced by a vaccine or pathogen, (4) IgG subclasses[231] or allotypes[232] and (5) type of infecting agent[230,233–235]; still, the role of FcRn in these processes has not been specifically investigated.

Human FcRn-mediated regulation of cross-presentation by DCs can be inhibited by a therapeutic anti-FcRn antibody[20]. In a colorectal cancer model, FcRn-dependent cross-presentation by DCs is highly protective (see later)[116]. Interestingly, FcRn can mediate IgG-IC-induced cross-presentation in the absence of FcγRs if the extracellular pH is acidic and thus permissive for IgG binding to FcRn on the cell surface, as might occur in certain disease states such as cancer and infection[43]. However, optimal cross-presentation occurs if both FcRn and FcγR are engaged[43]. By demonstrating the role of FcRn in promoting cytokine production or antigen processing and presentation pathways, these studies support an important role for FcRn in innate and adaptive immunity.

Pathophysiological functions of FcRn

FcRn–IgG interactions can either be beneficial or detrimental to the host: they offer the necessary protection from most infectious diseases and may participate in antitumour responses, yet FcRn interactions with pathogenic and self-reactive IgGs can promote autoimmune diseases.

Infectious diseases

FcRn participates in immune responses to several bacterial and viral infections, for which the direct evidence mainly comes from animal studies. For instance, in a mouse *Citrobacter rodentium* infectious colitis model, the presence of FcRn limited clinicopathological damage[85,124]. In the gastrointestinal tract, FcRn has a dual function wherein it is involved in the transcytosis of IgGs and also delivers antigen in the form of IgG-ICs from the intestinal lumen to myeloid cells for the induction of regional and systemic immune responses[84,85]. Similarly, FcRn dramatically lessens the severity of intestinal *Clostridioides difficile* infection in mice, but only when mice are first immunized with the toxin B carboxy-terminal domain, which is necessary for the generation of protective IgGs[125]. The levels of faecal, but not serum, IgGs specific for the carboxy-terminal domain were much higher in immunized mice that expressed FcRn, and antibody transfer to the lumen of the intestine is likely to be responsible for these effects[125]. In mice, infections by *Helicobacter heilmannii* and *Helicobacter pylori*, which are causative agents of stomach ulcers, are limited by FcRn[126]. The levels of both *H. heilmannii*-specific IgG and *H. pylori*-specific IgG antibodies were higher in the gastric juice of wild type mice than in *Fcgrt*$^{-/-}$ mice, whereas no differences in circulating antigen-specific IgG levels were seen. This suggests that FcRn in epithelial cells mediates local protection via its transport functions[126]. FcRn also plays a role in protection from Lyme disease-associated arthritis, caused by *Borrelia burgdorferi*. Specifically, FcRn-deficient mice exhibited increased joint histopathology and ankle-swelling post-intradermal infection, and had lower levels of serum *B. burgdorferi*-specific antibodies[127].

IgGs are the major subtype of antibody in vaginal secretions and are important for protection against viral sexually transmitted diseases, through FcRn-mediated transcytosis[128]. Herpes simplex virus type 2 (HSV-2) infection in mice can be prevented by passive transfer of anti-HSV-2-specific IgGs in wild type mice but not in *Fcgrt*$^{-/-}$ mice, probably through FcRn-mediated transport of antibodies across the vaginal epithelium[129]. FcRn plays a role in preventing Zika virus infection[130], as serum IgGs from infected (but not uninfected) mice injected intraperitoneally can confer protection from intravaginal Zika virus infection, and the virus-specific antibodies were found within the vaginal lumen[130]. FcRn transport of influenza virus haemagglutinin (HA)-specific antibodies may play a role in the neutralization of this virus as well in the lung, another organ that is a major site of IgG transport[131]. Interestingly, fusion proteins comprising Fc and viral-derived antigens, such as HA or HSV-2 glycoprotein, used in models of mouse vaccination were successful in enhancing transport of the antigen across the nasal epithelium, and might provide a novel FcRn-based immunization strategy[94,132].

In the infectious disease setting, the role of FcRn can also be detrimental depending on the specificity of the antimicrobial IgGs. In the case of *Chlamydia muridarum* infection, IgGs recognizing chlamydial extracellular antigens enhanced infection in a FcRn-dependent manner, whereas IgGs recognizing intracellular determinants were protective[133]. Indeed, accumulating data indicate that certain pathogens have evolved to use FcRn to their advantage (Box 4).

