

Review

Placental transport of immunoglobulin G

Neil E. Simister*

Rosenstiel Center for Basic Biomedical Sciences and Biology Department, Brandeis University, 415 South Street, Waltham, MA 02254-9110, USA

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Abstract

Maternal antibodies transported across the placenta protect the newborn. Maternal immunoglobulin G (IgG) concentrations in fetal blood increase from early in the second trimester through term, most antibodies being acquired during the third trimester. IgG1 is the most efficiently transported subclass and IgG2 the least. Transfer across the syncytiotrophoblast of the chorionic villi is mediated by the neonatal Fc receptor, FcRn. Immune complexes are absorbed in the stroma of the villi, probably by FcγRI, FcγRII, and FcγRIII on placental macrophages. The mechanism of IgG transport across the endothelium of fetal capillaries is not understood. Endothelial cells in terminal villi express FcγRIIb. However, it is not known whether this receptor transports IgG or prevents transport of immune complexes to the fetus. © 2003 Elsevier Science Ltd. All rights reserved.

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1. Introduction

If maternal immunization is to protect the newborn, a protective level of specific IgG must be present in the mother's blood at a time when it can be transferred to the fetus (if the antibody is poorly transported, the maternal level must exceed the protective level). The more specific IgG the fetus receives above the protective level, the longer a protective level will be maintained after birth. The time period in which maternal immunization is effective depends on the timing of the mother's immune response to the vaccine, and also the timing of maternal–fetal IgG transport. The maternal response is influenced by the vaccine and vaccination protocol and by the mother's health and immunologic history, and will not be considered here. The timing of the transmission of maternal IgG to the fetus will be discussed. What is known of the mechanism of IgG transport and the limited extent to which this explains its timing will also be considered.

2. Timing of IgG transport

Two types of study have addressed the development of the capacity to transmit IgG from mother to fetus. Most of the information comes from measurements of the concentrations of endogenous antibodies in maternal and fetal sera

at different gestational ages. These include measurements of total IgG, of subclasses of IgG, and of antibodies of particular specificities for antigen. In fewer studies the transport of exogenous antibodies has been measured.

Very little maternofetal transfer of radiolabeled IgG was detected at around 12 weeks gestation (WG) [1]. Consistent with this, very little IgG is present in the villous stroma of placentas at 8–10 WG [2]. Because most IgG in fetal blood is maternal in origin [3], its concentration reflects transport from the mother. Fetal IgG remains low until the second trimester [4–9].

Studies by Gitlin and coworkers revealed a rise in fetal IgG levels in the second half of the second trimester [4,5]. These studies showed a sharp increase between 22 and 26 WG. However, subsequent studies have shown a smooth rise in fetal IgG from the earliest ages examined (13–18 WG, [6–9]). The discrepancy may have arisen because the earlier studies did not include fetuses between 22 and 26 WG, and used different ways of estimating gestational age up to 22 WG and from 26 WG. Malek and coworkers obtained a large number of second trimester sera by cordocentesis [9]. They found an average increase in fetal IgG concentration from 1.4 ± 0.7 g/l at 17–22 WG (approximately 10% of the maternal concentration) to 5.6 ± 1.1 g/l at 28–32 weeks (approximately 50% of maternal). Fetal IgG levels continue to increase during the third trimester [8,10–12]. Indeed, the rate of increase in fetal IgG concentration between 29 and 41 WG is roughly double than seen between 17 and 28 weeks [9]. At term, fetal IgG typically somewhat exceeds maternal levels [13,14].

* Tel.: +1-781-736-4952; fax: +1-781-736-2405.

E-mail address: simister@brandeis.edu (N.E. Simister).

3. Subclass differences

The levels of the four subclasses of human IgG in cord blood have been extensively investigated. Particular attention has been paid to IgG2, which is often detected in lower amounts in serum from cord blood than maternal blood, and to IgG1, which is generally found to be more abundant in cord than in maternal samples.

An early study reported cord IgG2 in only trace amounts, in contrast to the other subclasses, which approximately equaled those of the mother in abundance [15]. However, subsequent work has shown substantial amounts of cord IgG2. These concentrations are generally [8,9,11,12,16–18], but not always [10,19–23], lower than the mothers'. In two recent studies by Malek and coworkers fetal IgG2 was at approximately 60% of the maternal level at term [9,12].

