Passive Transfer of Maternal Immunity; A Comparative Immunology Viewpoint

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Abstract

Passive transfer of maternal immunity is essential to the growth, development, and reproductive success of future generations in all mammals. In this minireview, I compare the routes of maternal passive transfer of antibodies and immune cells in cattle, swine, humans, and mice and identify gaps in the scientific literature relevant to dairy cow and calf health. Further, I discuss antibody effector functions, ,including blocking infection and replication of an infectious organism (called 'neutralizing') or inducing innate immune cells to engage in phagocytosis, cytotoxicity or complement deposition (called 'non-neutralizing'). I also discuss the potential role of colostrum and milk immune cells on fetal tolerance, reproductive fitness, and neonatal health. This minireview is relevant to anyone engaged in the betterment of dairy cow and calf health.

What Are Antibodies and What Do They Do?

Antibodies are the secreted product of antibody-producing plasma cells and are a major component of the adaptive immune system. Secreted antibodies exist as multiple isotypes, including immunoglobulin G **(IgG)**, IgA, IgM, and IgE, each having multiple effector functions (Forthal, 2014). Antibodies can be divided into two regions, an antigen binding fragment (or 'Fab' region) or a constant fragment (or 'Fc' region). The Fab region binds to a specific target antigen which can be from a pathogen, microbe, self, or anything found in an individual's environment (Chiu et al., 2019). When the antibody Fab region binds to an infectious organism at key locations on the pathogen's surface, it renders it unable to productively infect a host cell (Figure 1A). This is called antibody 'neutralization' and can be measured *in vitro* using cell culture systems (Parren and Burton, 2001). While antibody neutralization is an important measure of protection against infection, it is not the only function antibodies perform. For example, the Fc region can bind Fc receptors **(FcRs)** which are expressed by multiple cells of the innate immune system like monocytes, macrophages, neutrophils, natural killer cells, and even epithelial and endothelial cells (Lu et al., 2018; Tay et al., 2019). FcRs are as numerous and they are diverse and Fc/FcR binding can induce both activating and inhibitory functions (Ravetch and Bolland, 2001, Ben Mkaddem et al., 2019). Some key 'non-neutralizing' Fc/FcR-driven functions shown to be important in protection against infection and disease include antibody-dependent cellular phagocytosis **(ADCP)**, antibody-dependent cellular cytotoxicity **(ADCC)**, and antibody-dependent complement deposition **(ADCD)** (Figure 1B). In these ways, antibodies provide a link between the specificity of the adaptive immune system and fast-acting nature of innate immune system.

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Antibody functional diversity exists between the different isotypes. For example, IgG, the dominant antibody in circulation, is a monomeric molecule demonstrated to have potent neutralizing and non-neutralizing effector functions (Vidarsson et al., 2014). IgG antibodies can have high affinity, a measure of the strength of binding between an antibody and its target antigen (Doria-Rose and Joyce, 2015). However, IgG is less likely found at mucosal sites where IgA and IgM antibodies dominate. IgA and IgM antibodies are found in dimeric and pentameric forms, respectively, at mucosal sites, including the respiratory tract, gastrointestinal tract, and some regions of the reproductive tract (Mantis et al., 2011; Chen et al., 2020). In some cases IgA and IgM are demonstrated to have high avidity, a measure of the overall strength of interactions between an antibody and antigen, as their dimeric and pentameric nature allows for increased binding sites (Moor et al., 2017; Oostindie et al., 2022). IgE antibodies are monomeric and are well known for their role in mediating allergic reactions through ability to activate mast cells and basophils through Fc/FcεRI interactions (Gould and Sutton, 2008; Sutton et al., 2019). An antibody's ability to perform its effector function is directly related to the level of antibodies that exist and where they are located. This is highly relevant to the passive transfer of maternal antibodies from mom to offspring across different species.

