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Brief Reviews

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# FcRn: The Architect Behind the Immune and Nonimmune Functions of IgG and Albumin

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**The neonatal FcR (FcRn) belongs to the extensive and functionally divergent family of MHC molecules. Contrary to classical MHC family members, FcRn possesses little diversity and is unable to present Ags. Instead, through its capacity to bind IgG and albumin with high affinity at low pH, it regulates the serum half-lives of both of these proteins. In addition, FcRn plays an important role in immunity at mucosal and systemic sites through its ability to affect the lifespan of IgG, as well as its participation in innate and adaptive immune responses. Although the details of its biology are still emerging, the ability of FcRn to rescue albumin and IgG from early degradation represents an attractive approach to alter the plasma half-life of pharmaceuticals. We review some of the most novel aspects of FcRn biology, immune as well as nonimmune, and provide some examples of FcRn-based therapies.** *The Journal of Immunology*, **2015, 194: 4595–4603.**

It was more than 120 years ago that Paul Ehrlich described the ability of maternal Abs to cross to offspring and protect them from infections in early life (1). From the available studies, it was then recognized that the acquisition of this passive immunity varied, depending on species. For instance, in humans and rabbits, Ab transfer occurred mainly before birth (antenatally), either transplacentally or via the yolk sac, respectively. However, in ruminants, horses, and pigs, postnatal transmission took place: Abs were transferred in colostrum or milk and were then absorbed transintestinally. In mice, rats, dogs, and cats, Ab transfer occurred both before and after birth, being more predominant in the neonatal period (2). Nonetheless, it was unknown whether all types of globulins were transferred, how they were transported, and whether identical, equivalent, or diverse transfer systems were operating in different species. In the 1950s and 1960s, by studying these phenomena, F.W. Rogers Brambell and colleagues showed that γ-globulins (consisting mostly of Igs), in particular, were selected for transmission, whereas most other proteins from maternal circulation were not (3). Further, it was recognized that such transfer was completely dependent on the Fc region of Ig and not on the Fab region (4). Brambell also investigated the fate of γ-globulins outside of pregnancy, reflecting on their long persistence in adult circulation (~20 d versus ~5 d for most other plasma proteins) and the characteristics of their elimination. He recognized that the long half-life of Ig required the Fc region and that very rapid elimination occurred upon high-dose administration, indicating that a saturable rescue process was involved (5, 6). Thus, Brambell postulated that a singular receptor may control both the transport of IgG during early life and the protection of IgG from catabolism in later life. Concurrently, Hermann E. Schultze and Joseph F. Heremans, observing fractional catabolic rates of different serum proteins, made similar predictions about the existence of an albumin-specific protection receptor (7).

Next, in parallel to the demonstration of Fc-dependent in utero rabbit Ab transfer, neonatal transmission of only IgG across the intestinal mucosa in neonatal rats was defined at the functional and biochemical levels (8). In the 1970s, the proximal intestine was identified as the main site of transmission of passive immunity in neonatal rats (9). Subsequently, it was shown that this neonatal FcR (FcRn) of the rat or human intestine preferentially bound IgG under acidic conditions (8, 10). In the acidic environment typical for the duodenum and jejunum during early life, IgG was bound by FcRn on enterocyte surfaces, endocytosed, and transcytosed, traveling from the lumen of the intestine to the basolateral side, where it was released at physiological pH (Fig. 1B) (11, 12). Following the purification of the heterodimeric receptor consisting of H chains (p51) and L chains (p14) from rat enterocytes, cloning of the FcRn was achieved in 1989 (13, 14). During the same period, the initial observations on the cellular and temporal expression of FcRn were extended. Crystallization of the receptor and the identification of

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Abbreviations used in this article: DC, dendritic cell; FcRn, neonatal FcR; IC, immune complex; $\beta_2$m, $\beta_2$-microglobulin; PTC, proximal tubular cell; $T_C1$, T cytotoxicity 1; WT, wild-type.



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physical domains and amino acid residues responsible for Fc binding were accomplished rapidly thereafter (15–17). In the 1990s, the demonstration that animals deficient in the gene encoding the p14 L chain did not express the p51 H chain, were unable to acquire IgG from maternal milk, and had low IgG circulating levels undeniably demonstrated that the receptor responsible for IgG protection and fetal/neonate transfer were the same and only receptor: FcRn (18–20).

Albumin possesses an equally long half-life (~20 d) in circulation and the existence of an albumin protection receptor also had been hypothesized. Although several receptors able to bind albumin exist, such as cubulin and megalin, none of them could account for the long albumin persistence (21). Because it was subsequently shown that FcRn binds albumin at acidic pH, prolonging its half-life in the circulation, FcRn was recognized as the receptor responsible for rescuing albumin from destruction (22). In support of this conclusion, the identification of patients with defective FcRn function due to p14 L chain deficiency or the genetic deletion of the p51 H chain in animals clearly illustrated that this resulted in the reduction of both albumin and IgG levels in the circulation (23, 24).

