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Vaccine 21 (2003) 3382–3388
Vaccine
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Review

Mucosal immunity: integration between mother and the breast-fed infant

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Received 8 December 2002; accepted 25 March 2003

Abstract

Lactating mammary glands are part of an integrated mucosal immune system with local production of antibodies, mainly consisting of secretory immunoglobulin A (SIgA). These antibodies generally reflect antigenic stimulation of mucosa-associated lymphoid tissue (MALT) by common intestinal and respiratory pathogens. Antibodies in breast milk are thus highly targeted against infectious agents in the mother's environment, which are those likely to be encountered by the infant shortly after birth. Therefore, breast-feeding represents an ingenious immunological integration of mother and child. The mucosae are favored as portals of entry by most infectious agents, and the neonatal period is particularly critical in this respect. Mucosal pathogens are a major killer of children below the age of 5 years, being responsible for more than 14 million deaths annually. Diarrheal disease alone claims a toll of 5 million children per year in the developing countries. Epidemiological data suggest that the risk of dying from diarrhea could be reduced 14–24 times in breast-fed children. A beneficial clinical effect is also apparent in the industrialized world, even in relation to relatively common diseases such as otitis media and acute lower respiratory tract infections.

Keywords: Secretory IgA; Antibodies; Breast milk

1. Introduction

Mucosal epithelia cover an area at least 200 times that of the skin. This extensive and vulnerable surface barrier is protected by numerous innate mechanisms in intimate cooperation with adaptive (acquired) mucosal immunity. The main humoral mediators of this local first-line immune system are secretory immunoglobulin A (SIgA) and secretory immunoglobulin M (SIgM); the former class of antibodies constitutes the largest non-inflammatory defense system of the body [1,2]. The secretory antibody system performs immune exclusion by inhibiting colonization of pathogens and penetration of harmful soluble antigens. Interestingly, innocuous proteins and components of commensal bacteria do not only stimulate the secretory antibody system, but also activate suppressive mechanisms collectively called 'oral tolerance' when induced via the gut [3,4]. This mucosally induced hyporesponsiveness probably explains why most individuals normally show no adverse immune reactions to persistent contact with harmless environmental and dietary proteins [5].

Successful interactions between innate and adaptive immunity is a prerequisite for health because the various mucosae are favored as portals of entry by most pathogens, allergens, and carcinogens. The neonatal period is particularly critical in this respect, because the newborn is immediately exposed to a large number of microorganisms, foreign proteins and chemicals. This brief review focuses on the regulation and function of mucosal immunity as a basis for immune exclusion. Such a layer of adaptive defense is virtually lacking during a variable period after birth [6]. Breast-feeding is therefore important, not only as a natural immunological 'substitution therapy' or 'passive vaccine', but also because immune-modulating factors in breast milk may exert an important impact on the suckling's developing immune system [4,7,8].

2. Stimulation and dispersion of mucosal immunity

B-cell responses that give rise to secretory antibodies are elicited mainly in organized lymphoepithelial structures where antigens are sampled from the mucosal surface [2,9]. Gut-associated lymphoid tissue (GALT) is comprised of aggregated (Peyer's patches) and isolated B-cell follicles. In humans, the former are found mainly in the distal ileum, whereas most of the isolated or solitary follicles occur in the distal large bowel. All components of GALT, probably including the appendix, are believed to be functionally similar;

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doi:10.1016/S0264-410X(03)00338-4

they contain a characteristic follicle-associated epithelium with 'membrane' (M) cells capable of transporting live and dead antigens from the lumen into the underlying lymphoid tissue [10,11].

Although GALT constitutes the major part of organized mucosa-associated lymphoid tissue (MALT), induction of mucosal immune responses can also take place in Waldeyer's ring, which includes nasopharynx-associated lymphoid tissue such as the adenoids and the palatine tonsils [2,12]. Evidence suggests that the mucosal immune system is integrated with regard to differentiation and homing properties of B cells, but that some regionalization also exists—especially a dichotomy between the gut and the upper aerodigestive tract [2,13]. This disparity may be explained by microenvironmental differences in the antigenic repertoire, as well as in adhesion molecules and chemokines/chemokine receptors involved in local leukocyte extravasation. It appears that primed immune cells preferentially home to effector sites corresponding to the inductive sites where they initially responded to antigens.