Passive Transfer of Maternal Antibodies

Neutralizing and non-neutralizing maternal antibody functions in cattle

In mammals, antibodies are passively transferred from mom to baby either through the placenta, during lactation (via colostrum or milk), or both to provide protection against infectious diseases and promote microbiota colonization and stability (Hurley and Theil, 2011; Niewiesk, 2014; Atyeo and Alter, 2021; Langel et al., 2022). However, how they are transferred and in what ratios is different depending on the species. In cattle, IgG antibodies are the dominant antibody in colostrum and mature milk and uptake into neonatal circulation within 24 to 36 hours of life. Inadequate passive transfer of maternal antibodies (defined as 10 g IgG/liter of serum in calves) results in high morbidity and mortality early in life (Godden et al., 2019). Due to the nature of the bovine placenta, antibodies are not transferred through the placenta during pregnancy (Chucri et al., 2010). Neutralizing functions of maternal antibodies have been studied in cattle. In a recent study, calves were either fed 4 L of colostrum sourced from bovine respiratory syncytial virus-vaccinated cows or non-vaccinated cows and were challenged at 21 days of age (Meyer et al., 2023). Calves born to vaccinated dams with increased RSV-specific neutralizing antibodies had increased RSV-specific neutralizing titers in serum and after RSV challenge had decreased peak viral loads in nasal secretions and bronchoalveolar lavages and decreased clinical scores. However, neutralizing antibodies in bovine colostrum against a particular infectious organisms may only represent a fraction of the 10 g of total IgG/liter of serum required to achieve adequate passive transfer according to industry standards. Therefore, maternal immunization against infectious agents that represent a significant burden to that farm or region is highly important to make sure that maternal neutralizing antibodies are passively transferred in appropriate amounts. Interestingly, Fc-mediated antibody functions have not been thoroughly assessed in bovine colostrum or in dairy calves. This would be an important area of future investigation for bovine immunologists as Fc-mediated functions in theory could contribute to protection against mastitis in the bovine mammary gland and decrease the burden of infectious organisms in the neonate.

In swine and other species; Mechanisms of maternal IgG and IgA transfer to colostrum

Swine, like cattle, also do not transfer maternal antibodies to their offspring through the placenta during pregnancy (Macdonald and Bosma, 1985). Therefore, neonatal piglets receive protective maternal antibodies during the first days of life via uptake through the intestine. Interestingly, in swine while IgG is typically dominant in colostrum, IgA antibodies are the dominant antibody in mature milk like humans (Markowska-Daniel et al., 2010; Hurley and Theil, 2011; Enger et al., 2021; Langel et al., 2022). It is intriguing to consider why IgG is the dominant antibody in mature milk in cattle, but in pigs and humans, IgA is dominant. Understanding why this is the case allows us to reflect on the fundamental biology of how antibodies traffic to the mammary gland and into mammary secretions. IgG in colostrum of most species studied (including humans) is mostly transmitted from blood to the mammary gland and into colostrum. Evidence in mice suggest this is a neonatal Fc receptor (FcRn)-mediated process. Additionally, when bovine FcRn is over expressed in mouse mammary glands, IgG levels in milk increase (Lu et al., 2007). However, recent work in pigs where the FcRn gene has been removed ('knocked out') suggests that FcRn may not be the major receptor in IgG transport into colostrum (Ke et al., 2021). It's possible that IgG uses non-canonical receptors or non-specific pinocytosis to move across mammary gland epithelial cells into colostrum in pigs. While IgG is mostly derived from circulation, the majority of IgA in colostrum is from local plasma cells in the mammary gland (Figure 2) (Roux et al., 1977; Watson, 1980). Local IgA+ plasma cells secrete dimeric IgA which covalently binds its cognate receptor polymeric immunoglobulin receptor on the basal side of epithelial cells and is transported to the lumen as secretory IgA (Figure 2) (Brandtzaeg, 2010). IgA+ plasma cells migrate to the mammary gland during late pregnancy and throughout lactation. It was demonstrated in mice that chemokine **(C-C motif)** ligand 28 **(CCL28)** secretion from the mammary gland binds to IgA+ plasma cells that express chemokine receptor 10 **(CCR10)** (Wilson and Butcher, 2004; Morteau et al., 2008). The CCL28/CCR10 axis is likely active in trafficking IgA+ plasma cells to the mammary gland in cattle, swine, and humans as well. Why cattle do not secrete as much IgA in mammary secretions as pigs and humans may be related to the general levels of CCL28 secretion from their mammary glands and/or CCR10 expression on bovine IgA+ plasma cells. While CCL28 has been detected from bovine milk samples (Pallister et al., 2015), an assessment of chemokine receptor expression on bovine IgA+ plasma cells has not been conducted and may hold clues for why IgG dominates in mammary secretions but not IgA in cattle.