Recent years have brought forth several important advances in the study of FcRn biology. These include the recognition that FcRn expression continues after the neonatal period and is more widespread than initially suspected (25). Equally, in polarized epithelial cells FcRn is uniquely responsible for the bidirectional transcytosis of IgG, in contrast to the polymeric IgR that transports polymeric IgA and IgM unidirectionally (26). This is critically important to the immune responses at barrier surfaces that contain IgG. Further, FcRn is now recognized to exhibit significant expression throughout the hematopoietic system, notably in myeloid cells (27). Such targeted expression endows FcRn$^+$ cells with particular function: to distinguish between monomeric IgG and multimeric IgG–immune complexes (ICs). The former recognition results in protection from degradation and the maintenance of serum IgG levels, whereas the latter initiates routing of the IgG–IC for breakdown in Ag-presentation compartments that leads to improved MHC class I and II presentation and the production of inflammatory cytokines (18, 28–30). The insights into the biology of FcRn over the last 60 y are also now being converted into new therapeutic approaches for several diseases. This review summarizes these recent advances and their implications.

### *General aspects of FcRn: from gene to protein*

The *FCGRT* (*Fcgrt*) gene is encoded on chromosome 19q13 in humans and 7 in mice (31–33). Orthologs have been

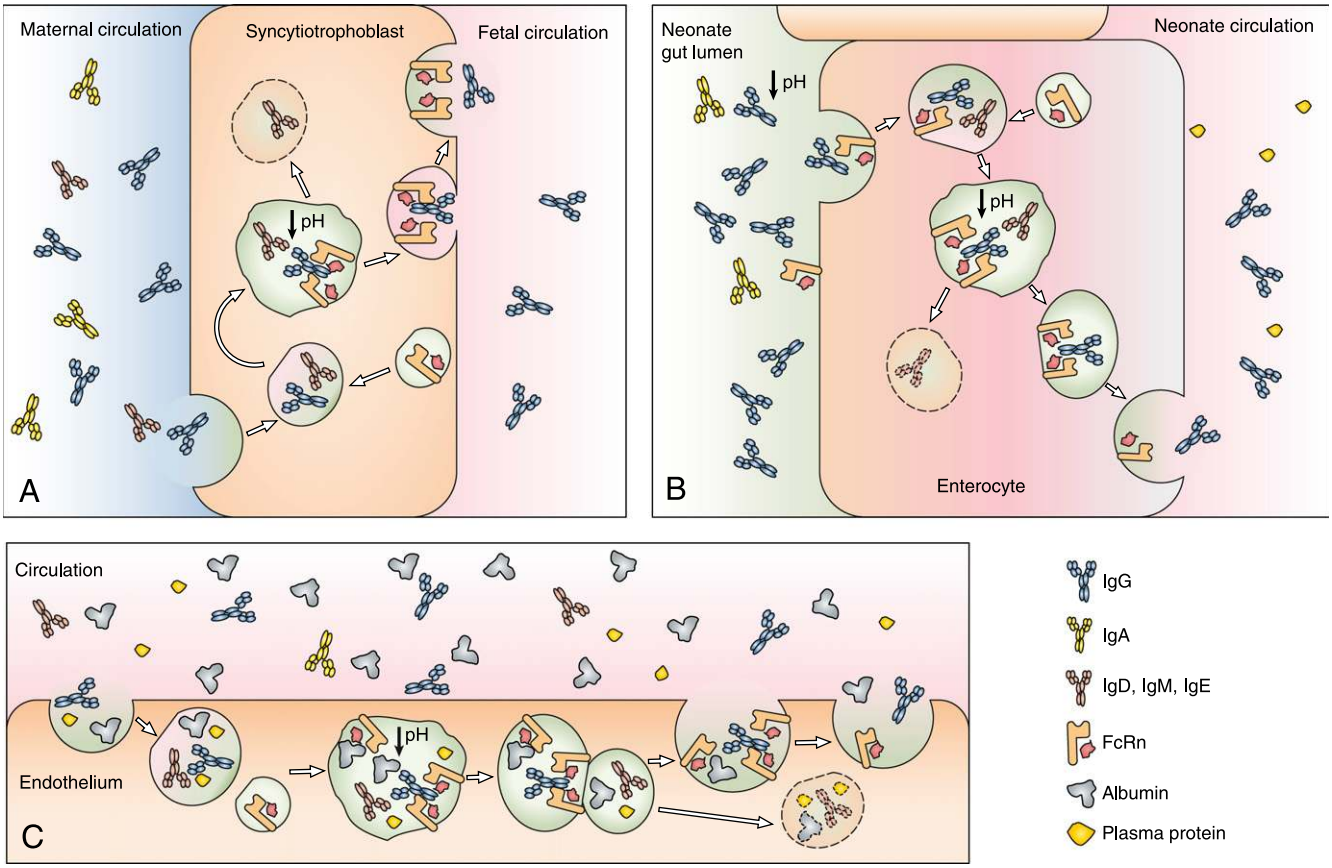


**FIGURE 1.** (**A**) Transport of IgG across the placenta in humans or fetal yolk sac of rabbits. In the endoderm of the fetal yolk sac, IgG is internalized by fluid-phase endocytosis and encounters FcRn in early endosome. (**B**) Transport of IgG across the intestine in rodents or ruminants. In newborn rats, IgG is taken up by fluid-phase endocytosis or through binding to FcRn at the apical cell surface of enterocytes. This enables active FcRn-mediated transport of IgG across the cell and its subsequent release on the opposite, extracellular side at neutral pH. In such circumstances, FcRn transcytosis exhibits a dominant vector of transport from apical to basolateral directions, which likely reflects concentration and pH gradients, as well as cell-dependent factors. (**C**) The catabolism of IgG (and potentially albumin) by FcRn in endothelial cells or hematopoietic cells (not shown here). Serum IgG is internalized by fluid-phase endocytosis and binds to FcRn in an acidic endosomal compartment. FcRn then recycles IgG back into the neutral pH milieu of the circulation, thus extending its serum half-life. IgGs not bound to FcRn, because of levels that exceed FcRn capacity or other serum proteins, are destined for lysosomal degradation.

identified broadly in numerous mammalian and marsupial species (34, 35). The human *FCGRT* encoded receptor shares overall 66% homology with mouse FcRn, whereas *Fcgrt* is highly conserved between mice and rats. The allelic diversity of *FCGRT/Fcgrt* gene is low, with few polymorphisms identified (31–33). Of note, five alleles of variable number of tandem repeats (*VNTR1–5*) in the 5′-flanking region of *hFCGRT* have been described, with *VNTR2* and *VNTR3* being the most common (7.5 and 92% in whites and 3.2 and 96.8% in Japanese, respectively) (36, 37). Presence of the *VNTR3* variant results in higher *FCGRT* transcriptional activity compared with the *VNTR2* allele, yet no significant effect on materno–fetal IgG transfer or on the elimination of therapeutic Abs has been observed (38, 39). *FCGRT* encodes MHC class I–like α, H chain (p51) that noncovalently associates with L chain (p14), also known as $\beta_2$-microglobulin ($\beta_2$m), forming