Cancer

FcRn is expressed by both tumours and tumour-infiltrating immune cells, where it can engage IgGs and albumin, affecting the outcome of disease in both mouse models and humans[105,134,135]. Compared with wild type mice, *Fcgrt*$^{-/-}$ mice develop more tumour lesions in a melanoma lung metastasis model in association with defects in NK cell development, maturation and impaired ability to degranulate and secrete IFNγ[136,137]. This is interesting as FcRn is not expressed by NK cells, so the observed phenotype might indirectly depend on interactions with other FcRn^{+} immune cells. FcRn expression also confers protection in both colorectal cancer and melanoma lung metastasis models in mice through activation of CD8^{+} cytotoxic T cells by FcRn-dependent cross-presentation of IgG-complexed antigen by DCs, which also secrete high amounts of IL-12[116]. Remarkably, in humans, high FcRn expression by CD11c^{+} DCs in colorectal cancer tissue is predictive of long-term survival and, as in mouse studies in vivo, FcRn expression by CD11c^{+} cells is positively correlated with the infiltration of CD8^{+} T cells into the tumour site[116]. These results are consistent with the survival analysis of patients with non-small-cell lung cancer wherein the average survival of *FCGRT* high-expressing patients in one of the cohorts tested was 62.0 months compared with 37.3 months in *FCGRT* low-expressing patients, with the majority of the *FCGRT* mRNA expression detected in immune cells[138].

Our understanding of the role that FcRn expression plays in the tumour cells themselves is still emerging. For instance, some tumours have been shown to downregulate FcRn expression[139,140], whereas others upregulate it[134]. Given that, besides IgGs, FcRn also engages albumin, both immune and non-immune activities of FcRn can be involved[58]. In this regard, FcRn downregulation might lead to reduced recycling and increased intracellular accumulation of albumin or albumin-carried cargo, which can provide an alternative source of energy to the tumour[139,141]. Understanding FcRn functions within the context of cancer biology is also leading to the development of new antitumour therapies or improved theranostics[142,143]. For example, engineered albumin that exhibits increased FcRn binding can be used to deliver cytotoxic drugs to tumour cells, such as doxorubicin[140]. Others have developed engineered antibodies with enhanced FcRn binding (Abdeg based) known as Seldegs (selective degradation of antigen-specific antibodies)[144] that when coupled to tumour antigens can be deployed to improve diagnostic imaging[145]. This approach showed promise in mouse models whereby excess levels of unbound radiolabelled diagnostic antibodies were reduced, resulting in decreased imaging background.

Autoimmunity

IgG-mediated autoimmune diseases represent a broad class of clinical conditions that result in chronic, incurable symptoms that potentially affect nearly every organ in the body. The autoantibodies that cause these diseases do so through several complex mechanisms, such as by direct cell lysis or by induction of pro-inflammatory mediators, which have been elegantly reviewed elsewhere[146]. IgG-mediated autoimmune diseases can be classified into two groups: the first includes diseases in which the specificity of the autoantibodies has been clearly identified and is directly involved in the pathogenesis of the disorder, such as myasthenia gravis (MG) and pemphigus-related disorders. The second encompasses complex autoimmune diseases such as inflammatory bowel disease (IBD), rheumatoid arthritis (RA) and multiple sclerosis (MS), in which the IgG antibodies are involved in a much broader range of immunological pathways[147,148].

The role of FcRn in these disorders was initially recognized in the 1990s through the use of *B2m*$^{-/-}$ mice, in which the absence of β_2m results in functional deficiency in FcRn, and ultimately in 2003 with the development of *Fcgrt*$^{-/-}$ animals[62–65,111,149,150]. In this way, it was shown that