Anti-microbe antibodies in colostrum and milk

It is well-established in swine and somewhat to a lesser extent in mice that the majority of IgA+ producing plasma cells in the mammary gland are derived from the intestine (Lindner et al., 2015; Langel et al., 2016a; Langel et al., 2020). Considering the intestine contains the majority of IgA+ plasma cells (Fagarasan and Honjo, 2003; Bemark et al., 2016), many of which are producing anti-microbe antibodies (Weis and Round, 2021), it is logical to suggest that the purpose for intestine-derived IgA-producing plasma cells to end up in the mammary gland is so that they can produce anti-microbial antibodies that assist in intestinal microbial colonization of the neonate (Rogier et al., 2014; Rodríguez et al., 2021; Sanidad et al., 2022). Anti-microbial antibodies could do this in multiple ways, eliminating toxins and/or microbial molecules, limiting motility

and invasion, aggregation of rapidly dividing bacteria, preventing biofilm formation, anchor beneficial microbe to the epithelial surface, alter bacterial gene expression patterns and likely more (Weis and Round, 2021). Indeed, studies in humans have demonstrated that mom's milk is a main driver of microbiota colonization in the intestine (Fehr et al., 2020; Laursen et al., 2021; Lyons et al., 2022). What contribution anti-microbial antibodies have in cow colostrum and calf microbiota development and intestinal health are unknown. Considering a larger percent of the total antibody pool in cattle is derived from serum may suggest that fewer anti-microbial antibodies exist in bovine colostrum compared to humans or swine. However, breast milk IgG antibodies in mice were found to be anti-microbial and contributed to microbiota colonization (Sanidad et al., 2022). This would be an important area of future research as dairy calf intestinal health is suggested to impact overall growth and future milk production (Osorio, 2020).

Passive Transfer of Maternal Immune Cells

There are many other components of breast milk that are likely to have an impact on protection against infectious pathogens, development of the immune system, and regulation of the microbiome. Viable immune cells including both innate (monocytes, macrophages, natural killer cells, and neutrophils) and adaptive (B and T cells) can be found in colostrum and milk (Laouar, 2020; Gleeson et al., 2022). The contributions of each of these cell types in neonatal health is not fully understood; however, there are a few studies in different species that demonstrate their importance. In dairy calves, calves fed cell-free colostrum had altered immune subtypes in blood both immediately (within 28 days of colostrum feeding) and after vaccination more than 1 year later (Langel et al., 2015, 2016b) when compared to calves fed colostrum with immune cells. Other studies also support a role for colostral cells in neonatal health in cattle (Riedel-Caspari, 1993; Reber et al., 2008; Meganck et al., 2016) and swine (Bandrick et al., 2008; Bandrick et al., 2014). In mice, maternal cells and non-inherited maternal antigens help promote tolerance during pregnancy and multigenerational reproductive fitness (Kinder et al., 2015; Kinder et al., 2017; Molès et al., 2017). While it is difficult to demonstrate that this same phenomenon exists in humans, one group has shown that exclusive breastfeeding may be associated with higher levels of maternal immune cells across infancy compared with nonexclusive breastfeeding (Balle et al., 2022). Additionally, a study in non-human primates suggests that breast milk-derived maternal cells can traffic to the intestine, liver and spleen (Jain et al., 1989). More work is needed to better understand the contribution of breast milk immune cells to neonatal protection against diseases.

Conclusion

Passive transfer of maternal immunity is essential to sustain the next generation in all mammals (Langel et al., 2022). There is still much to learn regarding the full potential of passively transferred maternal immunity whether it be through the placenta (as in humans) or solely through colostrum (in domesticated species like cattle and swine). Using comparative immunology approaches, we can better define the mechanisms of maternal passive transfer of immunity across multiple species to improve maternal and neonatal health.