Lactating mammary glands are part of the integrated mucosal immune system, and milk antibodies reflect antigenic stimulation of MALT both in gut and airways. This has been documented by showing that SIgA from breast milk exhibits specificity for an array of common intestinal as well as respiratory pathogens [14]. The secretory antibodies are thus highly targeted against infectious agents in the mother's environment, which are those likely to be encountered by the infant during its first weeks of life. Therefore, breast-feeding represents an ingenious immunological integration of mother and child (Fig. 1). Although the protection provided by this defense mechanism is most readily demonstrable in populations living in poor sanitary conditions [15,16], a beneficial clinical effect is also apparent in the industrialized world [17], even in relation to relatively common diseases such as otitis media and acute lower respiratory tract infections [18,19]. Antibodies to various dietary antigens, such as cow's milk proteins [20] and gluten [21], are also present in breast milk.

3. Postnatal development of mucosal immunity

Peyer's patches and other MALT structures such as the tonsils are well developed at birth—discrete T- and B-cell areas being apparent as early as at 19 weeks' gestation [6,22]. However, secondary follicles with germinal centers signifying B-cell activation, do not occur until some weeks after birth; this reflects their dependency on exogenous stimuli. The germinal-center B cells of Peyer's patches express mainly surface IgA along with some IgM or IgG [23]. Such isotype skewing is a result of B-cell heavy-chain gene switching in the course of clonal differentiation to precursors for IgA-producing immunocytes, whose preferential induction is the hallmark of GALT [2,9,10].

The fact that the postnatal immune activation of GALT is retarded, parallels the temporary immaturity of systemic immunocompetence observed in the neonatal period [4,24,25]. Thus, very few B-cell blasts with IgA-producing capacity are present in the peripheral blood of newborns—presumably