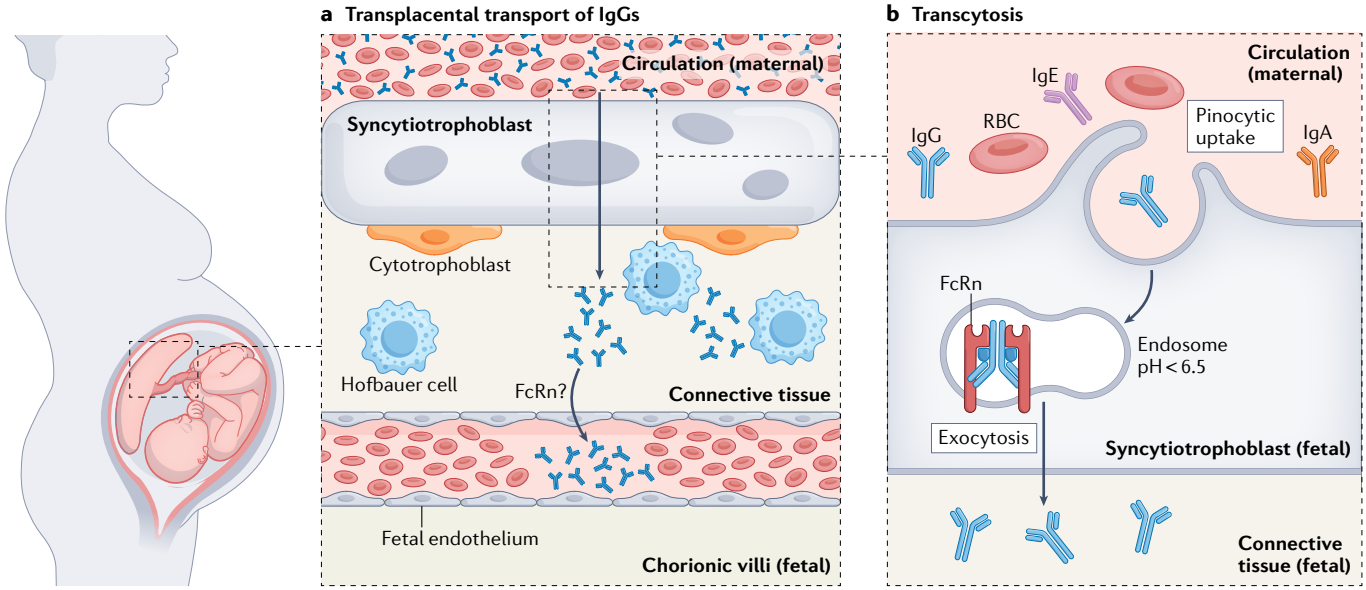


Fig. 3 | FcRn-mediated transplacental transfer of maternal IgG to the offspring. a, In humans, maternal and fetal circulations are separated by a single layer of polarized epithelium called the syncytiotrophoblast, which the antibody must intially pass to reach the fetus. **b**, Transport of IgGs is largely mediated through the presence of neonatal Fc receptor (FcRn) at this site. The initial step of internalization of maternal IgGs is thought to occur via fluid-phase pinocytosis. The formed vesicles containing IgGs then fuse with endosomes, where at a mildly acidic pH, the interaction with FcRn allows transport of the antibody to the basolateral membrane and release into the stroma at neutral pH. From there, IgG is hypothesized to passively diffuse and reach fetal endothelial cells; whether a similar FcRn-dependent transcytosis of IgG across fetal endothelium occurs in vivo is currently unknown. RBC, red blood cell.