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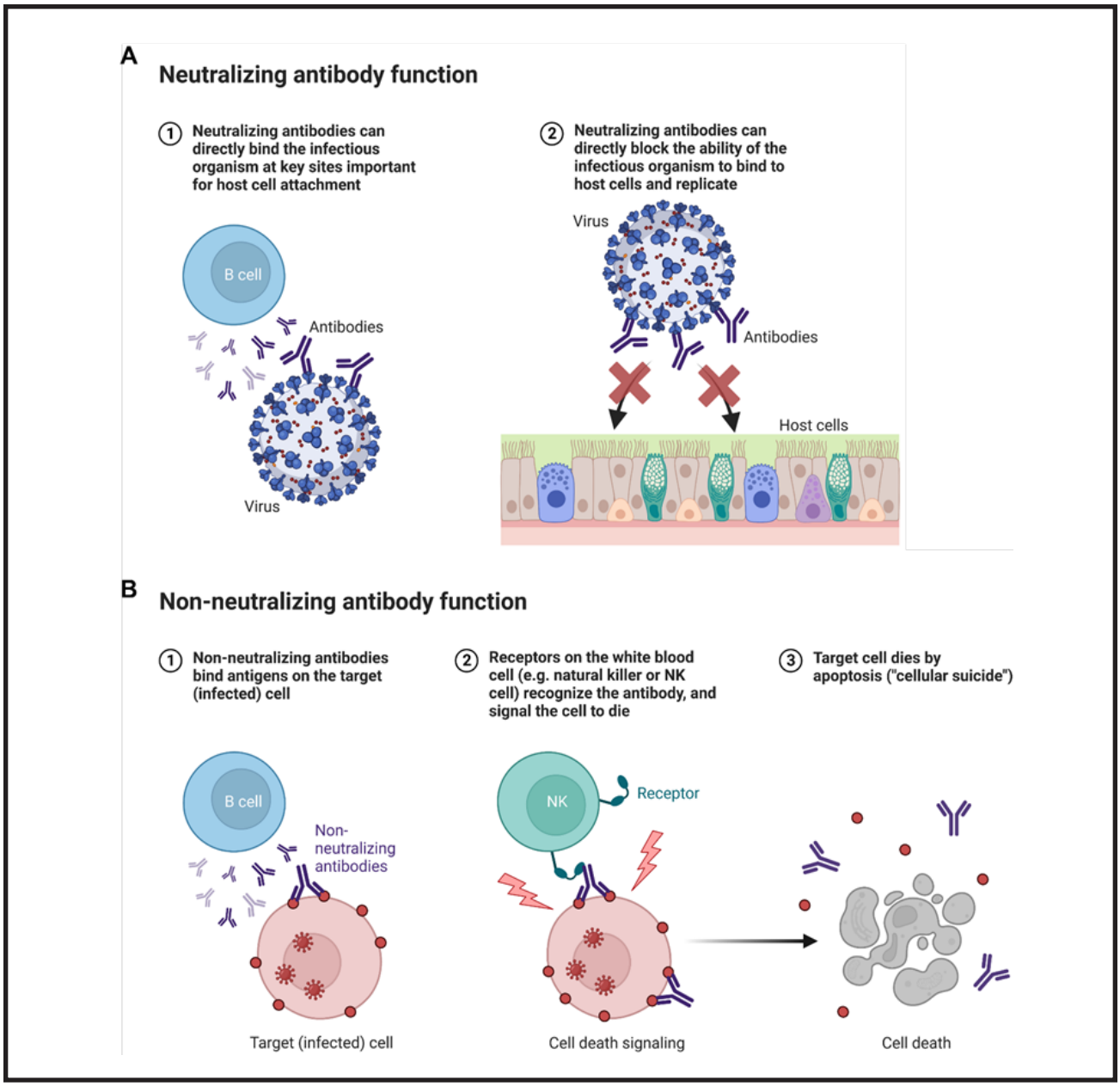

Figure 1. Neutralizing and non-neutralizing antibodies functions.
(A) Antibodies can bind to key sites on infectious organisms that are important for host cell binding through their antigen binding fragment ('Fab' region). In this way, neutralizing antibodies prevent the infectious organism from attaching and entering a host cell, blocking replication.
(B) Antibodies can bind to antigens expressed by infected cells through their Fab region. The constant fragment ('Fc' region) of the antibody can bind to Fc receptors on innate immune cells (like natural killer cells) and signal to the cell to undergo apoptosis. This is called a non-neutralizing antibody function.
(Figure generated using BioRender.com)