a heterodimer (13). The reported molecular mass of the α-chain varies from 45 to 55 kDa, depending on the species or cell type from which it is isolated and relates mostly to variability in glycosylation with a single *N*-glycosylation site in human FcRn compared with three in rodent FcRn (40). FcRn shares high sequence and structural homology with MHC class I molecules; however, it is encoded outside of the *HLA* or *H-2* loci and is nonpolymorphic (31, 41). Thus, FcRn is a type I glycoprotein consisting of α1, α2, α3 extracellular domains, a transmembrane region, and cytoplasmic tail. The α1, α2 domains form a narrow groove that is unable to present peptides but, nonetheless, in conjunction with the α3 domain and $\beta_2$m, form the ligand-binding regions (13, 16).

FcRn expression is now recognized to be widespread, occurring throughout life. FcRn is expressed by a wide variety of parenchymal cell types in many different species. These include vascular endothelium (including the CNS), most epithelial cell types, such as placental (syncytiotrophoblasts), epidermal (keratinocytes), intestinal (enterocytes), renal glomerular (podocytes), bronchial, mammary gland (ductal and acinar), retinal pigment epithelial cells, renal proximal tubular cells (PTCs), hepatocytes, and melanocytes, as well as cells of the choroid, ciliary body, and iris in the eye (42, 43). FcRn is also widely expressed by hematopoietic cells, including monocytes, macrophages, dendritic cells (DCs), neutrophils, and B cells, where, in contrast to polarized epithelial cells, it is detected in significant quantities on the cell surface (27). In epithelial cells, which possess distinct apical and basal membranes, FcRn is predominantly intracellular, with a variable distribution along the vesicular network and cell surface in a cell- and species-specific manner (44). For instance, a greater quantity of FcRn has been observed in the apical regions of syncytiotrophoblasts and rodent enterocytes or primary renal PTCs, whereas in model polarized cells, such as MDCK cells, human FcRn is predominantly expressed basally, including expression at the basolateral surface (45). This differential distribution has been attributed to the presence of dileucine and tryptophan motifs and several serine phosphorylation sites within the cytoplasmic tail, as well as the glycosylation status of the extracellular portion of the receptor (40, 45–47). The variable cellular localization of the receptor also affects the direction of IgG transport: in transfected model systems and cell lines, apical-to-basal transcytosis is greater with rodent FcRn in comparison with human FcRn, where basal-to-apical transport dominates (45, 47).

FcRn expression is also temporally and developmentally modulated. During fetal life, FcRn expression in the syncytiotrophoblasts of the placenta is responsible for passive IgG transfer (Fig. 1A). In rodents during the first weeks of life, the receptor is present at high levels in proximal intestinal epithelium, coinciding with ingestion of mother's milk (Fig. 1B), and it is rapidly downregulated after weaning (12, 48). In contrast, FcRn expression in human enterocytes is lower than observed in neonatal rodents, but it does not decrease with age (26, 49). Further, exposure of epithelial cells, human THP-1 (macrophage-like) cells, or human PBMCs to TNF-α, LPS, or CpG induces a significant increase in FcRn expression in an NF-κB–dependent manner, whereas IFN-γ priming results in FcRn downregulation (50, 51). These results suggest that FcRn expression can be modulated by the immunological context of the surrounding milieu. Whether additional modes of spatiotemporal regulation of FcRn expression, in humans or rodents, occur is unknown.