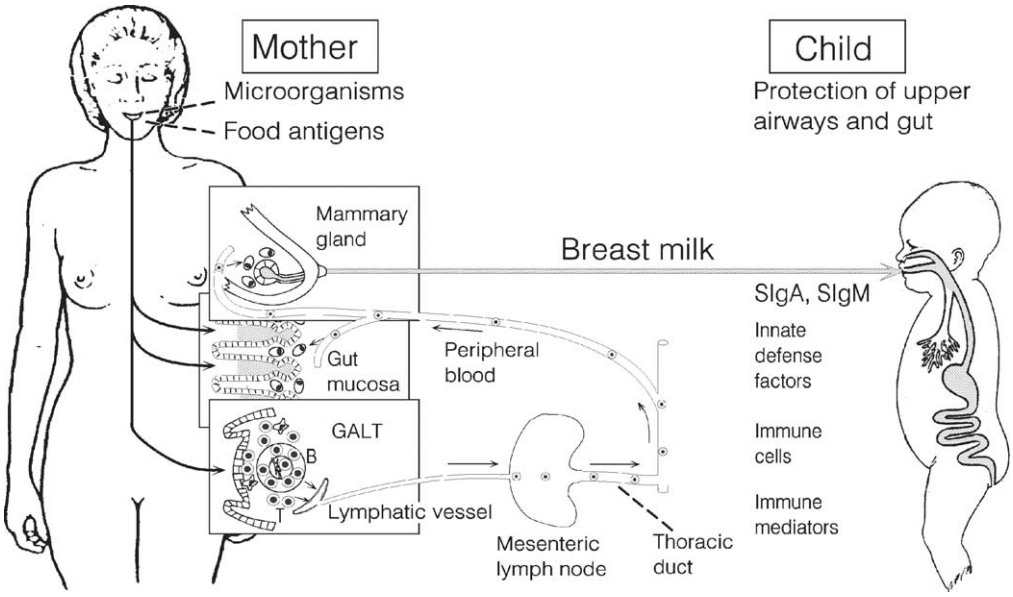

Fig. 1. Integration of mucosal immunity between mother and the newborn, with emphasis on migration of primed B (and probably T) cells from Peyer's patch via lymph and peripheral blood to the lactating mammary gland. Such distribution (arrows) beyond the gut of precursors for IgA plasma cells is crucial for glandular production and subsequent occurrence in breast milk of secretory antibodies (SIgA and SIgM) specific for enteric antigens (microorganisms and food proteins). By this mechanism, the breast-fed infant will receive relevant secretory antibodies directed against the microbiota colonizing its mucosae (initially reflecting the microflora of the mother) and hence be better protected both in the gut and in the upper airways (hatched areas) in the same way as the mother's gut mucosa is protected by similar antibodies (hatched areas).

Table 1
Increase in Ig-secreting cells (Ig-SCs) in peripheral blood of normal neonates during the first month of life[a]

Day of life (Ig-SCs/10^6 PBMCs)[b]	Sample nos.	Increment (%) of positive samples		
		IgA	IgM	IgG
0–5 (<8)	67	0	0	0
6–14	24	58	38	46
15–21	15	67	33	40
22–31 (∼500)	13	78	31	39

[a] Based on data from Nahmias et al. [26] and Stoll et al. [27].
[b] PBMCs, peripheral blood mononuclear cells.

being mainly GALT-derived and on their way to mucosal effector sites (Fig. 1). After 1 month their numbers are remarkably increased (Table 1), signifying the progressive microbial and environmental stimulation of GALT [26,27]. An initial early elevation of positive cells can be seen in pre-term infants, especially in those with intrauterine infections, although IgM production dominates in these cases [27]. In agreement with such observations in peripheral blood, only occasional IgM- and IgG-producing intestinal plasma cells are present at birth, and mucosal IgA cells are either absent or extremely rare even until after 10 days of age [6]. The numbers of intestinal IgM- and IgA-producing cells increase rapidly after 2–4 weeks, the latter class becoming predominant at 1–2 months—usually peaking at about 12 months.

An early SIgM antibody response is probably of some protective value, but it is known that specific immunity to certain bacterial capsular polysaccharides is poor or lacking before 2 years of age. This creates a window of susceptibility at the time of disappearance of protective maternal IgG antibodies, especially when combined with weaning (which usually means deprivation of breast milk SIgA). The basis for the impaired immune response to polysaccharides is unclear, but reduced levels of complement receptor 2 (CR2, CD21) expression on B cells and follicular dendritic cells in germinal centers, together with low complement activity in newborns, may result in lack of CR2/B-cell receptor synergy and thereby suboptimal B-cell activation [28]. Compelling evidence shows that interaction of the complement split product C3d with CR2 is an extremely important link between innate immunity and specific B-cell responses [29].

4. Importance of secretory immunity in infancy

Full-term babies that grow up under privileged conditions generally show satisfactory resistance to mucosal infections, as long as their innate defense mechanisms are normal. Adequate systemic antibody protection of their mucosae is provided by maternal IgG, of which at least 50% is distributed extravascularly. Placental transfer of IgG in the fetus is unique for primates, and postnatal uptake of breast milk-derived macromolecules such as SIgA appears to be of no importance in supporting systemic immunity in humans [30], except perhaps in pre-term babies [31,32].

When most maternal IgG has been catabolized after approximately 2 months, the protective value of breast-feeding is highlighted in relation to mucosal infections, particularly in the developing countries. At least 90% of microorganisms infecting humans, use the mucosae as portals of entry; such pathogens are a major killer of children below the age of 5 years, being responsible for more than 14 million deaths annually. In the developing world, diarrheal disease alone claims a toll of 5 million children per year, or about 500 deaths every hour. These sad figures document the need for mucosal vaccines to enhance surface defense against infectious agents, in addition to the importance of advocating breast-feeding. Epidemiological data indicate that the risk of dying from diarrhea could be reduced 14–24 times in breast-fed children [15,16]. Even in ‘westernized’ countries exclusively breast-fed infants are better protected against a variety of infections [17–19,33]—and apparently also against childhood celiac disease [34,35], allergy and asthma [36,37]—although the latter issue is still being debated [38,39].