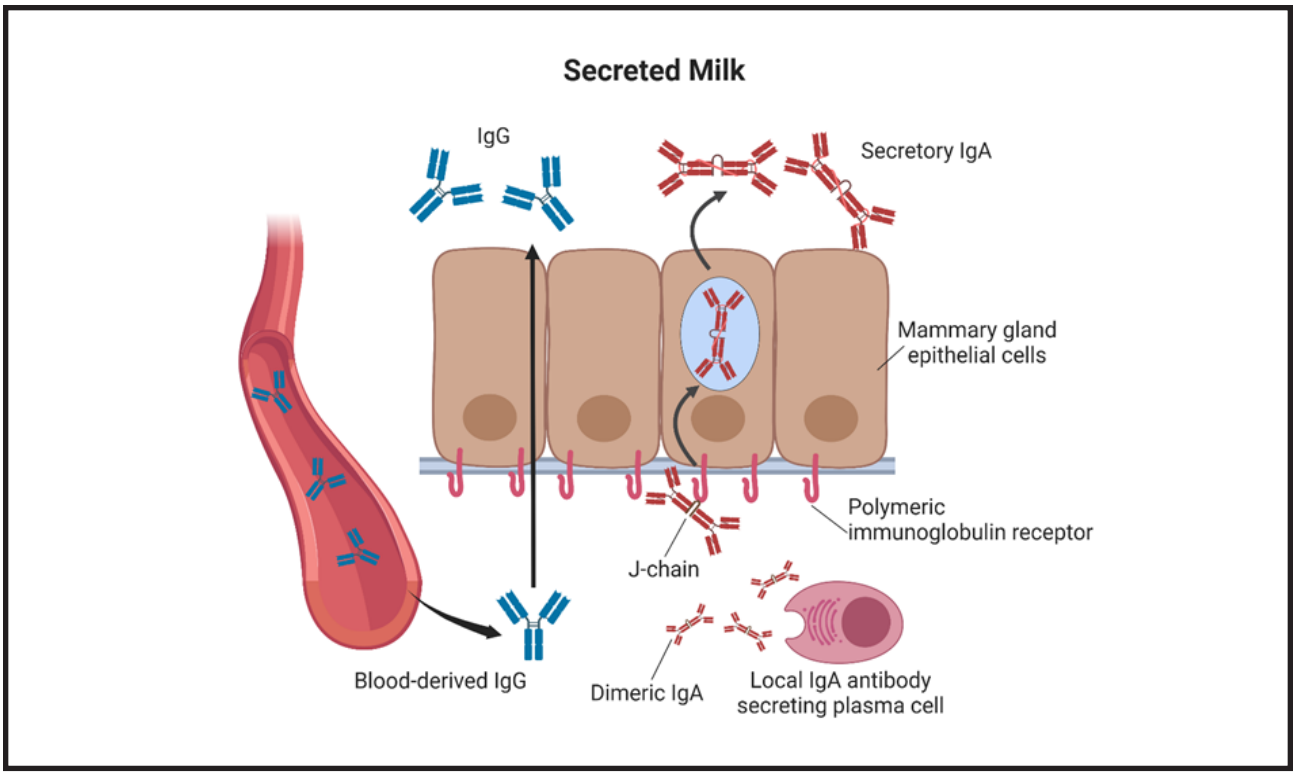

Figure 2. Mechanisms of maternal IgG and dimeric IgA transfer into secreted milk.
Blood-derived IgG traffics to the mammary gland epithelium and migrates through mammary gland epithelial cells through either a receptor-driven or non-specific process. Local IgA secreting plasma cells secrete dimeric IgA. Dimeric IgA covalently binds its cognate receptor polymeric immunoglobulin receptor (pIgR) via the joining chain (J-chain) and is transcytosed across the mammary gland epithelium. Dimeric IgA retains pIgR and becomes secretory IgA on the apical side of mammary gland epithelial cells. The 'secretory component' (i.e., covalently bound pIgR to the J-chain) gives secretory IgA increased resistance to degradation from high pH, stomach enzymes, and microbial proteases compared to IgG. (*Figure generated using BioRender.com*)