### *The ligands of FcRn*

FcRn binds IgG and albumin at acidic pH, which is characteristic of early and late endosomes, the proximal intestine during neonatal life, and, potentially, the extracellular milieu associated with inflamed tissues (52). Albumin is the most abundant protein in mammalian plasma (~65% of the circulating proteins); it transports many endogenous and exogenous molecules, maintains colloidal osmotic pressure, and exerts antioxidant functions (53). Albumin is a 65–70-kDa protein consisting of three globular domains (DI, DII, and DIII). More than 60 variants of human albumin have been identified (53). Some, like the Casebrook variant, contain a single point mutation that decreases its affinity for FcRn (54). Likewise, IgGs represent the second most abundant protein in serum and are the most frequent Ig isotype found in the circulation. Of the four IgG subclasses in humans (IgG1, IgG2, IgG3, and IgG4), binding affinity to FcRn ranges from 20 nM (IgG1) to 80 nM (IgG4) (55). IgG3, with a longer hinge region relative to other IgG subclasses, has the lowest potential to bind FcRn and possesses a half-life of only 9 d in circulation (56). In mice, a similar range of affinities among the IgG subclasses (IgG1, IgG2a, IgG2b, IgG3) to bind FcRn was demonstrated (57). Several polymorphisms and allotypes of the human IgG H chain exist but whether these have differential binding to FcRn is unknown (58). Changes in the CDR of IgG also were reported to affect FcRn binding, even though these are distant from the FcRn binding site (59, 60). Furthermore, variation in binding specificity is seen between FcRn orthologs. Although rat and mouse FcRns are more liberal in their ability to bind IgG from different species (including human, rabbit, mouse, and bovine), human FcRn mainly interacts with human, rabbit, and guinea pig IgG (61). Such disparity also was illustrated for albumin binding: rodent FcRn binds weakly to rhesus monkey or human albumin compared with strong binding to mouse and rat albumin, whereas human or rhesus monkey FcRn binds more strongly to mouse and rat albumin than to the human or rhesus ortholog (62).

Structural studies showed that FcRn binds to IgG with 1:1 or 2:1 stoichiometry under nonequilibrium or equilibrium conditions, respectively (63, 64). In contrast, one FcRn receptor binds to one albumin molecule (65). FcRn interacts

with each of its two ligands through contacts associated with opposite surfaces, such that FcRn can bind IgG and albumin simultaneously without competition or cooperation occurring between each other (65). Biochemical and crystallographic data indicate that, upon binding at pH 6, neither FcRn nor IgG undergoes major conformational changes. Instead, it is the protonation of histidine residues (H310, H435, H436) in the $C_H2$–$C_H3$ hinge region of IgG1 that enables binding (66). This allows for the formation of salt bridges at the FcRn–Fc interface, specifically the acidic residues on the C-terminal portion of the α2 domain (E117, E132, and D137) in FcRn, and the first residue of $\beta_2$m (55, 66, 67). Notably, the sites within IgG that bind to FcRn competitively overlap with IgG Fc binding to staphylococcal protein A (68). In contrast, FcRn binding to albumin is mostly hydrophobic in nature and is thought to be stabilized by a pH-dependent hydrogen-bonding network internal to each protein. This interaction involves two tryptophan (W53 and W59) residues of FcRn and three histidine (H464, H510, and H535) residues within the albumin third domain (DIII), which are fundamental for pH-dependent FcRn binding, as well as some contribution of the first domain (DI) (54, 69, 70). Contrary to FcRn–IgG interactions, no pH-dependent intermolecular salt bridges exist in hydrophobic FcRn–albumin binding. Available data suggest that FcRn possesses higher affinity for IgG than for albumin (54, 65). These unique interaction properties of FcRn and its ligands form the basis for a wide variety of physiologically important FcRn-driven functions.

*FcRn functions: not just a bidirectional transporter*

*FcRn-mediated recycling and the protection of monomeric IgG and albumin from degradation.* FcRn plays a major role in the maintenance of serum IgG levels. Early studies with FcRn suggested that the major cell type involved in this process was vascular endothelium (71). Yet, chimerism of WT mice with *Fcγrt*$^{-/-}$ bone marrow and conditional, Tie-2-Cre–driven deletion of *Fcgrt* revealed that cells of hematopoietic origin participate in the IgG-salvage pathway (28, 72, 73). Given that only small amounts of FcRn receptor expression have been detected on the surface of endothelial cells, IgG uptake is believed to occur mostly via nonspecific, fluid-phase pinocytosis rather than by receptor-mediated endocytosis (18). Once inside the cell, IgG binding to FcRn is thought to occur as the early endosome becomes increasingly acidic and permissive for pH-dependent interaction of FcRn with IgG. FcRn-bound IgG is then sorted into common recycling endosomes that recycle IgG away from lysosomes and back to the cell surface via rapid and slow release routes where IgG is extruded into the extracellular milieu as a result of the neutral pH in that locale (Fig. 1C) (74).

