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Immune and non-immune functions of the (not so) neonatal Fc receptor, FcRn

Kristi Baker,
Division of Gastroenterology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA, Department of Medicine, Harvard Medical School, Boston, MA 02115, USA

Shuo-Wang Qiao,
Rikshospitalet University Hospital, 0027 Oslo, Norway, University of Oslo, 0027 Oslo, Norway

Timothy Kuo,
Division of Gastroenterology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA, Department of Medicine, Harvard Medical School, Boston, MA 02115, USA

Kanna Kobayashi,
Division of Gastroenterology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA, Department of Medicine, Harvard Medical School, Boston, MA 02115, USA

Masaru Yoshida,
Department of Gastroenterology & The Integrated Center for Mass Spectrometry, Kobe University Graduate School of Medecine, Hyogo, Japan

Wayne I. Lencer, and
Harvard Digestive Diseases Center, Boston, MA 02115, USA, GI Cell Biology, Division of Pediatric Gastroenterology and Nutrition, Children's Hospital, Harvard Medical School, Boston, MA 02115, USA, Department of Pediatrics, Harvard Medical School, Boston, MA 02115, USA

Richard S. Blumberg
Division of Gastroenterology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA, Department of Medicine, Harvard Medical School, Boston, MA 02115, USA, Harvard Digestive Diseases Center, Boston, MA 02115, USA

Masaru Yoshida: myoshida@med.kobe-u.ac.jp; Richard S. Blumberg: rblumberg@partners.org

Abstract

Careful regulation of the body's immunoglobulin-G (IgG) and albumin concentrations is necessitated by the importance of their respective functions. As such, the neonatal Fc receptor (FcRn) which, as a single receptor, is capable of regulating both of these molecules, has become an important focus of investigation. In addition to these essential protection functions, FcRn possesses a host of other functions that are equally as critical. During the very first stages of life, FcRn mediates the passive transfer of IgG from mother to offspring both before and after birth. In the adult, FcRn regulates the persistence of both IgG and albumin in the serum as well as the movement of IgG, and any bound cargo, between different compartments of the body. This shuttling allows for the movement not only of monomeric ligand but also of antigen/antibody complexes from one cell type to another in such a way as to facilitate the efficient initiation of immune responses towards opsonized pathogens. As such, FcRn continues to play the role of an immunological sensor throughout adult life, particularly in regions such as the gut which are

Correspondence to: Richard S. Blumberg, rblumberg@partners.org.

exposed to a large number of infectious antigens. Increasing appreciation for the contributions of FcRn to both homeostatic and pathological states is generating an intense interest in the potential for therapeutic modulation of FcRn binding. A greater understanding of FcRn's pleiotropic roles is thus imperative for a variety of therapeutic purposes.

Keywords

Neonatal Fc receptor; Immunoglobulin G; Albumin; Immune complexes; Gastrointestinal tract

The mucosal surfaces of the body represent the boundary between ourselves and our environment. Regulation of this sensitive region requires careful coordination of all facets of our complex immune system in order to maintain the finely tuned homeostasis our bodies require for survival. Starting at the earliest stages of life, development and maintenance of systemic immunity is regulated by the events occurring at mucosal surfaces. In many animals, one of the key steps in this process is the passive acquisition of antibodies from the mother. These transferred immunoglobulins serve as one of the first lines of defense during early life when the immune system is incompletely developed. The neonatal Fc receptor (FcRn), as its name suggests, plays an important role in this process by mediating the maternal transfer of IgG from either serum, across the placenta, to the human fetus or from breast milk, across the intestinal epithelium, to the neonatal rodent [1]. The function of FcRn, however, extends not only throughout an individual's lifetime but also to many other sites within the body where it plays an important role in modulating lifelong humoral and cell-mediated immune responses.

The concept of a single receptor being responsible for three related phenomena, namely, the catabolism of circulating immunoglobulins, the passive transmission of immunity from mother to offspring, and anaphylactic sensitization, was first proposed by Brambell many years ago [2, 3]. This receptor was proposed to be specific, saturable, and exhibit reversible ligand binding that could, in many cases, be inhibited by immunoglobulins of other animal species. Its expression was recognized in intestinal epithelial cells and cells of the placenta or yolk sac and was theorized to also exist elsewhere in the body. More than a decade later, it was demonstrated that IgG binding within the gut of neonatal rats was strongly pH-dependent and, as such, occurred at different rates in varying regions of the intestine [4, 5]. The first isolation of this putative Fc receptor from the gut of neonatal rats revealed a heterodimer consisting of both a 41–50- and 15-kDa component, the larger of which was recognized to be differentially glycosylated and downregulated upon weaning [6]. Subsequent cloning of the FcRn gene and identification of its binding partner as β2-microglobulin [7, 8] opened up the field for study and the subsequent testing and validation of Brambell's initial hypothesis.

Recent work has sought to explore the mechanisms of FcRn action, its distribution both within the body and across species, and its potential as a therapeutic target. The emerging picture is one of a lifelong role played by the neonatal Fc receptor in the development and maintenance of physiological function through its actions as a homeostatic regulator and, as is increasingly being recognized, an immunological sensor.

Basic mechanisms of FcRn function

Structure

FcRn is a type I transmembrane protein containing three extracellular domains (α1, α2, and α3), a single pass transmembrane domain, and a short cytoplasmic tail [9–11]. The functional FcRn molecule has been shown to require heterodimeric association of the FcRn

α-chain with β2-microglobulin (β2M) [7, 12, 13]. Thus, while the major recognized ligands for FcRn are immunoglobulins and albumin, FcRn is most closely structurally related to major histocompatibility complex (MHC) class I molecules with which it shares 22–29% sequence homology [7]. The genes for mouse and human FcRn, however, are located outside of the MHC class I gene regions on chromosomes 7 and 19, respectively [14, 15]. In further divergence from classical MHC-I molecules, the region corresponding to the peptide binding groove on FcRn is collapsed such that peptides cannot functionally be loaded there, making direct FcRn-mediated antigen presentation unlikely [11]. Since many of the α-chain-to-β2M-chain contact sites are conserved between MHC-I and FcRn, it has been hypothesized that FcRn shares a common molecular ancestor with both MHC-I and CD1 molecules, having diverged at a point after a requisite association with β2M arose [16].