Experiments in neonatal rabbits strongly suggest that SIgA is the crucial protective component of breast milk [40]. The role of secretory antibodies for mucosal homeostasis is furthermore supported by the fact that knock-out mice lacking SIgA and SIgM show increased mucosal leakiness [41] and reduced protection against certain epithelial infections [42,43].

5. Receptor-mediated epithelial transport of secretory antibodies

The remarkable magnitude of GALT as an inductive site for mucosal B cells is documented by the fact that at least 80% of all Ig-producing blasts and plasma cells (collectively called immunocytes) are located in the intestinal lamina propria, amounting to approximately 10^{10} cells/m of adult gut [2]. Some 90% of these terminally differentiated B cells normally produce dimers or larger polymers of IgA (collectively called pIgA), which are efficiently transported externally as SIgA antibodies by an epithelial ∼100 kDa glycoprotein called membrane secretory component (SC) or the polymeric Ig receptor (pIgR). This transport mechanism is shared by pIgA and pentameric IgM (Fig. 2), because both types of Ig polymer contain a common 15 kDa polypeptide called joining (J) chain, which is produced preferentially by mucosal immunocytes [2,44]. The J chain constitutes an essential part of the pIgR binding site in the Ig polymers [45,46].

After transcytosis of the Ig polymers to the luminal surface, SIgA and SIgM are released by cleavage of pIgR, and only the C-terminal smaller receptor domain remains apically for degradation in the epithelial cell (Fig. 2); the 80 kDa extracellular part is incorporated into the secretory