Less is known about the FcRn-dependent salvage of albumin, which is partly extrapolated from insights derived from IgG–FcRn interactions. Based upon this, an equivalent pathway for FcRn receptor–mediated salvage of albumin is thought to exist (22). However, the efficiency of these two processes is vastly different, and it is estimated that for every six FcRn-recycled albumin molecules in humans, only one IgG molecule is rescued; the ratio in mice is even lower, at 30:1 (75). Nonetheless, this level of recycling is sufficient for sustaining high IgG plasma concentrations, with a relatively minor contribution provided by IgG production. In contrast, high serum albumin levels depend more on a high rate of hepatic synthesis than on FcRn-dependent salvage (75). Thus, the manner in which FcRn maintains IgG and albumin in the circulation may share some, but not all, mechanistic features. Furthermore, it remains unknown whether cells of hematopoietic and parenchymal origin participate equivalently in IgG and albumin retention.

The FcRn-dependent diversion of IgG and albumin away from lysosomal degradation is the basis for designing new or modified drugs with enhanced FcRn-binding capacity and, thus, prolonged serum half-lives and potentially improved pharmacokinetics. A large number of modifications within the $C_H2$–$C_H3$ domains of IgG spanning the FcRn contact surface (such as L253, H410, and H435 residues) were described to significantly enhance pH-dependent binding of IgG to FcRn (reviewed in Ref. 76). Although they have not yet entered clinical use, a number of preclinical studies in nonhuman primates showed increased efficacy of such engineered therapeutics in anticancer and anti-infection therapeutic approaches (77–79). Alternatively, pharmacologic FcRn inhibition using peptide mimetics, anti-FcRn mAbs, or Abs modified to possess Fc-dependent and low pH–independent binding (so-called "Abdegs") were shown to decrease circulating levels of pathogenic IgG and confer protection in models of myasthenia gravis, systemic lupus erythematosus, rheumatoid arthritis, and experimental autoimmune encephalomyelitis (77). Similarly, engineering IgGs to lack the ability to bind to FcRn (such as the mutation of the I253, H410, and H435 residues [$IgG_{IHH}$]) enables accelerated catabolism of IgG-radioimmunoconjugates during molecular imaging, endowing them with fewer toxic side effects than conventional chemotherapeutic drugs (80). Similar approaches aiming to develop long-lived albumin-based therapies demonstrate the enormous potential derived from understanding the mechanisms associated with FcRn-mediated recycling.

*Transcytosis of IgG and its implications for drug delivery and vaccine development.* In polarized cells, such as the epithelium, FcRn is able to transport IgG bidirectionally via transcytosis, which allows for the transfer of IgG from mother to young (Fig. 1A, 1B), as well as the delivery of IgG-complexed environmental Ags and microbial products into the host, resulting in the induction of tolerance or immunity (see later discussion) (81, 82). Similar to the recycling pathway, IgG is likely internalized by fluid-phase pinocytosis into polarized epithelial cells. Still, the trafficking of FcRn is highly dynamic, and although most of the receptor occupies endosomal compartments at any single time, there is always some FcRn located at the cell surface, with a flux of FcRn moving through the plasma membrane over time. Thus, receptor-mediated endocytosis is also thought to occur in light of early observations wherein FcRn expression was detected on the apical enterocyte surface membrane and in the context of an acidic microenvironment in the neonate proximal intestine (74, 83, 84). That said, there is a paucity of data in support of the existence of an acidic pH environment in the neonate intestine, which is further complicated by the fact that the uptake of IgG by neonatal rodent enterocytes was observed to take place in the absence of FcRn; this raises the possibility that the initial internalization of IgG in the neonatal enterocyte might be FcRn and pH independent (85). Whether fluid-phase– and receptor-mediated pathways of IgG uptake

operate concurrently and whether they escort IgG to the same intracellular compartments still need to be assessed.

Subsequent to internalization, IgG is diverted into early sorting endosomes and then the common recycling endosome (86). The acidification of endosomes allows for FcRn to bind IgG in these compartments, thereby enabling active FcRn-mediated transport of IgG across the cell and its subsequent release on the opposite side, once exposed to the neutral extracellular pH (Fig. 1B). The intracellular mechanisms that determine whether apical or basal recycling versus apical-to-basal or basal-to-apical transcytosis occurs have only recently begun to come to light. Apical-to-basolateral transport, for example, depends on motifs present in the cytoplasmic tail, as well as on the ability of FcRn to bind calmodulin in polarized epithelial model systems (46, 87, 88).

