Veterinary Immunology and Immunopathology 128 (2009) 171–177

Contents lists available at ScienceDirect

Veterinary Immunology and Immunopathology

journal homepage: www.elsevier.com/locate/vetimm

Review paper

The neonatal Fc receptor plays a crucial role in the metabolism of IgG in livestock animals

Judit Cervenak [a], Imre Kacskovics [a,b,*]

[a] Department of Immunology, Institute of Biology, Faculty of Science, Eötvös Loránd University, Pázmány Péter s. 1/C, Budapest H-1117, Hungary
[b] Immunology Research Group of the Hungarian Academy of Sciences at Eötvös Loránd University, Budapest, Hungary

ARTICLE INFO

Keywords:
IgG metabolism
Neonatal Fc receptor
Maternal immune transport

ABSTRACT

The role of the FcRn is fundamental in IgG metabolism. It is involved in transporting maternal immunity and protects IgG from fast degradation throughout life. While the acquisition of the humoral immunity through the transfer of IgG from mother to offspring shows species-specific differences, the mechanism how FcRn protects IgG from degradation is highly similar in all species analyzed so far. This review summarizes the current understanding of the FcRn-mediated IgG metabolism in livestock animals (cattle, sheep and pig) and point out those aspects that remain to be exposed for better understanding the function of this system in these species and also to take advantages of it for economical purposes.

© 2008 Elsevier B.V. All rights reserved.

Contents

1. Introduction

Following vaccination or infection, immunoglobulins (Igs) in a specific immune reaction are secreted. They are protective, in that they neutralize or eliminate the pathogen and its toxic products. Sera of immune competent donors mainly contain antibodies of the IgG, IgA and IgM classes. IgD and IgE are present in serum at only low concentrations, together making up less than 1% of total serum immunoglobulin. Although IgA is the main antibody associated with the gut, IgG is the predominant isotype in the blood and extravascular space playing an essential role in mediating immunity (Waldmann and Strober, 1969). The importance of this isotype is highlighted by the facts that maternal immunity is dependent on IgG transport from mother to newborn or neonate and that IgG has a long half-life in the circulation.

* Corresponding author. Tel.: +36 1 381 2175; fax: +36 1 381 2176.
E-mail address: ikacsko@elte.hu (I. Kacskovics).

Abbreviations: FcRn, neonatal Fc receptor; β2m, beta 2-microglobulin; Ig, immunoglobulin; IgG, immunoglobulin G.

0165-2427/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.vetimm.2008.10.300

The acquisition of humoral immunity in mammals, through the transfer of IgG from mother to offspring, shows species-specific differences. While, in primates and rabbit, all maternal IgG is transported through placenta during fetal life; in rodents, maternal IgG is transmitted both across the yolk sac to the fetus and also postnatally from milk via the neonatal small intestine (Roberts et al., 1990; Simister and Rees, 1985). In ungulates, IgG with all other macromolecules are acquired from the colostrum during in the first 12–18 h after birth (Butler and Kehrli, 2005). Though, maternal immune transport is different in mammals, maintenance of the serum IgG level uniformly requires continuous secretion of it by plasma cells and its protection from fast elimination. In 1958, Brambell described a hypothetical saturable receptor system involved in the maternal IgG transport (Brambell et al., 1958); then, he inferred the presence of a similar or identical receptor that protected IgG from fast catabolism to make it the longest surviving of all plasma proteins (Brambell et al., 1964). The Brambell receptor (FcRB) was eventually shown both to mediate the transmission of IgG in antenatal and/or neonatal periods, in this expression termed FcRn (neonatal Fc receptor), and the protection of IgG from catabolism (Junghans, 1997; Roopenian and Akilesh, 2007). Recent data support the hypothesis that FcRn binds albumin as well and prolongs the half-lives of both of these important serum proteins by diverting them from the endothelial intracellular degradation (Anderson et al., 2006).

This article is an overview of the current understanding of the FcRn-mediated IgG metabolism in livestock animals (cattle, sheep and pig) and summarizes those aspects that remain to be exposed for better understanding the function of this system in these species and also to take advantages of it for economical purposes.