Considerable interspecies variations in FcRn structure have been described and are likely to account for differences in function and ligand binding specificity. Human FcRn shares approximately 68% sequence homology with rat FcRn [17], which itself shares 91% homology to mouse FcRn [15]. Bovine FcRn, in contrast, shares approximately 77% homology with its human counterpart and diverges further from rodent FcRn [18]. While the main structure of the FcRn molecule remains consistent across species, differences in specific amino acids are known to alter some properties. For example, while human FcRn possesses a single carbohydrate side chain protruding from Asn-102 in its α2 domain, rodent FcRn contains three additional N-glycan modifications within the α1, α2, and α3 domains [9, 15, 17, 19]. These additional carbohydrate chains have been implicated in the binding of rodent FcRn to IgG [1] and, as will be discussed below, their addition to human FcRn has been shown to alter membrane distribution of the molecule on polarized epithelial cells and the vector of FcRn-mediated IgG transport [19]. A further postulated consequence of amino acid variations between species is the extent of FcRn “promiscuity,” or the degree to which FcRn of one species will bind IgG molecules from another species. While mouse and rat FcRn bind a wide array of IgGs, including those of human, rabbit, and bovine origin, human FcRn shows a very limited binding range which, of the species tested so far, extends only to rabbit IgG [20].

These minor amino acid variations may also contribute to the observed differences in FcRn tissue distribution across species. Most notably, FcRn is heavily expressed in the intestinal epithelium of neonatal rodents but is significantly downregulated within this cell type upon weaning. In contrast, FcRn continues to be functionally expressed throughout adult life in intestinal epithelial cells of the human gut. Such differential expression may also be attributed to differences in the promoter regions of the human and mouse FcRn genes [21, 22]. Within both of these species, however, FcRn shares a broad and largely overlapping tissue distribution. In addition to intestinal epithelial cells, FcRn is also expressed in placental syncytiotrophoblasts [23], endothelial cells [24, 25], pulmonary epithelial cells [26], mammary epithelial cells [27], kidney podocytes [28], hepatocytes [1, 29], and a host of hematopoietic cells including monocytes, macrophages, dendritic cells, polymorphonuclear leukocytes [30] and, probably, B cells [31]. Such a wide tissue distribution within the body is consistent with the notion that FcRn and its ligands play important, and varied, physiological roles.

Interaction with ligand

Of the two principle ligands of FcRn (IgG and albumin), the most studied is the IgG molecule. Crystal structure analysis of soluble FcRn has revealed that FcRn binds to the Fc portion of IgG in a 2:1 receptor/ligand ratio [32]. This stoichiometry is believed to result from binding of two single FcRn molecules to the Fc regions of the IgG heavy chain dimer [17, 32]. Each FcRn molecule binds to the C_H2–C_H3 interface of one IgG heavy chain, and several residues critical in mediating this interaction have been identified on each molecule.

While the exact position of these residues varies slightly between species, the charge of each is consistently and critically dependent upon pH, thereby conferring on the FcRn–IgG interaction a strict pH dependence [9, 33].

FcRn binds to its ligands at pH≤6.5 but releases them at pH7.0. This pH dependence is related to the titration of several salt bridges at the FcRn–IgG interface which form between histidine residues in the Fc region of IgG and acidic FcRn amino acids [17, 33–35]. At the physiological pH of 7.0, these histidines become deprotonated and allow dissociation of the ligand from its receptor. This is likely to be the main means of receptor ligand binding for FcRn since no pH-dependent conformational changes have been reported [36]. Additionally, a hydrophobic isoleucine residue at position 253 of the IgG Fc region has been shown to be critical for binding in the presence of the stabilizing histidine salt bridges [1]. Such stringent pH requirements for ligand binding have important implications for the physiological function of FcRn, as will be discussed below.

Binding of FcRn to its other main ligand, albumin, is also highly dependent upon an acidic pH and is mediated by histidine residues in both the receptor and ligand [36, 37]. In particular, His166 in FcRn is conserved across homologs in nine mammalian species and is thus likely to be one of the most critical residues involved in this interaction. Albumin binds to FcRn in a 1:1 ratio and exhibits greater promiscuity in terms of cross-species ligand interaction with FcRn than does IgG [37]. The binding of albumin to FcRn occurs at a distinct site from that of IgG such that receptor binding of these two ligands is neither cooperative nor competitive. Despite these differences, however, FcRn interaction with its two ligands is remarkably similar and is strongly related to its role in protecting each from degradation.

Intracellular distribution and trafficking

When considering the ligands of FcRn, IgG and albumin, it seems at first counterintuitive that the bulk of FcRn in a given cell type is intracellularly distributed rather than being localized to the cell surface [20, 38, 39]. Such intracellular localization is important, however, when considering the pH restrictions on ligand binding. Although FcRn is expressed in a variety of cell types, the majority of studies examining intracellular trafficking of FcRn have focused on its movements within epithelial cells because of intense interest in the role of FcRn in transcytosis of its ligands.