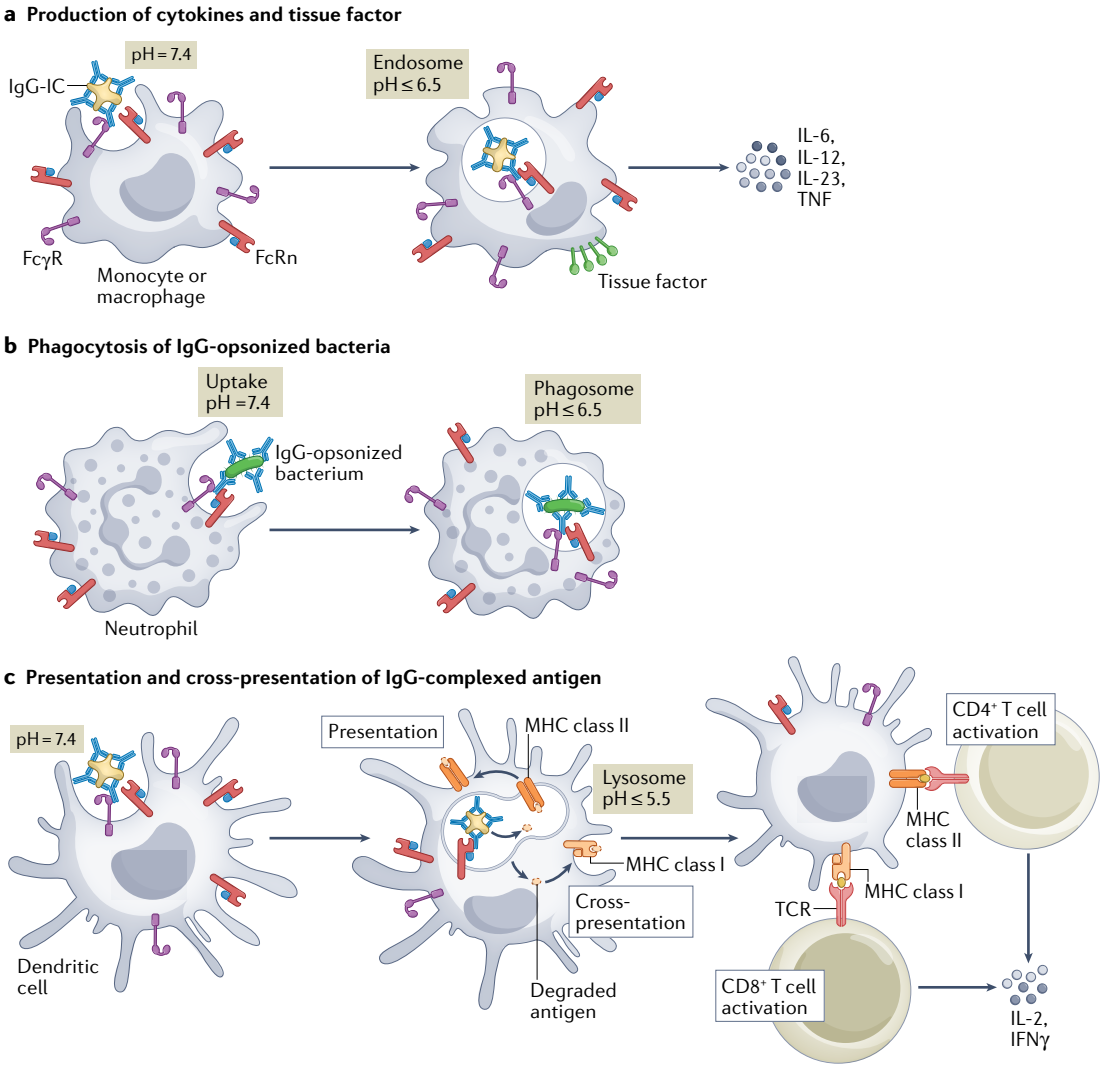


Fig. 4 | Active immune functions of FcRn in innate immune cells. a, IgG immune complexes (IgG-ICs) bind Fc receptors for IgG (FcγRs) on the cell surface at neutral pH. As the IgG-ICs are taken up into endosomes, they engage neonatal Fc receptor (FcRn) at a slightly acidic pH. In response to IgG-ICs, FcRn actively induces the production of pro-inflammatory cytokines IL-12, IL-23, tumour necrosis factor (TNF) and IL-6 by neutrophils, monocytes, macrophages and dendritic cells and the induction of tissue factor expression in monocytes and macrophages, through co-operation with FcγRs. **b**, FcRn promotes phagocytosis of IgG-coated *Streptococcus pneumoniae* in neutrophils. The IgG-opsonized bacteria bind to the neutrophil cell surface at neutral pH, likely by FcγRs, whereas FcRn binds to the IgGs at a slightly acidic pH and actively enhances phagocytosis. **c**, Once IgG-ICs are taken up by FcγR-expressing cells, FcRn enhances both antigen presentation to $CD4^+$ T cells by dendritic cells and macrophages, and antigen cross-presentation to $CD8^+$ T cells by dendritic cells. FcRn-associated antigen presentation by MHC class II occurs via degradation and peptide loading within the acidic endosome, whereas antigen cross-presentation by MHC class I occurs via a separate cytoplasmic and proteasomal processing pathway. The active participation of FcRn in these antigen-presenting pathways results in greatly enhanced T cell activation, expansion and production of IL-2 and interferon-γ (IFNγ) by the interacting immune cells, which probably further amplifies the immune response. TCR, T cell receptor.

autoimmune diseases such as pemphigus-related disorders required FcRn for the ability of autoantibody to cause disease[150,151]. Importantly, these studies also showed that FcRn was required for evincing the phenotype associated with complex diseases such as IBD and RA[152,153]. These pioneering studies led to the development of therapeutic approaches that impede FcRn function, which fall into three broad classes: engineered Fc fragments, antibodies and peptides. Here, we summarize some of the preclinical, proof-of-concept studies that represent the forerunners of current clinical approaches by focusing on a select group of classical and complex IgG-mediated autoimmune diseases.

Autoantibody-mediated diseases of the skin, such as epidermolysis bullosa acquisita (EBA), bullous pemphigoid and pemphigus, involve FcRn. FcRn-deficient mice were protected from blistering in type VII collagen-immunization or passive antibody transfer EBA models, and these mice had lower levels of type VII collagen-specific serum antibodies[154]. Mice that develop EBA can be successfully treated with FcRn

blockade, causing a reduction in circulating pathogenic anti-type VII collagen IgGs and IgG deposition in the skin[155]. *Fcgrt*$^{-/-}$ mice were also highly resistant to developing the blistering and pathological damage of pemphigus after treatment with rabbit anti-BP180, or with human anti-desmoglein 1 and anti-desmoglein 3 IgG antibodies, showing reduced neutrophil infiltration in the bullous pemphigoid model along with the expected reduction of pathogenic antibodies in the serum[151].