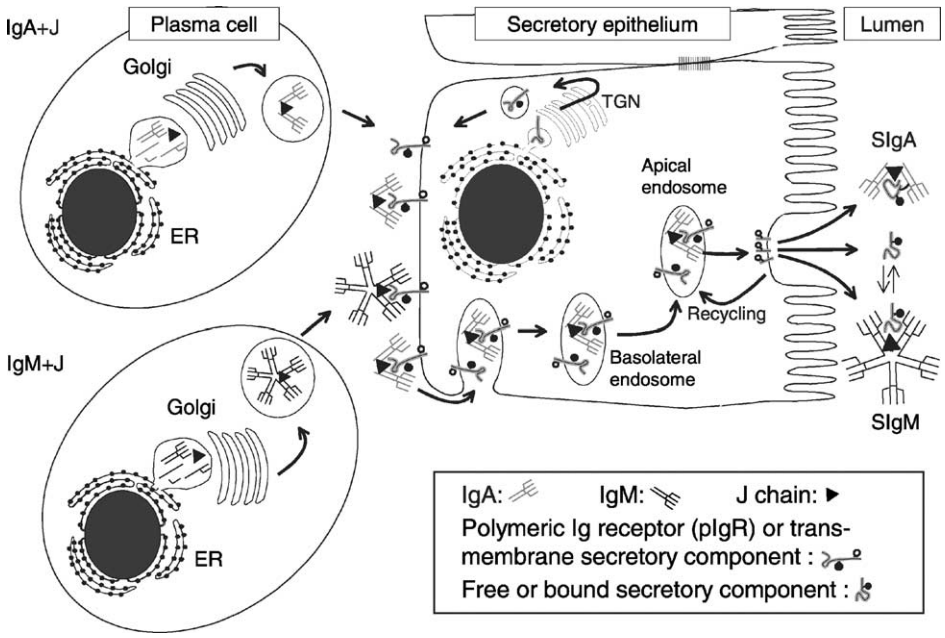

Fig. 2. Model for local generation of secretory IgA (SIgA) and secretory IgM (SIgM). J chain-containing dimeric IgA (IgA + J) and pentameric IgM (IgM + J) are produced by local plasma cells (left). Polymeric Ig receptor (pIgR), or membrane secretory component (SC), is synthesized by secretory epithelial cell in the rough endoplasmic reticulum and matures in the Golgi complex by terminal glycosylation (●). In the trans-Golgi network (TGN), pIgR is sorted for delivery to the basolateral plasma membrane. The receptor becomes phosphorylated (✪) on a serine residue in its cytoplasmic tail. After endocytosis, ligand-complexed and unoccupied pIgR is delivered to basolateral endosomes and sorted for transcytosis to apical endosomes. Some recycling from basolateral endosomes to the basolateral surface may occur for unoccupied pIgR (not shown). Receptor recycling also takes place at the apical cell surface as indicated, although most pIgR is cleaved to allow extrusion of SIgA, SIgM and free SC to the lumen. During epithelial translocation, covalent stabilization of SIgA regularly occurs (disulfide bond between bound SC and one IgA subunit indicated), whereas free SC in secretions stabilizes the non-covalently bound SC in SIgM (dynamic equilibrium indicated). Modified from Brandtzaeg et al. [2].

antibodies as bound SC, thereby providing protection against proteolytic degradation [47], particularly in SIgA where SC becomes covalently linked [46,48]. Thus, the stability of SIgA antibodies in external secretions such as saliva, as well as in feces, is remarkable [49,50].

In adult humans, ~40 mg/kg body weight of pIgA is translocated to the intestinal secretions by the pIgR every day, which is more than the total daily production of IgG [51]. Excess of unoccupied pIgR is released to the lumen by proteolytic cleavage in the same manner as SIgA and SIgM to form so-called free SC (Fig. 2). This 80 kDa fragment (identical to bound SC) occurs in most secretions and, by equilibrium with the bound component, it exerts a stabilizing effect on the quaternary structure of SIgM in which SC remains non-covalently linked [2,48]. In various ways, free SC may also contribute to innate mucosal defense (see below).

The daily output of IgA per kilogram wet weight of parenchymal tissue is similar for salivary and lactating mammary glands [52]. It remains unclear how terminal B-cell differentiation is driven in these effector organs at considerable distances from antigen-exposed mucosal surfaces, although the density of plasma cells is much less than in the intestinal lamina propria [2]. Nevertheless, because of its size, one human lactating mammary gland has on average an IgA-producing capacity similar to 1 m of intestine [52]. Moreover, the large capacity for storage of pIgA/SIgA in the mammary gland epithelium and duct system explains the remarkable output of SIgA during feeding [52].

6. Protective role of SIgA antibodies and SC

The main purpose of the secretory antibody system is, in cooperation with innate mucosal defense mechanisms, to perform immune exclusion. Most important to this end, SIgA inhibits colonization and invasion by pathogens, and pIgR-transported pIgA and pentameric IgM antibodies may even inactivate viruses (e.g. rotavirus and influenza virus) inside of secretory epithelial cells and carry the pathogens and their products back to the lumen, thus avoiding cytolytic damage to the epithelium [48]. Both the agglutinating and virus-neutralizing antibody effect of pIgA is superior compared with monomeric antibodies [9,53], and SIgA antibodies may block microbial invasion quite efficiently. This has been particularly well documented in relation to human immunodeficiency virus [54], and specific SIgA antibodies isolated from human colostrum has been shown to be more efficient in this respect than comparable IgG antibodies [55].

Induction of SIgA responses has likewise been reported to interfere significantly with mucosal uptake of soluble macromolecules in experimental animals [9], and bound SC