Following its synthesis in the endoplasmic reticulum, FcRn must associate with β2-microglobulin before further trafficking can occur [40]. Failure to associate results in the formation of disulfide bonded FcRn oligomers that are retained within the ER and, presumably, routed for degradation. Despite the considerable sequence homology in β2-microglobulin across species, proper maturation and efficient trafficking of FcRn appear to require species matched β2-microglobulin [12]. This is a particularly important consideration in transfected systems where the absence of the appropriate β2-microglobulin chain can produce misleading results when examining intracellular FcRn routing. Several chaperone proteins have been demonstrated to assist in the proper folding of the FcRn heterodimer. In the earliest stages of its synthesis, and prior to binding of β2-microglobulin, FcRn associates with calnexin within the endoplasmic reticulum where it then undergoes intramolecular disulfide bond formation with the help of ERp57 [41]. Following N-linked glycosylation, FcRn associates with β2-microglobulin and, subsequently, with calreticulin before it can be routed along the normal secretory pathway and distributed to the appropriate cellular compartments [12].

The majority of FcRn under steady-state conditions seems to accumulate in subapical vesicles of polarized epithelial cells such as those of the gut lining [42, 43]. This is true of

both human and rodent FcRn despite the fact that surface distribution of FcRn differs between these species. Of the fraction of FcRn expressed on the cell surface, the majority is localized to the apical membrane in neonatal rodents, but to the basolateral membrane in humans [44, 45]. This distribution pattern is also reflective of the predominant direction of transcytosis of IgG across epithelial cells of these species, being predominantly apical→basolateral in rodents but basolateral→apical in humans. These differences can be attributed to variations in the cytoplasmic tails of the two species, which have been shown to play a major role in targeting FcRn towards either the basolateral or apical pole of the cell [44, 46]. Recent research also suggests that the opposite polarization of FcRn in these two species is related to the differential glycosylation state of the two molecules, since addition of rodent N-glycans to human FcRn converts its usual polarization to that of its rodent homolog [19].

In spite of the predilection of FcRn for one or another pole of epithelial cells, one of the most distinguishing characteristics of FcRn is its capability, in all species studied, for bidirectional transcytosis of cargo [39, 42, 45]. In fact, transcytosis of human FcRn across polarized cells transfected with human FcRn has been found to progress at the same rate in both directions despite the preponderance of membranous FcRn being located basolaterally [42]. While the exact mechanisms controlling transcytosis remain obscure, it is clear that the cytoplasmic tail of FcRn plays a dominant role in regulating this phenomenon. Aside from containing a tryptophan-based endocytosis sorting signal [47], a dileucine-based sorting motif, [48], and two serine phosphorylation sites [44], the cytoplasmic tail of FcRn has recently been found to contain a binding site for calmodulin [49]. Binding of calmodulin to FcRn was found to be calcium-dependent and reversible and to shuttle cargo-bound FcRn away from a degradative route and towards a transcytotic one.

The decision of which route FcRn and its cargo will take is recognized to be an increasingly complicated one, as a greater appreciation of the complex endolysosomal system trafficked by FcRn is gained. A recent study has identified a structurally and functionally heterogenous endosomal compartment that routes FcRn–IgG complexes towards either recycling or transcytosis [50]. Certain components of the recycling endosome, myosin Vb and Rab25, regulate sorting of FcRn into transcytotic pathways and do so in a polarized manner, somehow distinguishing between FcRn–IgG complexes moving in opposite directions across the cell. Thus, the apically directed and basally directed transcytosis pathways are distinct. Rab11a, however, perhaps the most well-established component of the recycling endosome in non-polarized cells, is completely dispensable for transcytosis, but regulates trafficking of IgG–FcRn back towards the basolateral membrane. This is in support of the findings of a previous paper which identified Rab11 as an important player in FcRn exocytosis in endothelial cells [51]. Interestingly, Rab11a in polarized epithelial cells has no role in recycling of the transferrin receptor, providing the one example so far where sorting of FcRn and transferrin receptor diverges. The result shows that trafficking of FcRn in polarized cells cannot be stochastic. In addition to the molecular components involved in FcRn trafficking, several of the structural elements transited by FcRn in the epithelial cells lining the gut of neonatal rats have now been identified. These include multivesicular bodies, early, late, and recycling endosomal compartments and clathrin-coated pits [52]. Whether the same compartments are visited by FcRn in the cells of the adult human gut remains unknown, as does the effect of cargo valency on intracellular epithelial routing.

At least one study of FcRn transcytosis has documented that the process is strictly dependent upon endosome acidification in order to enable binding of FcRn to its ligand [39]. Considering both the near-neutral pH of the extracellular milieu and the predominantly intracellular localization of FcRn, ligand–receptor interaction in many instances first occurs after internalization of the ligand either passively or via another receptor. Upon entering an

acidified endolysosomal compartment, IgG is able to interact with FcRn and be actively directed towards an appropriate destination via a route which may include transit along tubules protruding out from one internal compartment to another or towards the cell membrane. Upon reaching the apical or basolateral cell membrane, FcRn and its cargo are extruded via several possible exocytosis mechanisms. Studies have demonstrated that while the “complete fusion” mechanism of classical clathrin-mediated extrusion predominates, a small portion of ligand-bound FcRn is released via a more “prolonged release” pattern [25, 53, 54]. As a variant of the “kiss-and-run” exocytosis method utilized by some neuroendocrine cells, prolonged release involves only partial fusion of the endocytic compartment with the plasma membrane such that the vesicle remains a distinct and separate structure and releases only a fraction of its contents to the extracellular milieu. An important implication of this model relates to the pH dependence of FcRn binding. Single-molecule fluorescence microscopy has demonstrated that during these partial fusion events, IgG-bound FcRn can diffuse into the cell membrane away from the exocytosis site and return to the epicenter of this same site for reinternalization into the original vesicle [53]. In the apical-to-basolateral model of transcytosis, this represents an important opportunity for direct FcRn capture of lumenal IgG. Due to the action of a sodium–hydrogen exchange pump located in the apical membrane of the intestinal brush border, the immediate surface of the mucosal border is an acidic environment that has been predicted to permit binding of FcRn to its ligand [42]. Indeed, Ober et al. were able to demonstrate that IgG-bound FcRn exiting from these prolonged release vesicles remained bound to its cargo for several seconds before release [53], thereby providing support for the ability of FcRn to directly bind and extracellularly recruit its own cargo in some instances.