FcRn promotes the development and progression of diseases of the nervous system, including Guillain–Barré syndrome (GBS), MS and MG. In an antibody-mediated model of axonal GBS, reduced levels of pathogenic anti-glycan/ganglioside antibodies were found both in wild type mice therapeutically treated with IgG1$^{MST\text{-}HN}$ (or Abdeg) and in *Fcgrt*$^{-/-}$ mice, and there was improved nerve regeneration[156]. In experimental autoimmune encephalomyelitis (EAE) or antibody-mediated EAE models of human MS, Abdegs caused degradation of total IgGs, including disease-specific antibodies in the brain and spinal cord, and reduced disease activity. In addition, using the previously mentioned Seldeg approach, which consisted of an Abdeg Fc mutant fused with myelin oligodendrocyte glycoprotein (MOG), also reduced disease activity by exclusive degradation of pathogenic autoantibodies[157,158]. FcRn blockade also limited optomotor defects in a similar IgG-mediated EAE model of MS, reduced spinal demyelination and specifically altered macrophage infiltration into the spinal cord, with no differences in B cells, T cells or complement deposition[159]. In a passive transfer model of anti-muscle-specific kinase IgG4 from patients with MG, IgG1$^{MST\text{-}HN}$ effectively ameliorated muscle weakness, weight loss and improved calf compound muscle action potentials, which correlated with lowering of serum pathogenic antibodies[160]. Acetylcholine receptor-specific antibody-mediated MG was also ameliorated by FcRn blockade in both immunization and passive transfer models in rats, which coincided with a decrease in inflammatory macrophages[161].

Autoimmune haematological diseases, such as experimental immune thrombocytopenic purpura (ITP), can be therapeutically ameliorated through FcRn blockade. Prophylactic or therapeutic use of a mouse anti-FcRn antibody restored platelet numbers in the anti-CD41 passive transfer model of ITP and prophylactic blockade with an engineered Fc construct targeting both FcRn and FcγRs prevented the short-term loss of platelets in an ITP model involving passive transfer of a human anti-platelet antibody[121,162].

In the K/BxN passive serum transfer model of RA, which relies on mouse anti-glucose 6-phosphate isomerase (GPI) antibodies, FcRn is required for the development of disease[152]. Total serum antibodies and anti-GPI-specific IgG antibodies were substantially lower in *Fcgrt*$^{-/-}$ mice, which indicates that the lowering of pathogenic antibodies plays a major role in this disease model[152]. Abdegs, or IgG1$^{MST\text{-}HN}$, enhanced degradation of IgGs and dramatically lowered ankle swelling and histological joint damage in the K/BxN model[162,163]. Low-dose antibody blockade of mouse FcRn also ameliorated disease severity in mice expressing the low-affinity human FcγRIIA^{R} variant in the K/BxN model, but without lowering circulating total or pathogenic IgGs; this suggests that FcRn may promote RA through multiple mechanisms that potentially include cooperation with FcγRs in myeloid cells in addition to effects on IgG recycling[43]. Consistent with this, disease burden is also reduced by simultaneously targeting FcRn and FcγRs in the K/BxN and collagen-induced arthritis models, which show the important roles that each of these receptors have in promoting RA[162].

FcRn contributes to autoimmune kidney damage. In mice immunized with the non-collagenous domain of the α3 chain of type IV collagen, subepithelial ICs caused glomerular pathology and proteinuria, and an FcRn-inhibitor peptide was able to effectively limit disease[164]. Podocyte-specific FcRn promoted glomerulosclerosis and glomerular crescents in a nephrotoxic serum nephritis model, whereas it did not affect disease in an acute anti-glomerular basement membrane nephritis model[165]. Serum from patients with lupus nephritis or transplant glomerulopathy[166], but not from healthy donors, induced expression of calcium/calmodulin-dependent protein kinase 4 and CD86 in human podocytes in vitro, and this activation pathway was confirmed to cause lupus nephritis-associated damage and proteinuria in vivo[167,168], in an FcRn-dependent manner.

FcRn is also involved in the pathogenesis of IBD, as IgGs against commensal microorganisms and potentially autoantibodies can contribute to this disease[169,170]. A colitis model induced by bacterial flagellin immunization and dextran sulfate sodium treatment was more severe in wild type mice, with greater clinicopathological damage, than in *Fcgrt*$^{-/-}$ mice[153]. These differences were associated with the haematopoietic rather than the non-haematopoietic compartment in a study using bone marrow chimeras, although whether the effects observed were due to their role in extending IgG half-life versus regulation of a direct immune response was not assessed[153].

Altogether, these studies have clearly established a role for FcRn in the pathogenesis of infectious, neoplastic and autoimmune diseases. Moreover, it is likely that FcRn's involvement in these disorders occurs at many levels, including its activities in half-life extension (recycling), the delivery of IgG and/or IgG-ICs across tissues (transcytosis), the regulation of immune effector functions and its relationship with classical FcγRs. In addition, it is possible that FcRn also mediates its disease-related effects through expression in specific cell types at the site of tissue damage[171].