Table 2
Antimicrobial effects of pIgA/SIgA antibodies

Immune exclusion (non-inflammatory)
Exceptionally stable with prolonged function in secretions
Operate outside of, and within, mucosal epithelia
Inhibit epithelial adherence and penetration
Efficient microbial agglutination and neutralization
Extensive polyreactive activity (cross-protection)
Mucophilic properties enhance immune exclusion
May inhibit growth factors, enzymes and plasmids
Immune elimination (potentially proinflammatory)
Phagocytosis and cytotoxicity via FcαRI (CD89)

provides secretory antibodies with mucophilic properties, which enhance immune-exclusion function in the airways [56]. Collectively, therefore, the function of locally produced pIgA/SIgA antibodies would be to inhibit mucosal colonization of microorganisms as well as penetration of soluble antigens (Table 2). Such immune exclusion is most likely enhanced by the relatively high levels of polyreactive SIgA antibodies in human secretions, including breast milk [57]. In the gut, interaction of SIgA with the hepatic superantigen protein Fv (Fv fragment binding protein) may, moreover, build an immune fortress by forming large complexes of intact or degraded antibodies with different specificities [58], thereby reinforcing immune exclusion. It has also been reported that specific SIgA can interfere with growth factors (e.g. iron) and enzymes necessary for pathogenic bacteria and parasites [9], and have a positive impact on the inductive phase of mucosal immunity by promoting antigen uptake in GALT via IgA receptors on the M cells [59]. The latter possibility adds to the importance of breast-feeding in providing a supply of relevant SIgA antibodies to the infant's gut.

Interestingly, free SC—which is abundant in breast milk—may on its own block epithelial adhesion of—and thereby limit infection by—enterotoxigenic *Escherichia coli* [60,61]. In addition, a pneumococcal surface protein (SpsA) has been shown to interact with both free and bound SC [62]. SC may furthermore inhibit the effect of certain bacterial toxins such as *Clostridium difficile* toxin A [63]. In its bound state, therefore, SC may reinforce the adaptive immune exclusion functions of secretory antibodies. Together, these observations suggest that SC phylogenetically has originated from the innate defense system before being exploited by the adaptive secretory immune system to function as pIgR.

7. Other immunological factors in breast milk

Numerous constituents of breast milk, in addition to antibodies and free SC, are though to protect the suckling. These include innate defense factors such as lysozyme, lactoferrin, peroxidase, complex oligosaccharides (receptor analogues), fatty acids (lipids) and mucins [14,17,18]. Moreover, a variety of leukocytes occur in colostrum ($\sim 4 \times 10^6\,ml^{-1}$) and later milk ($\sim 10^5\,ml^{-1}$). Macrophages (55–60%) and neutrophilic granulocytes (30–40%) dominate over lymphocytes (5–10%)—the latter being mainly (75–80%) T cells [14,17]. Oral administration of macrophages in newborn mice showed survival of these cells for several hours in the gut and even some mucosal uptake [64]. The macrophages contain engulfed SIgA, which they may release on contact with bacteria in the gut [65], and they may also secrete an array of important immunoregulatory factors. Thus, it has been reported that unfractionated supernatants of breast milk cell cultures preferentially stimulate IgA production by peripheral blood lymphocytes [65]. An explanation for this effect may be the various cytokines that are secreted by stimulated milk macrophages [17].

The same cytokines are found in breast milk [14,17], and the presence of transforming growth factor-β (TGF-β), interleukin-6 (IL-6), and IL-10 is of particular interest for the development and differentiation of IgA-producing cells [2]. Direct evidence to this end has been provided for colostral IL-6 [66]. Even if these cytokines are unable to survive the passage through the gastrointestinal tract, they may be locally released from milk macrophages stimulated in the neonatal gut and thereby enhance the development of mucosal immunity. Thus, in addition to the remarkable reinforcement of mucosal defense provided by maternal SIgA and SIgM antibodies as a natural immunological 'substitution therapy', it is important to emphasize the positive effects that breast-feeding may exert on immune development—including its nutritional value—apparently enhancing in an indirect way even the long-term health of the individual [7,17,18]. There are also reports showing enhanced secretory as well as systemic immune responses to oral and parenteral vaccines in breast-fed babies [67,68].

Acknowledgements

This study was supported by the Research Council of Norway, the Norwegian Cancer Society, and Anders Jahre's Fund. Hege Eliassen and Erik K. Hagen are gratefully acknowledged for excellent assistance with the manuscript.

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