An important caveat to almost all of these intracellular trafficking studies is that only monomeric ligand was examined. While binding of monomeric IgG is not known to alter the distribution of FcRn [42], evidence now exists that the valency of its ligand can affect the route of FcRn trafficking within antigen-presenting cells. Qiao et al. [55] have demonstrated that FcRn targets large multimeric immune complexes towards lysosomal compartments within dendritic cells (DCs), whereas it mediates recycling of monomeric complexes back to the cell surface. The mechanisms of this differential trafficking within DCs remains to be determined, but one can envision an analogous system of endocytic vesicles to that found in epithelial cells in which increased ligand avidity cross-links multiple FcRn molecules and directs either the maturation of the vesicle or rapid trafficking of the receptor–ligand complex towards a pre-acidified compartment for speedy degradation. Whether ligand valency affects FcRn trafficking within other cell types and the physiological significance of this remain unknown.

Functions of FcRn

Catabolism and homeostasis

A primordial role for FcRn is the protection of its two ligands (IgG and albumin) from catabolism [37, 56]. Together, IgG and albumin make up approximately 80% of the protein mass in plasma and serve as both determinants of oncotic pressure and transporters of a variety of other molecules [36]. It is no coincidence that these molecules also have the longest half-lives of any serum protein. Considering the large amount of each of these proteins that are needed for optimal body function, it is energetically favorable to recycle as much of each as possible rather than to continually engage in the manufacture of new protein. In fact, FcRn has been demonstrated to recycle an equivalent amount of albumin in a day as the liver can produce [57]. The numbers for IgG salvage are even more impressive, with four times as much being saved by FcRn-mediated recycling than can be produced [58]. FcRn has thus evolved to fill an important homeostatic evolutionary niche.

Following uptake of IgG or albumin by passive routes such as pinocytosis, FcRn is capable of binding its ligands within acidic endosomal vesicles. By sequestering IgG or albumin from the soluble components of these endosomal compartments, FcRn is capable of actively shuttling its cargo back into the extracellular milieu and away from the degradative fate awaiting much of the remaining vesicle contents. The exact shuttling pathway employed by FcRn during this exocytic process is unknown, but IgG-complexed FcRn-containing tubules have been observed to project outwards from the sorting endosomes in the direction of the cell membrane and likely represent one path employed by cells [25]. In any case, the neutral pH outside the cells promotes rapid dissociation of ligand from receptor, since the affinity of one for the other decreases by two orders of magnitude at such non-acidic pH [36].

Considering the broad tissue distribution of FcRn, several studies have investigated which are the primary sites of IgG and albumin salvage. The emerging consensus has identified both endothelial cells and hematopoietic cells as the main effectors. $FcRn^{-/-}$ mice exhibit decreased levels of IgG in comparison to wild-type mice [56]. In contrast, wild type mice reconstituted with bone marrow from $FcRn^{-/-}$ mice exhibit lower serum IgG than wild-type mice, but similar to $FcRn^{-/-}$ reconstituted with wild-type bone marrow [55, 59, 60]. These studies suggest that parenchymal and hematopoietic cells that express FcRn play an equally important role in IgG homeostasis. In recent studies, endothelial cells have been subsequently confirmed to represent the major parenchymal cell type responsible for IgG protection. This was accomplished by the creation of a floxed FcRn mouse which was intercrossed with a Tie2-*Cre* mouse to generate conditional deletion of FcRn in the vascular endothelium [61]. These mice exhibited a profound deficiency in IgG homeostasis, thereby pinpointing the vascular endothelium as a major contributor to the IgG homeostasis. In line with this, the observation that IgG and albumin levels are low in mice that express only minimal levels of FcRn in gastrointestinal epithelial cells [1, 62] implies that FcRn at this site contributes only minimally to this function.

The physiological importance of FcRn-mediated IgG and albumin protection are illustrated by the phenotypes of mice deficient in either FcRn or β2-microglobulin. $FcRn^{-/-}$ mice display profoundly reduced half-lives of both IgG (1.4 vs 9 days) [56] and albumin (1 vs 1.6 days) [37]. Furthermore, serum IgG levels of all isotypes are reduced by almost fourfold in these mice and albumin levels by twofold. Values for β2-microglobulin-deficient mice are similar [37] or even lower [63]. Indeed, a human syndrome analogous to the latter mouse knockout has been described. Familial hypercatabolic hypoproteinemia was first documented in two siblings showing severely reduced serum levels of IgG and albumin despite normal production levels of the two proteins [64]. The catabolic rates in these patients were found to be fivefold greater than in healthy controls, and much later, testing revealed a single nucleotide transversion in the β2-microglobulin gene which reduced expression of β2-microglobulin-associated proteins to ≤20% of normal levels [65]. These two patients concomitantly presented with chemical diabetes and a skeletal deformity, although it remains unknown whether these are directly related to the β2-microglobulin deficiency.

A wide range of autoimmune diseases, however, are known to depend directly on the presence of excess self-reactive antibodies, and, as outlined below, modulation of FcRn binding is increasingly being studied as a possible therapeutic tool in their treatment.

Transcytosis

In addition to its role in the homeostatic regulation of IgG and albumin, FcRn is also critically involved in the transport of IgG across cells from one compartment to another. Such transcytosis represents an important function for the movement of molecules too large to diffuse between cells and across otherwise impermeable barriers. As such, the

implications of FcRn-mediated transcytosis depend on the location of action, but each can be seen as physiologically important.