FcRn-dependent transcytosis of IgG, and likely albumin, also occurs in vivo. In rodents, forced FcRn expression restricted to intestinal epithelial cells results in IgG secretion into the gut lumen (82). In addition, Fc-dependent absorption of IgG was described in the lungs and intestines of humanized mice that only express human FcRn (*FCGRT/B2M* Tg/*Fcgrt*$^{-/-}$ mice) (Fig. 2A) (89). Similarly, Fc-fusion proteins, but not Fc-fusion proteins disabled in FcRn binding, can be absorbed in the lungs of mice and nonhuman primates (90, 91). Further, consistent with the near absence of serum proteins in the urine, albumin is reabsorbed in the renal PTCs through an active process involving FcRn, suggestive of transcytosis (92). In this pathway, albumin in the renal ultrafiltrate is internalized by binding to the megalin–cubulin complex via receptor-mediated endocytosis on the apical surface of PTCs. Subsequently, this complex is trafficked to late endosomes where, at acidic pH, albumin is captured by FcRn and directed back into the circulation (87, 93, 94). The involvement of FcRn in albumin reabsorbtion by PTCs requires additional substantiation and consideration, because FcRn-deficient mice, for instance, may not display significant albuminuria (95). This may be due to low albumin levels in the circulation of these animals (hypoalbuminemia), which results in reduced amounts of albumin in the glomerular ultrafiltrate. As such, the loss of albumin in the urine of FcRn-deficient mice should be investigated in animals with normal circulating albumin levels. FcRn-mediated IgG handling in the kidneys differs from albumin. To prevent potential accumulation of protein complexes that could obstruct glomerular filtration, IgG is removed from the glomerular basement membrane in an FcRn-mediated process that allows for the movement of IgG across the podocyte and its excretion into the glomerular capsular space away from the circulation (96). Because IgG is not subsequently reabsorbed by the PTCs, it is lost in the urine (93). The latter process may be the basis for immune protection within the urinary excretory system.

The transcytosis of IgG or IgG–ICs by FcRn at mucosal barriers, such as the lung, intestines, or genitourinary tract, can have important consequences for the host immune response. In addition to conferring passive immunity, mouse dams tolerized to Ags are able to confer tolerance to their offspring during the period of suckling by transfer of specific IgG or IgG–ICs (97, 98). Intriguingly, IgG–ICs that formed in the context of Ab excess were found to be immunosuppressive, in contrast to IC formation in the setting of Ag excess, which are immunogenic (99). More recently, using the prototype Ag OVA in an allergic airway disease model, airborne Ag exposure of lactating mice resulted in decreased airway hyperreactivity only in breastfed offspring (100). It was subsequently shown that the milk from OVA-sensitized mothers contained TGF-β, as well as IgG–IC, which was transferred to the newborn via FcRn and that both are required for the induction of tolerance (101). Moreover, as a result of the production of IgG with anti-IgE specificities, FcRn can mediate the transfer of IgE from the lumen into the circulation in the form of IgG anti-IgE–ICs, which also may play a role in pathways of early life tolerance (102).

In vivo studies with FcRn-humanized mice demonstrated that circulating IgGs can be delivered into the intestinal lumen where they bind orally administered Ags and form IgG–ICs that are transported back into the lamina propria in an FcRn-dependent manner (Fig. 2A) (82). Because the IgG–ICs subsequently were shown to be taken up by CD11c$^{+}$ DCs that induced Ag-specific CD4$^{+}$ T cell responses, the FcRn-mediated transcytosis of IgG and IgG–ICs across mucosal barriers in adult life confers a sensing capacity on IgG, which scavenges luminal Ags and permits their efficient delivery to the immune system. Indeed, the presence of anti-pathogen–specific IgG reduced disease severity only in FcRn-competent mice upon challenge with pathogens such as *Helicobacter pylori*, *Citrobacter rodentium*, and *Chlamydia muridarum* (90, 103, 104).

In the context of viral infection, the protective role of FcRn can be variable. Analysis of HSV-2 infection showed that HSV-2–specific Abs are transcytosed from the systemic circulation into the genital lumen in wild-type (WT) mice, but not in FcRn-deficient mice, and that this confers protection against intravaginal viral challenge (105, 106). Similar protective FcRn-mediated effects were noticeable after administration of anti-influenza hemagglutinin-specific mAb upon influenza infection (107). In contrast, during CMV infection, infectious virions were able to disseminate to the placenta via their associations with poorly, but not strongly, neutralizing anti-CMV Abs when transported by FcRn (108). FcRn transcytosis of IgG–virion complexes across mucosal genital surfaces also was illustrated for HIV infections (109, 110). In a study designed to test the ability of neutralizing and non-neutralizing Abs to protect macaques from vaginal simian HIV challenge, the strongly neutralizing IgG provided sterilizing immunity, whereas nonneutralizing IgG did not (111). Indeed, passive administration of a highly neutralizing human anti-HIV Ab (VRC01) engineered to enhance pH-dependent binding to FcRn protected from the mucosal transmission of simian HIV infection (78). Thus, depending on Ab-neutralizing capacities, site, and tissue pH, FcRn may be responsible for shuttling infectious agents that either facilitate or prevent infection.