FcRn blockade in the clinic

Currently, several strategies are used to address the damage provoked by the presence of pathogenic IgGs and IgG-ICs, such as corticosteroids, immunosuppressants, B cell depletion (with rituximab), high doses of intravenous immunoglobulin and plasmapheresis[146]. Unfortunately, a large proportion of the patients affected by autoimmunity still have unmet clinical needs in addition to the high cost, broad effects on the immune system, and drug shortages associated with some of these treatments (such as plasma donations for intravenous immunoglobulin)[172]. More recently, an approach to prevent FcRn–IgG interactions has gained momentum. Five antibody-based drugs (batoclimab, efgartigimod, nipocalimab, orilanolimab and rozanolixizumab) have successfully passed through phase I clinical trials and have demonstrated their ability to reduce total circulating IgG levels (Supplementary Table 1), but not other types of antibodies, in healthy participants[20,173–176]. Most of these drugs have advanced to phase II/III trials for treatment of several classical IgG-mediated autoimmune diseases in which pathogenic IgGs are clearly involved, with published data in patients with ITP, MG or pemphigus (Table 1). Altogether, the available data from clinical trials in healthy subjects and patients with severe generalized MG, primary ITP and pemphigus indicate that blocking FcRn–IgG interactions in humans is well tolerated and results in disease amelioration, with reductions in circulating pathogenic IgGs, total IgGs and circulating ICs[20,79,173–183]. For example, in the largest study so far, efgartigimod treatment of people with generalized MG reduced pathogenic antibodies and significantly decreased disease severity (Table 1). There are indications emerging that these therapies may also be disease modifying by mechanisms that are yet to be understood but are probably linked to the cellular effects that

Table 1 | Clinical trials with FcRn antagonists

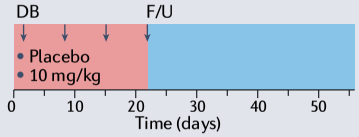
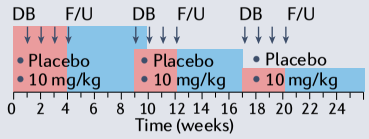
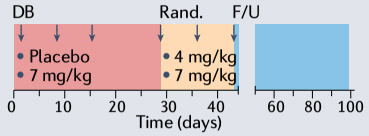
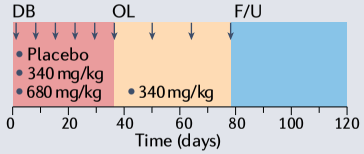
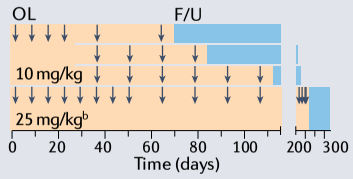
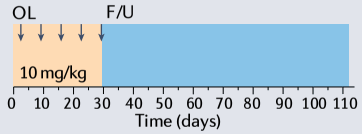
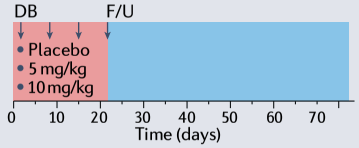
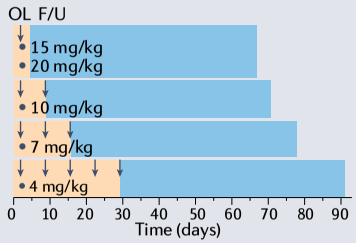
Autoimmune antibodies	Drugs (study identifier)	Phase	Number of patients (cohorts); route of administration	Study design	IgG levels	Disease clinical evaluation
Myasthenia gravis						
IgGs directed against the postsynaptic membrane at the neuromuscular junction[184]: Anti-AChR present in 80% of patients, mostly IgG1 and IgG3 Anti-MuSK present in 1–10% of patients, mostly IgG4 Anti-LRP4 present in varying frequencies of patients, mostly IgG1	Efgartigimod[178,179] (NCT02965573, NCT03669588, NCT03770403)[a]	II	24 (n_P=12, n_{D10}=12); intravenous		70.7% reduction of total IgG; 40–70% reduction of anti-AChR	QMG score reduced by 4 points; MG-ADL score reduced by 2 points; MGC disease severity score reduced by 5 points; MG-QoL15r scale reduced by 4 points
		III	167 (n_P=83, n_{D10}=84); intravenous		Period 1: 61.3% reduction of total IgG; 57.3% reduction of anti-AChR	QMG score reduced by 6 points; MG-ADL score reduced by 3 points; MGC disease severity score reduced by 7 points; MG-QoL15r scale reduced by 5.5 points
	Rozanolixizumab[177] (NCT03052751)	IIa	43 (n_P=22, n_{D7}=21, $n_{D7/7}$=10, $n_{D7/4}$=10, $n_{P/D7}$=11, $n_{P/D4}$=11); subcutaneous		DB: 60% reduction of total IgG; 44% reduction of anti-AChR Rand.: 68% reduction of total IgG; 65% reduction of anti-AChR	DB: QMG score reduced by 0.7 points; MG-ADL score reduced by 1.4 points; MGC disease severity score reduced by 1.8 points Rand.: QMG score reduced by 5 points; MG-ADL score reduced by 3 points; MGC disease severity score reduced by 6 points
	Batoclimab[183] (NCT04346888)	II	30 (n_P=9, n_{D340}=10, n_{D680}=11); subcutaneous		DB: 74% reduction of total IgG	DB: QMG score reduced by 7 points; MG-ADL score reduced by 2.5 points; MGC disease severity score reduced by 5 points; MG-QoL15r scale reduced by 0.64 points
Pemphigus						
IgGs of IgG4 subclass directed against desmosomes[185]: Anti-DSG1 present in patients with PF and with PV Anti-DSG3 present only in patients with PV Anti-DSC1, anti-DSC2 or anti-DSC3 present in <5% of patients with PV and with PF	Efgartigimod[80,182] (NCT03334058)	II	34 (n_{C1}=6, n_{C2}=5, n_{C3}=8, n_{C4}=15); intravenous		62–66% reduction of total IgG; 61% reduction of anti-DSG1; 49% reduction of anti-DSG3	C1–3: 75% reduction in PDAI activity score C4: 52% reduction in PDAI activity score