As first hypothesized by Brambell [2] many years ago, passive transmission of immunity from mother to young is a receptor-mediated phenomenon involving the movement of IgG from the mother's circulatory system, across the placenta, to that of her offspring. In humans, this is a process that typically begins during the second trimester of pregnancy and peaks during the third [66]. FcRn has been identified as the key receptor involved in this process and, consistent with this function, has been found to be extensively expressed within the syncytiotrophoblasts of the placenta [23, 67]. It is widely accepted that IgG is passively taken up by syncytiotrophoblastic cells and, once inside, binds FcRn within early endosomal compartments before being actively transited across the cells and released at the pH-neutral basolateral membranes [66]. Transcytosed IgG may or may not then pass through the stroma before reaching the fetal blood vessels. Controversy remains as to whether or not FcRn is also expressed in the fetal vessel endothelium where greater evidence exists for the action of alternative Fc receptors in further movement of IgG [24, 66]. Although expression of FcRn has not been documented in the rodent placenta per se, it is clearly expressed in the rodent yolk sac, which has been identified as the site of maternofetal IgG transfer in mice and rats [68]. The site of action of FcRn appears to be the yolk sac endoderm, into which IgG constitutively enters before being chaperoned across by FcRn. Comparing IgG levels in 19- to 20-day-old fetuses, serum from $FcRn^{-/-}$ fetuses contained negligible amounts of IgG (1.5μg/ml), whereas their $FcRn^{+/-}$ and $FcRn^{+/+}$ siblings contained 176 and 336μg/ml, respectively. In addition to identifying FcRn as the sole molecule responsible for maternofetal IgG transfer, these results suggest a dose-dependent effect of FcRn on IgG transfer and are consistent with saturable kinetics. Of note is that albumin levels in the $FcRn^{-/-}$ fetuses were 32% lower than those in their $FcRn^{+/+}$ siblings, implying that FcRn may also transplacentally transfer maternal albumin, although further study will be required to rule out the effect of fetal catabolism in the knockouts.

The role of FcRn in the transfer of passive immunity from mother to offspring is not limited to antenatal life and continues during the neonatal suckling period, which, for rodents, is an even more critical period for acquisition of maternal IgG [1]. The presence of IgG in breast milk has long been recognized and is most likely explained by FcRn-mediated transport of IgG from the maternal circulation, across mammary glands, and into the mother's milk. This is supported by the documented expression of FcRn in the mammary glands of lactating mice and humans [27, 69]. Indeed, overexpression of bovine FcRn in the mouse mammary glands has been found to increase the amount of IgG in both the mother's milk and the pups' serum [70]. Within the gut, even before the isolation of FcRn, the importance of a saturable, membrane-bound IgG transporter within intestinal epithelial cells was documented in neonatal rodents [2, 71]. Once identified, the binding and trafficking characteristics of FcRn fit perfectly with this hypothesized model. Within the neonatal gut, the contents of the duodenum are still slightly acidic after leaving the stomach [1]. In combination with the acidifying effect of the apical sodium–hydrogen exchange pump acting at the mucosal border [42], a low extracellular pH encourages IgG in the ingested milk to quickly bind FcRn in the enterocytes. Solid evidence for the importance of FcRn in delivering maternal IgG to neonates is the approximately 190-fold lower level of maternal IgG that can be found in $FcRn^{-/-}$ pups compared to their $FcRn^{+/+}$ littermates [56].

While mice drastically reduce FcRn expression in their gut epithelial cells upon weaning, the enterocytes of many other animals, including humans [39, 72], continue to express FcRn throughout life. Considering the location of these intestinal epithelial cells at the mucosal border demarcating self from non-self and the bidirectional trafficking capacity of FcRn, this receptor is thus perfectly poised to play a role in mucosal immunosurveillance.

Antigen delivery

Although IgA is often recognized as the predominant immunoglobulin present at mucosal surfaces, a considerable amount of IgG is found in many mucosal secretions. This can range from 300μg/ml in nasal secretions up to 800μg/ml in the lumen of the adult rectum [62, 73]. Shuttling of each of these different immunoglobulin classes is mediated by a different receptor. IgA, in dimeric form, is bound by the polymeric IgA receptor (pIgR) at the basolateral surface of enterocytes [74]. Following endocytosis, IgA is then unidirectionally transported across the cell via a series of endocytic vesicles. Before its release at the apical surface, the dimeric IgA becomes permanently bound to a secretory component which consists of a cleaved region of pIgR that is proteolytically released during transcytosis. This permanently altered secretory IgA is then free to participate in the orchestration of lumen-oriented immune responses [74, 75].

In contrast to this, FcRn-mediated transcytosis of IgG does not lead to any modification of the IgG molecule, which, in its intact state, can then rebind to another molecule of FcRn on the apical surface and be returned to the basolateral side of the enterocyte in order to bind a subsequent load of cargo. This bestows upon IgG the rather unique opportunity to act as an immunological sensor for mucosal surfaces since it can retrieve antigen from the intestinal lumen and direct it towards other local and systemic immunological components, thereby allowing the body to monitor activity within the intestinal cavity [29, 62]. FcRn-mediated trancytosis of IgG in complex with its commensal bacterial ligands may represent one of the mechanisms by which intestinal bacterial antigens drive the maturation of both mucosal and systemic immunity [76].