Changes in the fetal concentrations of the IgG subclasses with gestational age have been followed using sera obtained after termination of pregnancy, from preterm newborns and by cordocentesis. Fetal IgG1 exceeds the other subclasses in concentration from the earliest ages [8–10,12,17,18]. Malek and coworkers found that the IgG1:IgG2 ratio at 17–22 WG already exceeds that in maternal blood [9]. This suggests that IgG1 begins to be transported before IgG2 or that IgG1 is preferred to IgG2 in the transport process. The rates of increase in the fetal:maternal ratios of IgG1, IgG3, and IgG4 accelerate in the third trimester, whereas that of IgG2 does not [9]. Excess fetal IgG1 above the maternal concentration accounts for most of the excess in total IgG normally found at term. Small-for-gestational age newborns have lower IgG concentrations than appropriate-for-gestational age newborns of the same gestational age [24]. This is largely, although not wholly, due to lower levels of IgG1 [17,18].

IgG4 levels are very variable (e.g. [18]), and in some studies exceed maternal levels at term [9].

4. Pathway of IgG transport

IgG is transported from mother to fetus across the placenta [1]. During the third trimester, transported IgG crosses the syncytiotrophoblast covering the chorionic villi and the endothelium of fetal capillaries within the villi. These cell layers are separated by their basal laminas, and in some regions by the connective tissue of the stroma (reviewed in [25]).

5. IgG receptors in barrier tissues

5.1. Syncytiotrophoblast

There is compelling evidence that the MHC class I-related Fc receptor, FcRn, mediates the transmission of IgG across the syncytiotrophoblast. FcRn is expressed in rat and mouse yolk sac [26,27] and is required for the transmission of IgG

from mother to fetus in mice [28]. Despite the differences in placentation, these observations raised the possibility that FcRn might also function in IgG transport to the human fetus. The gene encoding the α chain of mouse FcRn maps to a chromosome region syntenic with human chromosome 19 [27]. This study led to the cloning from a chromosome 19-specific library of the human orthologue [29], a fragment of which was used to clone human FcRn α chain cDNA from a term placental library [30]. FcRn was subsequently detected in placental membranes [31] and purified from them [32].

The localization of FcRn within the placenta has been investigated by *in situ* hybridization and immunohistochemistry. FcRn mRNA is present in syncytiotrophoblast and some stromal cells in first trimester and term placentas, but not in capillary endothelium [31]. FcRn α chain is readily detected in syncytiotrophoblast of first trimester [31] and term placentas [31–33]. The β 2-microglobulin subunit of FcRn is also present in syncytiotrophoblast [34,35]. The identification of an IgG transporting protein in the first cellular barrier between the maternal and fetal circulation suggested that FcRn mediated maternofetal transport of IgG. This is strongly supported by the observation of Ward and coworkers that Fc mutated in a way that decreases its binding to FcRn is markedly impaired in its transmission from the maternal to the fetal circuit in a perfused placental system [36].

A complication arises because human FcRn does not bind IgG at neutral pH [30], and therefore would not bind IgG at the pH of maternal blood. Rather, it binds at mildly acidic pH like the FcRn in the yolk sac endoderm of rats [26], which is the site of prenatal transport of IgG in that species [37]. In the yolk sac most FcRn is found in cytoplasmic vesicles [26]. Rodewald and coworkers suggested that these vesicles might be acidified endosomes, which could represent the initial binding site of IgG and FcRn [26]. Contractor and coworkers drew upon observations that the optimal pH for binding IgG to human trophoblast membranes was below 6.5 [38,39] to suggest that IgG might bind its, then unidentified, placental receptor in endosomes [40]. After the discovery of FcRn in human placenta [30], it has been widely accepted that IgG binds FcRn in early endosomes within the syncytiotrophoblast. Although it seems very likely, it is not yet known whether FcRn is located in early endosomes in syncytiotrophoblast.

Several studies show IgG in tubulovesicular structures in the syncytiotrophoblast, which may be early endosomes [40–43]. The mechanism of IgG uptake into endosomes is not known. A fluid phase marker, horseradish peroxidase, enters tubulovesicular structures along with IgG [40]. Because of the high concentration of IgG in maternal blood it is attractive to suppose that IgG can enter in the fluid phase and go to endosomes that way. It remains possible that other proteins in the syncytiotrophoblast plasma membrane carry IgG from the cell surface to endosomes, although no strong candidates have been identified (reviewed in [44]).

Wherever FcRn first binds IgG and however IgG gets there, the function of FcRn is to carry IgG into a vesicular pathway to the plasma membrane, avoiding lysosomal degradation. The extent to which IgG is broken down during transport is controversial. During transport from the maternal to the fetal circuit of perfused placental lobules most radioiodinated IgG is degraded [45], whereas no degradation of unlabeled IgG is detected [46]. Because denaturation during radiolabeling may increase the susceptibility of IgG to degradation, the latter result may better represent transport *in vivo*. FcRn would release IgG at a plasma membrane exposed to intercellular fluid of neutral pH. IgG released at the basal membrane of the syncytiotrophoblast passes through the basal lamina. Within the terminal villi are vasculosyncytial zones in which sinusoids of fetal capillaries lie adjacent to the syncytiotrophoblast, separated only by their basal laminae. In these regions IgG may pass from the syncytiotrophoblast to the fetal vessel endothelium without exposure to stromal cells. In contrast, in intermediate and stem villi, IgG percolates through the stroma before reaching the blood vessels.