Table 1 (continued) | Clinical trials with FcRn antagonists

Autoimmune antibodies	Drugs (study identifier)	Phase	Number of patients (cohorts); route of administration	Study design	IgG levels	Disease clinical evaluation
Pemphigus (continued)						
	Orilanolimab[79] (NCT03075904)[c]	Ib/II	8; intravenous		57.6% reduction of total IgG; 55.6% reduction of total circulating IgG-ICs; 26.3% reduction of anti-DSG1; 5.7% reduction of anti-DSG3	23.6% reduction in PDAI activity score
Immune thrombocytopenic purpura						
IgGs mainly of IgG1 subclass directed against platelet membrane glycoproteins in 50–60% of patients[186]	Efgartigimod[181] (NCT03102593)	II	38; (n_P=12, n_{D5}=13, n_{D10}=13); intravenous		DB: 60.4–63.7% reduction of total IgG	Proportion of patients ≥50×10^9 platelets per litre for more than 10 days: D5: 46.2%; D10: 30.8%; P: 0% Patients with decreased bleeding-related events: D5: 46.2% to 7.7%; D10: 38.5% to 7.7%; P: 33.3% to 25%
	Rozanolixizumab[180] (NCT02718716)	II	66; (n_{D20}=12, n_{D15}=12, $n_{D10\times2}$=12, $n_{D7\times3}$=15, $n_{D4\times5}$=15); subcutaneous		63.8–43.6% reduction of total IgG	Proportion of patients ≥50×10^9 platelets per litre overall visits: D20: 54.5%; D15: 66.7%; D10×2: 45.5%; D7×3: 35.7%; D4×5: 35.7%

For simplicity, the greatest reported decreases are represented in the table. Clinical trials of neonatal Fc receptor (FcRn) antagonists in various autoantibody-enhanced diseases: chronic inflammatory demyelinating polyneuropathy (NCT04280718, NCT04281472, NCT05327114, NCT05014724, NCT04051944 and NCT03861481); bullous pemphigoid (NCT05267600); neuromyelitis optica spectrum disorder (NCT04227470); thyroid eye disease (NCT05015127); warm autoimmune haemolytic anaemia (NCT05221619 and NCT04119050); rheumatoid arthritis (NCT04991753); primary Sjogren syndrome (NCT04968912); lupus nephritis (NCT04883619); systemic lupus erythematosus (NCT04882878); myelin oligodendrocyte glycoprotein antibody-associated disease (NCT05063162); and severe haemolytic disease of the fetus and newborn (NCT03842189 and NCT03755128). AChR, acetylcholine receptor; DB, double blind (light red); DSC, desmocollin; DSG, desmoglein; F/U, follow-up (light blue); IC, immune complex; LRP4, low-density lipoprotein receptor-related protein 4; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; MGC, Myasthenia Gravis Composite scale; MG-QoL15r, revised 15-item Myasthenia Gravis Quality-of-Life scale; MuSK, muscle-specific kinase; OL, open-label (light orange); PDAI, pemphigus disease area index; PF, pemphigus foliaceus; PV, pemphigus vulgaris; QMG, quantitative myasthenia gravis; Rand., randomized; ↓, administration. Patient cohorts: C1, cohort 1; D4×5, dose 4 mg/kg given five times; D5, dose 5 mg/kg; D7, dose 7 mg/kg; D7×3, dose 7 mg/kg given three times; D7/4, dose 7 mg/kg followed by 4 mg/kg; D7/7, dose 7 mg/kg followed by 7 mg/kg; D10, dose 10 mg/kg; D10×2, dose 10 mg/kg given twice; D15, dose 15 mg/kg; D20, dose 20 mg/kg; D340, dose 340 mg/kg; D680, dose 680 mg/kg; P, placebo; P/D4, placebo followed by dose 4 mg/kg; P/D7, placebo followed by dose 7 mg/kg. [a]Approved by the FDA and the Pharmaceuticals and Medical Devices Agency (PMDA) for the treatment of generalized MG. [b]Received until achievement of end of consolidation. [c]Discontinued.