The near absence of FcRn expression in the adult mouse gut has necessitated the creation of transgenic mouse models in order to investigate this principle. The first of these involved whole body expression of human FcRn under control of the endogenous human FcRn promoter in tandem with expression of human β2-microglobulin [29, 56]. These transgenes were maintained on a mouse $FcRn^{-/-}$ background in order to minimize confounding variables. Since human FcRn is incapable of binding significant amounts of mouse IgG, these mice possess IgG serum levels as low as their $FcRn^{-/-}$ counterparts [20, 56]. Nonetheless, they have served as an important tool to model FcRn expression in the human gut. Using rabbit anti-ovalbumin (OVA) antibodies, which are capable of binding human FcRn, studies with these mice have elegantly demonstrated that serum IgG can be transcytosed from the basolateral to apical side of small intestinal cells and that, once in the intestinal lumen, these IgGs are able to bind to their orally administered cognate antigen [29]. Following lumenal formation of immune complexes, FcRn was then able to bind these complexes and deliver them into the intestinal lamina propria where they were shown to be taken up by $CD11c^{+}$ dendritic cells, presumably for antigen processing and presentation. When the human FcRn transgenic mice were injected with anti-OVA antibodies, given a single feeding of OVA antigen and then adoptively transferred with carboxyfluorescein succinimidyl ester (CFSE)-labeled T cells expressing an OVA-specific T cell receptor, a clear increase in proliferation of these $CD4^{+}$ T cells was observed in the regional mesenteric lymph nodes and even the liver. No such expansion of T helper cells was observed in similarly treated $FcRn^{-/-}$ control mice, thereby clearly implicating intestinal epithelial cell expression of FcRn in the activation of a localized immune response to a lumenal antigen.

The involvement of mucosal epithelium-expressed FcRn in driving an actual pathological immune response towards a lumenal antigen has also been described using a slightly different mouse model. In these mice, mouse FcRn was expressed, in tandem with mouse β2-microglobulin, under control of the intestine-restricted fatty acid binding protein promoter [62]. By maintaining expression of this transgene on an $FcRn^{-/-}$ background, the authors were able to limit expression of FcRn to the intestinal epithelial cells and look

specifically at the role it plays in this location in protecting against an intestinal pathogen. In the presence of circulating anti-*Escherichia coli* IgG, fluorescein isothiocyanate (FITC)-labeled *E. coli* was observed within the intestinal epithelial cell of the transgenic mice, but not their $FcRn^{-/-}$ counterparts, thereby implicating FcRn in apical-to-basolateral transcytosis of IgG/ligand complexes across epithelial cells. The fact that FITC-labeled *E. coli* were also detected in $CD11c^{+}$ cells within the mesenteric lymph nodes of these mice demonstrates that the FcRn/IgG immune complex successfully traversed the epithelial cell, rather than being degraded there, and delivered Ag to lamina propria DCs. In order to investigate the role of epithelial FcRn directly in an active mucosal immune response, the authors chose an epithelial-cell-specific pathogen, *Citrobacter rodentium*, whose eradication had previously been demonstrated to rely on activation of an IgG, but not IgA [77]. $FcRn^{-/-}$ mouse infected with *C. rodentium* displayed considerably more severe pathology than their $FcRn^{+/-}$ counterparts and were found to have much lower levels of pathogen-specific serum IgGs both before infection and 7 days following exposure. When the intestinal epithelial-transgene-expressing mice were exposed to similar doses of pathogen, they were largely protected from *C. rodentium*-induced pathogenesis so long as they had also been administered anti-*C. rodentium* antibodies. Furthermore, when infected with *C. rodentium* engineered to express OVA and adoptively transferred with OVA-specific T cell receptor expressing $CD4^{+}$ T cells, robust proliferation of the pathogen-specific T cells was observed in the mesenteric lymph nodes of mice expressing the FcRn epithelium-specific transgene and not their $FcRn^{-/-}$ counterparts. Thus, epithelium-restricted FcRn is capable of driving an effective systemic immune response, but only in the presence of the appropriate serum IgG that provides defense of the epithelium against an invasive bacterium. Moreover, FcRn in the epithelium is able to sense luminal and epithelial infections and transmit evidence of these infections to the systemic immune system.

The recent documentation of FcRn expression in the airways of many mammalian species further illustrates its potential as a barometer of mucosal infection. FcRn-mediated transport of Fc-fusion proteins across the respiratory epithelium of adult mice, humans, and non-human primates highlights the potential for a biologic function of FcRn and IgG complex-mediated monitoring of respiratory pathogens [33]. In adult humans and non-human primates, FcRn expression and function is predominantly contained within the upper airways [33, 78]. FcRn expression has also been found in the lower bovine respiratory tract [79] and rat alveolar epithelial cells, which have been observed to saturably and bidirectionally transcytose monomeric IgG [26, 80]. Intriguingly, FcRn has been found in the endothelial cells of the central nervous system (CNS) and the choroid plexus [81, 82]. While the brain is generally held to represent an immunologically privileged site that would not seem to require the same level of monitoring as mucosal surfaces, it is likely that the primary role of FcRn in the blood–brain barrier is primarily related to protection in cases of existing infections, such as bacteremia. Under such circumstances, the main role of FcRn would be to shuttle IgG and immune complexes of pathogenic bacteria out of the CNS and back towards systemic circulation. This hypothesis is supported by the finding of FcRn expression in many structures of the rodent eye, another immunologically privileged site [83].

While the role of FcRn in epithelial cells has been the focus of much study, it would be wrong to assume that the immunological significance of this receptor is limited to this cell type. A variety of antigen-presenting cells (APCs) express FcRn [30, 55], and within this hematopoietic compartment, the role of FcRn in the intracellular routing of immune complexes has been investigated. Dendritic cells from wild-type mice loaded with multimeric immune complexes formed of 4-hydroxy-3-iodo-5-nitrophenylacetic acid (NIP)-conjugated OVA and anti-NIP IgG elicited strong, dose-dependent stimulation of OVA-specific T cells [55]. In contrast, DCs from $FcRn^{-/-}$ mice induced only mild T cell

proliferation. When wild-type DCs were loaded with immune complexes formed with anti-NIP IgG engineered to have mutations in the Fc region that abrogated FcRn binding, T cell stimulation was considerably blunted, clearly implicating FcRn in the routing of complexes towards MHC-II loading. These results were replicated in vivo using adoptive transfer of CFSE-labeled OVA-specific T cells and footpad injections of preformed immune complexes. Contralateral footpad injections of complexes formed with wild-type IgG or the mutated IgG led to robust proliferation of T cells in the draining popliteal lymph node only of the foot injected with the wild-type IgG complexes. Confocal microscopy of DCs loaded with fluorescently labeled wild-type immune complexes revealed that these were directed towards lysosomal compartments within 30 min of internalization. Complexes formed with mutant IgGs unable to bind FcRn, however, were not observed to traffic to LAMP1-containing compartments. This suggests that in contrast to the recycling pathway observed in epithelial and endothelial cells for monomeric IgG, multimeric immune complexes within DCs are rapidly targeted towards a degradative pathway leading to active antigen presentation. Indeed, multimeric immune complexes were observed to exhibit a much shorter in vivo half-life than monomeric immune complexes or uncomplexed IgG, and bone marrow chimera studies identified hematopoietic cells as the main cells responsible for this rapid degradation of large immune complexes.

