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Preview

Acquiring Maternal Immunoglobulin: Different Receptors, Similar Functions

The isolation of a novel Fc receptor (FcRY) from chicken yolk sac provides insight at the mechanistic level as to how avian maternal immunoglobulin (IgY) is transferred to offspring. This receptor is distinct from its mammalian counterpart and is a phospholipase A_2 receptor homolog. Biophysical analyses indicate that FcRY achieves pH-dependent binding to IgY through a conformational change.

The transport of maternal immunoglobulin (Ig) to offspring plays a pivotal role in conferring humoral immunity during the early stages of life. In mammals, delivery of maternal immunoglobulin G (IgG) is known to involve the MHC class I related receptor, FcRn (n = neonatal; reviewed in Ghetie and Ward, 2000). IgG transfer can occur at both the pre- and postnatal stages, with the proportion of transport at each stage varying across species (Brambell, 1970). Prenatal delivery occurs across the placental or yolk sac barrier, whereas postnatal transfer involves passage from mother's milk/colostrum across the neonatal intestine. FcRn orthologs have been isolated from multiple mammalian species, suggesting that the mechanisms of maternal IgG delivery are similar across mammalia.

Over the past decade, multiple studies have demonstrated that in addition to its role in transporting maternal IgG, FcRn regulates IgG levels throughout life at diverse sites in the body (Ghetie and Ward, 2000). For example, FcRn controls the serum half-lives of IgG molecules by salvaging them from lysosomal degradation. As a consequence, the affinity of an IgG for FcRn provides a good predictor of its serum persistence. FcRn is also involved in transporting IgG across cellular barriers such as lung epithelia (Spiekermann et al., 2002). The function of FcRn, which was originally believed to act solely during the prenatal/neonatal periods, has therefore required redefinition to encompasss a broader role in IgG transport.

A characteristic feature of FcRn is that it binds to IgG in a pH-dependent way, with relatively tight binding at pH 6 that becomes progressively weaker as neutral pH is approached (Ghetie and Ward, 2000). This pH dependence is essential for FcRn function and has resulted in models where, following uptake by fluid phase pinocytosis, IgG interacts with FcRn in acidic early endosomes. IgG bound to FcRn is sorted into the recycling or transcytotic pathway, whereas unbound IgG enters the lysosomal route (Ober et al., 2004). A minor variation of this model is that for cells such as neonatal intestinal cells that are bathed in a slightly acidic milieu, IgG can bind to cell surface FcRn. In general terms, this model can accommodate the known functions for FcRn, and in vitro studies provide support for its validity.

In birds and some reptiles, maternal immunoglobulin Y (IgY) is transported into the egg yolk prior to transfer at a late stage of embryonic development into the embryonic bloodstream. IgY has C_H2, C_H3, and C_H4 domains and is believed to be the evolutionary precursor of IgG and IgE (the C_H3 and C_H4 domains of IgY resemble the C_H2 and C_H3 domains of IgG, respectively) (Warr et al., 1995). IgY transport into the embryo is specific and binding of IgY to the yolk sac membrane is much greater at pH 6 than at pH 7.4. Given that the pH of yolk is 6, it therefore might be predicted that transport of IgY from yolk to the embryonic circulation resembles the FcRn-mediated delivery of IgG across the rodent neonatal intestine. On the other hand, FcRn does not bind to IgY and mammalian IgGs do not transfer into the chick embryo (Brambell, 1970), suggesting that a distinct receptor might be involved in IgY transport. Therefore, an important question concerns the nature of the receptor responsible for IgY transport from yolk to embryo. In a report from the Bjorkman lab (West et al., 2004, this issue of *Immunity*), an Fc receptor with the requisite properties for IgY transport has been isolated and characterized. The approach taken was to purify an Fc receptor from chicken yolk sac, using the property of pH-dependent binding to IgY as a tool for isolation. Interestingly, this receptor (called FcRY) bears no similarity to FcRn but is a homolog of the mammalian secretory phospholipase A_2 receptor (PLA_2R). As for PLA_2R, FcRY is a type I membrane protein for which the ectodomain comprises an N-terminal cysteine-rich (CysR) domain, a fibronectin type II (FNII) domain, and eight C-type lectin-like domains (CTLDs, a misleading classification as most of these domains do not have C-type lectin activity). This Fc receptor therefore falls into the heterogeneous mannose receptor (MR) family of proteins.