2. FcRn, the neonatal Fc receptor

FcRn was first identified in rodents as the receptor that transfers maternal immunoglobulins from mother to newborn via the neonatal intestine (Rodewald, 1976; Simister and Rees, 1985). The FcRn molecules that are located in the intestinal brush border bind ingested IgGs from maternal milk and transport them through enterocytes to the systemic circulation of the newborn (Rodewald and Kraehenbuhl, 1984). The functional molecule is expressed as a heterodimer, composed of two subunits, an integral membrane α-chain that resembles MHC class-I molecules and the beta 2-microglobulin (β2m) (Simister and Mostov, 1989). Binding of IgG to FcRn requires contact residues in the CH2 and CH3 domains of IgG Fc portion and the α1 and α2 domains of FcRn, together with a single contact site in β2m (Kim et al., 1995; Popov et al., 1996; Raghavan et al., 1994; Vaughn et al., 1997). This process is pH-dependent, showing high-affinity binding at acidic pH ($pH \leq 6.5$) and weak or no binding at neutral pH ($pH \geq 7.0$) (Raghavan et al., 1995; Vaughn and Bjorkman, 1998). This pH specificity ensures specific binding in some intracellular vesicles (e.g. early endosomes) and in some cases on the cell surface (duodenal enterocytes).

Shortly after its characterization in mice, the human ortholog of this receptor was isolated in human placenta (Story et al., 1994) and shown that it transports maternal IgG into fetus (Leach et al., 1996). While intestinal FcRn expression in rodents is limited to the suckling period (Martin et al., 1997), the human FcRn is expressed in both the fetal intestine, where it is involved in IgG uptake from the amniotic fluid into the fetal circulation (Shah et al., 2003), and also in the adult enterocytes serving an important role in intestinal immune surveillance (Dickinson et al., 1999; Yoshida et al., 2004, 2006).

Due to the complex structure of the placenta in ungulates, the maternal immune transport in ruminants, horses and pigs, is exclusively mediated by colostral Igs. There is a high selectivity in the transport of immunoglobulins from the maternal plasma across the mammary barrier into the colostrum, wherein IgG dominates (for review see Butler and Kehrli, 2005). Upon ingestion of colostrum, the Igs with other macromolecules are transported across the intestinal barrier of the neonates into their circulation. This intestinal passage appears to be non-specific and FcRn-independent, and can take place only during the first day of newborns and ends because of a still uncharacterized "closure" that terminates the intestinal permeability (Lecce and Morgan, 1962). Brambell himself doubted the relevance of the FcRB to this function, noting "*that the transmission is confined to such a brief period and is so intense in these animals that receptor if present at all, must be assumed to play a negligible part in the process as degradation within the phagosomes is probably minimal*" (Brambell, 1970). Despite the non-specific absorption, a large proportion of the ingested IgG selectively (IgG1) recycles back into the intestinal lumen of suckling young ruminants where it contributes to the protection of the gastrointestinal tract against infection (Besser et al., 1988). This recycling occurs through the crypt epithelial cells which are known to be responsible for the secretory processes in the gut (Newby and Bourne, 1976). Parallel to these data, we found FcRn expression in the duodenal crypt cells of the neonatal lambs, however no FcRn expression was detected in their duodenal enterocytes suggesting that in neonatal ruminants the primary function of intestinal FcRn is to recycle IgG into the gut (Mayer et al., 2002). The absence of FcRn in the enterocytes is consistent with the theory that intact IgG absorption from colostrum is due to a non-specific mechanism or at least FcRn-independent. In young and adult animals, FcRn was detected in pig intestinal enterocytes and was shown that it is involved in IgG absorption (Stirling et al., 2005). In contrast to the pig, our studies indicated that FcRn was detected only in the crypt epithelial cells both in the small and also in the large intestine in an adult bull (unpublished observations).

3. The role of the FcRn in the accumulation of IgG in colostrums

In mice, Cianga et al. localized the FcRn to the epithelial cells of the mammary gland acini and found that the transport of the IgG subclasses into milk showed an inverse correlation with their affinity to the FcRn, suggesting that the FcRn in the lactating mammary gland plays a role in

Download English Version:

https://daneshyari.com/en/article/5797058

Download Persian Version:

https://daneshyari.com/article/5797058

Daneshyari.com