### *FcRn-dependent regulation of IgG–ICs by hematopoietic cells and the role played in innate and adaptive immunity*

Both mouse and human hematopoietic cells were demonstrated to express FcRn (27). Notably, these include all subsets of DCs, macrophages, and monocytes, as well as neutrophils and B cells (27, 72, 73). Thus, most FcRn-carrying hematopoietic cells are proficient in Ag presentation or phagocytosis. Indeed, in addition to being a major site of monomeric IgG protection from degradation, FcRn expression by DCs

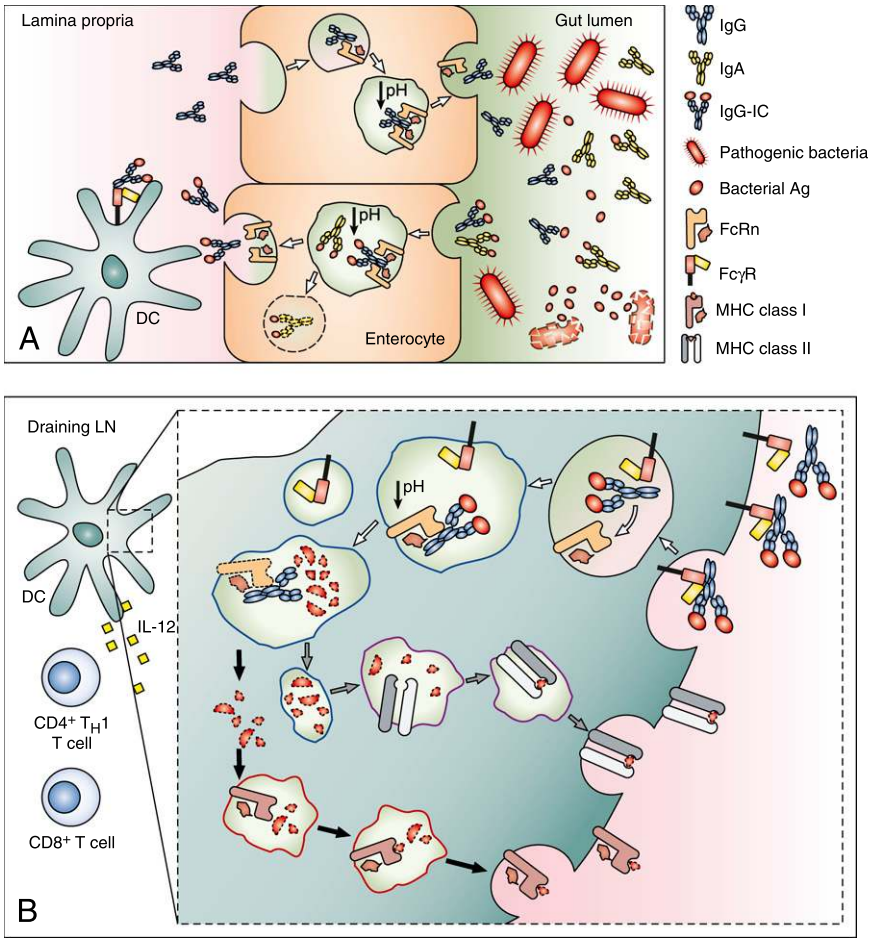


**FIGURE 2.** (**A**) In the adult human gut, both enterocytes and APCs in the lamina propria express FcRn. Enterocytes transcytose IgG into the gut lumen where it binds to Ags. The IgG–ICs are then delivered to DCs in the lamina propria. Ag-loaded DCs then migrate to the draining lymph nodes (LN) to prime T cell responses. (**B**) The IgG–IC can bind to FcγR on the surface of DCs at neutral pH, initiating receptor-mediated endocytosis. This delivers the IgG–IC into the endolysosomal compartments. As these vesicles mature they become more acidic. Acidification allows IgG–ICs to dissociate from FcγR and favors binding to FcRn. Such a "hand-off" enables efficient trafficking of the IgG–IC and the delivery of Ag into Ag-processing pathways that promote the loading onto MHC class I and MHC class II molecules. Ligation of FcRn by IgG–ICs also induces the production of IL-12 by the DCs. The peptide-loaded MHC molecules derived from IgG–ICs are then able to prime $CD8^+$ and $CD4^+$ T cells. Although the secreted IL-12 acts upon the primed $CD4^+$ T cells to induce Th1 polarization, it acts upon $CD8^+$ T cells to promote activation, cytotoxicity, and a $T_C1$ phenotype. For simplification, although a monomeric IgG–IC is shown in this figure, multimeric IgG–ICs are the types responsible for Ag processing and induction of IL-12 secretion.

was shown to play an important role in the ability of an Ag carried by IgG to be processed and displayed by MHC class I molecules via cross-presentation and MHC class II molecules for presentation to $CD8^+$ and $CD4^+$ T cells, respectively (29, 30). This is consistent with the importance of FcRn in facilitating the degradation of IgG–ICs in vivo (28, 73, 112). In neutrophils, such functions of FcRn were linked to the uptake of IgG-opsonized bacteria and their delivery into phagolysosomes (113). The size of the IC also determines the degree to which IgG and Ag are diverted to lysosomes; large IgG–ICs are more likely to meet this fate in comparison with small IgG–ICs (114). In the latter case, small IgG–ICs are handled similarly to monomeric IgG and are protected from degradation (28). In epithelial cells, IgG–ICs are also diverted to lysosomes, as shown by the behavior of neutralizing anti-influenza mAbs (107), making such observations a consequence of FcRn interactions with multimeric IgG rather than that of the cell type per se. These findings clearly indicate a fundamental functional difference in how FcRn traffics monomeric IgG and multimeric IgG in the form of IgG–ICs.