This body of work is consistent with a model in which FcRn acts as an immunological sensor. Since immunological complexes are likely to indicate the presence of an infection, their rapid targeting for degradation and loading onto MHC-II molecules for T cell activation may represent an important pathway to promote an active response against the pathogen. In contrast, monomeric IgG or monomeric complexes are more likely to represent a non-threatening physiological phenomenon and, as such, are simply recycled. It is of interest to note that FcRn has recently been demonstrated to traffic with the MHC-II pathway associated invariant chain molecule (Ii) [84]. In the absence of Ii, very little FcRn was observed to traffic into late endosomes or lysosomes, and fusion of a tailless FcRn to the cytoplasmic domain of Ii restored the ability of FcRn to traffic to these compartments. While this study did not examine the effect of different cargo on FcRn trafficking, it has shed important light on the intracellular route of FcRn migration.

Perhaps nowhere are immune complexes as likely to be as prevalent as within the gut, which contains not only considerable amounts of IgG especially under inflammatory conditions but also a host of commensal bacteria to which the body is normally tolerized [85, 86]. For reasons that remain somewhat obscure, however, this tolerance is often lost in inflammatory bowel diseases (IBD) [87, 88]. In addition to the elevated presence of circulating antibodies towards distinct bacterial antigens [89–92], there is often a switch towards IgG, rather than IgA, as being the dominant antibody within the colon [93]. Whether these antibodies play a protective or pathogenic role in the development and maintenance of IBD is a matter that has received little attention. A recent study has tackled this issue and shed considerable light on the role played by these IgGs. Wild-type mice having received anti-flagellin antibodies experienced more severe colitis than those having received an IgG control [94]. When wild-type mice were immunized with flagellin before treatment with dextran sodium sulfate (DSS), more anti-flagellin antibodies were found in their serum, and they exhibited significantly more severe colitis than mock-immunized animals. When these experiments were repeated in $FcRn^{-/-}$ mice, significant protection from disease development was observed. Since a confounding factor in these knockout mice is their low serum IgG titers, the experiments were repeated in both wild-type mice chimerized with $FcRn^{-/-}$ bone marrow and $FcRn^{-/-}$ mice chimerized with wild-type bone marrow. Circulating levels of anti-flagellin IgG in both sets of chimeras were virtually identical, yet the $FcRn^{-/-}$ mice reconstituted with wild-type bone marrow exhibited significantly more severe colitis upon treatment with DSS. These studies clearly pinpoint a pathogenic role for circulating

antibacterial IgG in the development of IBD and implicate FcRn expression within the hematopoietic compartment as a necessary participant in the process. It can be inferred that following disruption of the intestinal barrier, the ability of FcRn in APCs to rapidly shuttle immune complexes of anti-bacterial IgG and their cognate ligand into the lysosomal degradation pathway leading to MHC-II presentation and $CD4^+$ T cell activation is the mechanism producing the observed phenotype. Future studies will no doubt further dissect the pathway taken by FcRn within these APCs and provide new insights into how it may be harnessed as a possible future treatment target.

FcRn as a therapeutic target

Modulation of ligand–FcRn binding

Immunoglobulins have been identified as pathological agents in a wide range of diseases beyond IBD, most of which are autoimmune in nature. Illnesses such as rheumatoid arthritis, myasthenia gravis, Guillain–Barré syndrome, and lupus erythematosus, among others, have all been associated with the presence of circulating immunoglobulins directed towards specific autoantigens [95]. By binding self-antigens, these autoantibodies lead to the formation of immune complexes that are recognized as pathogenic and attacked by the body's immune system. Current treatment modalities for many of these ailments involve the administration of high-dose intravenous immunoglobulins (IVIG). It has been known for some time that doing so increases the catabolism of the pathogenic antibodies, thereby reducing symptoms. Among the myriad modes through which IVIG acts, saturation of FcRn is now recognized to be an important factor [95, 96]. By occupying a significant percentage of recycling FcRn receptors, the high dose of exogenously administered immunoglobulins effectively leaves a higher proportion of endogenous immunoglobulins, including the autoreactive IgGs, unbound and thus susceptible to degradation. There is thus a precedent for manipulation of FcRn binding in the treatment of autoimmune diseases. Considering the many non-specific effects associated with IVIG therapy, there is great interest in developing more specific modes of altering FcRn-mediated antibody regulation.

Resolution of the crystal structure of IgG bound to FcRn and elucidation of the key amino acid residues mediating this interaction have provided a basis for the engineering of IgGs with modified binding capabilities. Simultaneous mutation of Fc residue 250 to a large hydrogen bond acceptor and residue 428 to a large hydrophobic amino acid residue generated an IgG which bound FcRn 28 times more strongly at pH6.5, but did not exhibit improved binding at neutral pH [97]. When administered to rhesus monkeys, serum half-life of this double mutant IgG was observed to be twofold greater than control IgG. In contrast, simultaneous induction of M252Y, S254T, T256E, H433K, and N434F mutations produced an IgG with a 23-fold increase in binding affinity at pH6.0 and which remained bound, albeit with lower affinity, at pH7.2 [98]. This engineered IgG was dubbed an "AbDeg" (antibody which promotes degradation) because its administration to mice led to the pronounced and prolonged reduction in serum levels of endogenous IgGs. Work has also progressed into the development of small molecule inhibitors for FcRn. Following identification by phage display screening of a peptide library, several candidate molecules have been further chemically modified to optimize their FcRn binding ability [99, 100]. Administration of one of these candidate inhibitors to cynomolgus monkeys led to an almost 80% reduction in serum IgG levels. Importantly, due to differences in binding sites for the two ligands, none of these molecules influence albumin levels in the blood such that each represents a promising treatment strategy for immune complex mediated diseases while simultaneously minimizing side effects.