5.2. Stroma

IgG is readily detectable in the stroma [47], some of it as immune complexes [48]. The stroma contains fibroblasts and macrophages. Unlike syncytiotrophoblast, stromal cells express class I HLA molecules [49], including paternally inherited allotypes. Stromal absorption of maternal antibodies against paternal HLA and also of immune complexes impairs their transmission to the fetus [50,51] (reviewed in [52]). Stromal macrophages contain FcγRI, FcγRII and FcγRIII [53–56]. FcγRII binds immune complexes but does not bind monomeric IgG detectably [57]. Both the a and b isoforms of FcγRIII bind immune complexes [58,59] but only FcγRIIIa binds monomeric IgG [59,60]. FcγRI binds immune complexes and also monomeric IgG [61], which it can recycle [62]. Intestinal macrophages have recently been shown to express FcRn [63]. However, FcRn is not detected in stromal macrophages at term [31–33]. The Fc receptors on stromal cells could sequester immune complexes, but not prevent monomeric IgG reaching fetal capillaries.

5.3. Fetal vessel endothelium

The human placental endothelium is relatively tight (reviewed in [64]). IgG crosses the fetal vessel endothelium by a transcellular route, and not by a paracellular route between endothelial cells [40,42,43]. Endothelial cells bind immune complexes [65,66], perhaps preventing their transmission to the fetus [51]. FcRn mRNA is not detected in villous capillary endothelium by *in situ* hybridization [31]. Similarly, immunohistochemical studies have generally not found FcRn α chain in terminal villous capillary endothelium [31,67], although occasional staining has been reported [33]. FcRn appears to be present in endothelial cells further down the

villous trees and is expressed in umbilical vein endothelium [67]. Antohe et al. found FcRn in an endothelial cell line established from placental villi [68]. However, these cells do not express FcγRII and so probably represent the endothelium of the stem villus rather than the terminal villus [67,69] (see below). Because FcRn is expressed in capillary endothelia in some tissues [70], its absence from terminal villi requires explanation. FcRn in capillary endothelia is thought to protect IgG from catabolism [71–73]. It is possible that if FcRn were expressed in terminal villi it would carry IgG from the capillaries to the stroma and thus hinder transport to the fetus.

The only known Fc receptor consistently detected in terminal villous vessel endothelium at term is FcγRII [43,53–56]. Lang et al. noted a gradient of expression with high FcγRII in villous endothelium and none in umbilical vein endothelium [69]. Anderson and coworkers identified the type of FcγRII as FcγRIIb2 [67]. In the absence of other candidates, it is tempting to ascribe a role in IgG transport to FcγRIIb. This hypothesis is attractive because complexes of IgG2, the least efficiently transported subclass (above), are bound least strongly by FcγRII. However, there are two problems in understanding how FcγRII might transport of IgG across the endothelium. First, FcγRIIb has no detectable affinity for monomeric IgG [57]. Second, FcγRIIb has a higher affinity for complexes of IgG3 than complexes of IgG4 [74], a preference that is not reflected in the transport of these subclasses to the fetus. It therefore seems more likely that FcγRIIb prevents transmission of immune complexes into the fetal circulation.

6. Concluding remarks

In conclusion, the timing of maternofetal IgG transport in the light of what we know of its mechanism will be considered. During the first trimester of pregnancy, very little IgG is transported to the fetus [5]. IgG is present within the syncytiotrophoblast late in the first trimester [2]. FcRn is expressed in the syncytiotrophoblast by this time [31], and may protect IgG from intracellular degradation. At this stage of development, the syncytiotrophoblast covers a continuous cytotrophoblast layer. Cytotrophoblast cells neither express FcRn [31], nor contain IgG [2], and may prevent further penetration of the villi by IgG [2]. As gestation progresses, the syncytiotrophoblast expands and the cytotrophoblast becomes increasingly discontinuous [75]. These processes increase the surface area for IgG uptake from maternal blood and also allow access to the fetal vessel endothelium.

It is not known how IgG crosses the endothelium. Immunolocalization of FcγRII in endothelial cells during the first trimester have given both positive [43] and negative results [55,56]. Messenger RNA encoding FcγRIIb is detected only after 20 WG [76], but this isoform is present through term [67] and so is available during the period of maximal IgG transport. However, it remains to be discovered whether

it mediates transport of monomeric IgG or prevents transport of immune complexes.

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