Binding studies with soluble, recombinant FcRY fragments demonstrate that the interaction site for IgY can be reconstituted by mixing recombinant CysR-FNII domains with the eight CTLDs, whereas the smaller subfragments that are tested do not have binding activity (West et al., 2004). The binding site for FcRY on IgY is currently not mapped, although an FcY fragment comprising both C_H3 and C_H4 domains binds with properties similar to those of IgY. Despite the presence of CTLDs and a CysR domain, which for the MR have carbohydrate binding activity (East and Isacke, 2002), the data presented indicate that IgY carbohydrate is unlikely to be involved in the IgY-FcRY interaction. An inability to bind carbohydrate is a feature of the majority of CysR domains and CTLDs of MR family members (East and Isacke, 2002), indicating that FcRY is not an outlier in this respect.

A significant observation of the study of West et al. (2004) is that the mechanism by which pH-dependent binding by FcRY to IgY is achieved is distinct to that employed by FcRn. IgG-FcRn interactions involve several key histidine residues located at the C_H2-C_H3 domain interface of IgG that interact with acidic FcRn resi-

dues (Martin et al., 2001; Medesan et al., 1997). pH dependence for FcRn binding to IgG therefore entails a chemical change, involving deprotonation/protonation cycles rather than a conformational alteration. In contrast, a combination of surface plasmon resonance and sedimentation analyses indicate that a conformational change mediates the pH dependence of the IgY-FcRY interaction (West et al., 2004). A model is proposed in which the CysR-FNII domains fold back onto the CTLDs at pH 6 to form an IgY interaction site. By analogy, the CysR domain of the MR family member, Endo180, appears to contact the second CTLD in a mode that may resemble the "folded back" conformation of FcRY. At pH 8.0 the CysR-FNII domains of FcRY no longer interact with the CTLDs and the receptor forms a more extended conformation in which the IgY interaction site is lost.

Despite the differences in the nature of Ig-FcR interactions between mammals and chickens, the outcome of pH dependence is achieved. The data presented for FcRY also suggest further functional similarities with FcRn. First, the stoichiometry of the IgY-FcRY interaction is 1:2, as observed for IgG-FcRn complexes (Ghetie and Ward, 2000). Second, there is an ExxxLI motif in the cytosolic tail of FcRY. An analogous di-leucine motif (DxxxLL) plays an important role in the trafficking of FcRn (Wu and Simister, 2001). Third, Northern blotting shows that FcRY is expressed at multiple sites in adult chickens, indicating that it might have the generic immunoglobulin transport functions that are a hallmark of FcRn. In the context of considering possible functions for FcRY, Bjorkman and colleagues propose that a receptor distinct from FcRY is involved in delivering IgY from the maternal circulation into yolk. In support of this, human IgGs do not bind to FcRY (West et al., 2004) and yet are transported from the maternal circulation into chicken egg yolk (Morrison et al., 2002). Thus in chickens a division of labor appears to have evolved for the two-step transfer of maternal IgY to chick embryos, and it will be interesting to characterize the mechanism involved in the first step of transport.

The isolation of FcRY raises further questions about the molecular nature of the IgY-FcRY interaction that should be possible to address by biochemical and high-resolution structural studies. There are also issues at the cellular level that are of considerable interest. For example, how does this receptor traffic intracellularly, and does it play a more general role in regulating IgY levels throughout life? The properties of FcRY add to the diversity of functions that are exhibited by previously characterized members of the MR family (East and Isacke, 2002). Finally, but not least important, the study of West et al. (2004) has consequences at the evolutionary level insofar as it suggests that the role of MHC class I molecules in antigen presentation evolved prior to their ability to bind IgG.

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