The expression of classical FcγRs on the cell surface enables APCs to capture and internalize IgG–ICs (115). In doing so, APCs primed with IgG–ICs effectively activate $CD4^+$ and $CD8^+$ T cells (116–119). It was demonstrated recently that FcγR and FcRn cooperate in the processes of MHC class II presentation and MHC class I cross-presentation. Both of these receptors possess distinct pH-dependent binding to IgG: FcγR at neutral pH and the FcRn at acidic pH. This is consistent with the concept of IgG–IC "hand-off" within acidified endosomes; FcγR enables IgG–IC internalization initially, and FcRn shapes the subsequent fate of the IgG–IC (Fig. 2B). Consistent with this, DCs exposed to IgG–ICs, but not to the FcRn nonbinding $IgG_{IHH}$–ICs, induce greater $CD4^+$ T cell proliferation both in vitro and in vivo compared with FcRn-deficient DCs (28, 29). Therefore, FcRn cooperates with FcγR in Ag presentation and cross-presentation initiated by the uptake of IgG-captured Ags.

Although FcRn is expressed by all types of APCs, an analysis of the subsets of APCs involved in MHC class I cross-presentation showed that FcRn enables IgG-dependent cross-presentation most strongly in the $CD8^-CD11b^+$ DC subset. $CD8^-CD11b^+$ DCs, in contrast to $CD8^+$ DCs, possess acidic endolysosomal compartments conducive to IgG–FcRn binding (29). In a model of chronic colitis with high levels of antibacterial IgG Abs, inflammatory $CD8^-CD11b^+$ DCs expanded and, in WT mice but not in *Fcgrt*$^{-/-}$ mice, enabled efficient IgG-dependent activation of $CD8^+$ T cells (29). Similar mechanisms presumably account for the improved expansion of Ag-specific $CD8^+$ T cells after vaccination with haptenated Ag (120). Therefore, this suggests that FcRn couples IgG–IC responses with the efficient induction and activation of $CD4^+$ and $CD8^+$ T cells, depending upon the DC subset involved.

This is physiologically relevant in steady-state settings given that conditional deletion of FcRn within the $CD11c^+$ cell fraction results in decreased quantities of $CD8^+$ T cells at mucosal sites (30). Further, deficient $CD8^+$ T cell cytokine production and an inability to block the growth of induced or spontaneous colorectal or lung cancers also were observed

(30). This defect in $CD8^+$ T cell numbers was dependent on the FcRn-expressing $CD8^-CD11b^+$ DC fraction, because adoptive transfer of WT DCs conferred protection to $Fcgrt^{-/-}$ recipients. Interestingly, these cellular defects of $Fcgrt^{-/-}$ mice were not accompanied by decreased IgG levels within the intestine, despite the quasi absence of IgG in the serum (30). This supports the notion that a major function of FcRn in tissues is the maintenance of cellular immunity through the processing of Ag–Ab complexes.

Studies of multimeric IgG–IC interactions with FcRn further revealed that, upon cross-linking, FcRn is capable of orchestrating a signaling cascade that is associated with secretion of cytokines skewed toward Th1 and T cytotoxicity 1 ($T_C1$) responses, particularly IL-12 (Fig. 2B). In humans, immunohistochemical staining demonstrated that $FcRn^+$ $CD11c^+$ DCs were present in situ within colorectal cancers and adjacent colon in close juxtaposition to $CD8^+$ T cells. Most importantly, colorectal cancer patients with a higher frequency of $FcRn^+CD11c^+$ DCs at or near cancer sites had significantly longer survival times than did those with fewer $FcRn^+CD11c^+$ cells (30). These observations support the notion that $FcRn^+$ APCs regulate $CD8^+$ T cells and their function in anti-tumor and, presumably, other similar types of immunity. It may be surmised that a major function of FcRn in tissues is in its direct effects on innate and adaptive immunity through regulation of cytokine tone and Ag presentation that support Th1 and $T_C1$ responses.

# Conclusions

The name for FcRn largely originates from the initial historical observations focusing on the neonatal IgG transmission in rodents (10). With the rediscovery and confirmation of Brambell's, Hereman's, and Schultze's original hypotheses that FcRn regulates systemic IgG and albumin homeostasis, as well as documentation that FcRn is broadly expressed throughout life, this neonate nomenclature, although archaic, still applies.

FcRn's functions have recently expanded from passive immunity and IgG protection to an active IgG and Ag-trafficking receptor. The strategic presence at mucosal barrier sites takes advantage of FcRn's ability to bidirectionally transport IgG and to deliver Ags to the mucosal immune system. Then again, FcRn expression in APCs and specific transfer of multimeric IgG–ICs to Ag-processing vesicles allows for efficient MHC class I and II presentation. The ensuing effect is more potent elicitation of $CD4^+$ and $CD8^+$ T cell–dependent responses and enhanced protection against both bacterial and viral pathogens. This further suggests that, in tissues, FcRn-directed degradation of IgG–ICs might be its major function. The ability of FcRn to bidirectionally move IgG and to exploit IgG's abundance, in particular at mucosal sites, as well as its specificity toward diverse soluble Ags, allows this receptor to convey IgG–ICs for efficient T cell priming within APCs, reuniting ideally the humoral and cellular arms of immunity.

# Disclosures

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