An important concept to keep in mind when reengineering FcRn or its ligand for therapeutic purposes is the effect that these modifications will exert on in vivo kinetics. For example,

chimeric molecules containing Fc regions harboring the AbDeg modifications were able to more effectively deliver antigens to APCs, and induce a concomitantly more robust T cell proliferation, when studied in vitro [31]. However, when administered in vivo, the decreased physiological persistence of these chimeric molecules caused by their higher binding affinity led to a complete reversal of the effects observed in vitro; that is, in vivo, molecules with a wild-type Fc domain induced considerably stronger T cell expansion than did those with the AbDeg Fc domain. It is thus imperative to keep in mind the pleiotropic functions of FcRn when attempting to manipulate it for therapeutic purposes. With this caution in mind, manipulation of FcRn remains a promising tool and has already proven itself to be valuable for tumor imaging. Here, administration of excess IgG in conjunction with that of a specifically labeled antibody led not only to far better tumor-to-blood imaging contrast and finer image resolution but also to a more rapid whole body clearance of radioactivity and protection of tissues from bystander radiation [101].

More specifically, considerable evidence already exists for a range of ailments expressly linked to FcRn and which stand to benefit directly from FcRn blocking strategies. In a murine model of acquisita bullosa, an autoimmune blistering disease triggered by antibodies directed against type IV collagen, $FcRn^{-/-}$ mice exhibited much less extensive blistering that wild-type controls [102]. Treatment of rats with an FcRn-blocking antibody led to a reduction of symptoms in either acute or chronic mouse models of myasthenia gravis [103]. FcRn has also directly been implicated in the development of rheumatoid arthritis [104] and lupus, where IgG hypercatabolism was observed [105]. In autoimmune diseases such as these, blocking FcRn function is desirable in order to encourage the catabolism of the pathogenic antibodies. Alternatively, the development of IgGs with both enhanced FcRn binding and release, or an accelerated rate of transcytosis, would be of benefit in at least two diseases. FcRn transit of IgG-complexed beta-amyloid peptide across the blood–brain barrier plays a protective role in preventing the buildup of beta-amyloid plaques in the brain and thus in combating the onset of Alzheimer's disease [81]. FcRn in kidney podocytes also protects against immune complex-mediated nephrotoxic damage by encouraging clearance of IgG from the glomerular basement membrane and minimizing susceptibility to glomerular injury [28]. Finding a way to maximize FcRn's protective effects while minimizing its role in pathological autoimmune diseases remains a daunting challenge, but one which holds significant promise.

Mucosal delivery

The generation of new tools in order to facilitate this continuing pursuit represents another important area of progress. New techniques for the production of large amounts of soluble FcRn will facilitate the screening of novel small molecule inhibitors and engineered antibodies alike [106, 107]. In addition, the creation of fusion proteins containing natural or reengineered Fc regions joined to a potentially therapeutic molecule aims to exploit the basic transcytotic pathway followed by FcRn in order to facilitate drug delivery. Due to high-level expression of FcRn in epithelial cells lining human mucosal surfaces, this represents an important therapeutic strategy.

The large surface area of the lung makes this organ an ideal route for systemic drug delivery provided that the inhaled therapeutic agent can be adequately absorbed. While progress had been made in the aerosol administration of some small proteins such as insulin, the lung has remained impenetrable to many larger molecules [78, 108]. Exploitation of the presence of the endogenous expression of the FcRn as a transporter in the upper airways of humans represents an attractive opportunity to circumvent this problem [54, 78, 109]. Proof of the viability of this option comes from the successful pulmonary delivery of an Fc-erythropoietin fusion protein of greater than 100 kDa [108]. This molecule was found to peak in systemic circulation within hours of administration to cynomolgus monkeys and

demonstrated similar bioavailability to subcutaneously administered erythropoietin. These experiments have been successfully reproduced in human volunteers and development is currently underway for a host of other therapeutic Fc-fusion proteins including IFN-β-Fc, IFN-α-Fc, Factor IX-Fc, and FSH-Fc [78, 109]. As our ability to successfully manipulate the Fc region of IgG in order to modify its binding kinetics improves, the use of FcRn as a tool for mucosal delivery of therapeutic systemic molecules is likely to emerge as an important strategy for drug delivery.

Conclusion

That FcRn was predicted to exist long before its actual discovery accurately reflects the importance of the physiological functions it serves both throughout the body and across the lifespan of many different types of mammals. In addition to delivering the first tools of immunity to infants, FcRn continues to regulate physiological and immunological homeostasis in adult life and represents a sensitive immunological sensor from birth through death. Perhaps nowhere is its role more important than within the gastrointestinal tract where the rate of immune complex formation is highest in the body due to its proximity to the external environment. The extent of FcRn's contribution to gastrointestinal homeostasis is only now starting to be investigated, but is likely to move to the forefront as a greater understanding of how self/non-self interactions shape systemic immunity is gained. While the therapeutic potential of FcRn elsewhere in the body has already begun to be investigated, how it may be manipulated within the gut remains a largely unexplored territory. No doubt future study will shed more light on this as well as other aspects of FcRn biology. It is certain, however, that despite FcRn-related research having passed its infancy, there is no danger of a down-regulation of interest in its functions in the near future.

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