Box 6

FcRn blockade in diseases involving maternal transfer of pathogenic IgGs

Despite the prevailing beneficial role of maternal IgGs in neonates, several maternal conditions result in the transfer of pathogenic antibodies. Such transfer occurs in alloimmune and IgG-mediated autoimmune diseases, and in these instances, therapies antagonizing neonatal Fc receptor (FcRn) to prevent placental pathogenic antibody transfer are progressing to clinical trials. Notably, in mice with partial FcRn deficiency, or more importantly with FcRn blockade, considerable effectiveness was demonstrated in treating models of fetal and neonatal immune thrombocytopenia purpura[236,237], anti-NMDA receptor encephalitis[238] and arthrogryposis multiplex congenita[239]. In the arthrogryposis multiplex congenita model, the administration of FcRn antagonist to pregnant dams infused with human acetylcholine receptor-specific antibodies resulted in nearly significant decreases in pathogenic antibodies in the dams, and a major decrease of these antibodies in the fetuses[239]. Therefore, in the setting of passive immunity, FcRn blockade might be especially effective as it could lead to a decline of pathogenic antibodies in the fetus not only via inhibition of FcRn-mediated transcytosis but also via their FcRn-mediated maternal and fetal recycling. Remarkably, in the ex vivo human placental transfer model, the FcRn-blocking antibody was not efficiently transported across the placenta[115]. This suggests that the FcRn antagonist would be present in maternal circulation and at the placental interface but would not pass to great extent into fetal circulation. Still, besides removing pathogenic autoantibodies, this approach could also result in general depletion of fetal or neonatal protective IgGs and render the offspring more susceptible to early life infections, which needs to be assessed in future studies and clinical trials.

FcRn blockade has on disease-promoting immune cells[80]. Consistently, the observed treatment-emergent adverse events have been mild to moderate and generally comparable between patients in placebo and drug treatment groups, with the most frequent adverse event being headache. In December 2021, the first FcRn blocker was approved in the USA by the FDA, followed by similar approval in Japan, for the treatment of MG.

Blockade of FcRn–IgG interactions in humans is currently being evaluated in children with generalized MG (NCT05374590, NCT04833894); in pregnant women, to prevent transfer of pathogenic antibodies to the fetus (NCT03842189, NCT03755128, Box 6); and to treat numerous other autoimmune diseases (Table 1). All drugs in this class are associated with prolonged hypogammaglobulinemia and thus concurrent depletion of protective antibodies alongside the pathogenic ones, which could result in increased susceptibility to infections. The ongoing phase III trials with greater numbers of patients and longer exposure to the FcRn antagonists will provide a much clearer and needed understanding of the impact of FcRn blockade in humans. Nonetheless, FcRn blockade is now demonstrated to be a novel, effective therapeutic strategy to curtail autoimmune diseases associated with the presence of pathogenic IgGs.

Conclusions

Since the pioneering predictions of a transport and protection receptor by F.W. Rogers Brambell (Supplementary Fig. 1) in the 1960s, the studies over the past 30 years have allowed FcRn to gain a prominent place in numerous therapeutic approaches that involve leveraging its relationship with its two ligands: IgG and albumin. The translation of these insights includes the engineering of therapeutic antibodies and Fc fusion proteins, the development of engineered albumin molecules as carrier proteins and now the successful development of FcRn blockers. As the scientific community extends its understanding of FcRn biology and expands the use of these current approaches, many other therapeutic opportunities are likely to arise in this field.

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Author contributions

M.P., L.K.K. and A.G. researched data for the article and together with R.S.B. wrote the manuscript.

Competing interests

R.S.B. had equity interests in Syntimmune Inc., a company developing therapeutic agents to target FcRn. Syntimmune Inc. was a wholly owned subsidiary of Alexion Pharmaceuticals Inc., which was acquired by AstraZeneca. M.P., L.K.K. and A.G. declare no competing interests.

Additional information

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