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Mucosal immunity: The immunology of breast milk

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The mammary glands represent one part of the mucosal immune system, a definable, subunit of humoral and cellular immune functions in man that appears to have developed particular qualities well suited to guard our interface with the environment. As our understanding of secretory immunoglobulins and lymphocyte migration patterns continues to develop, the immunologic components found in breast milk appear increasingly likely to play a specific immunologic role in the protection of the nursing infant. The biologic basis for the observed protective effect of breast-feeding is reviewed with an emphasis on the mechanisms involved in the development and maintenance of mucosal immunity in general. (J ALLERGY CLIN IMMUNOL 1987;80:346-56.)

During the past several decades, an increasing emphasis has been placed on the importance of breast-feeding in decreasing the number and severity of intestinal and respiratory infections experienced by infants. This emphasis is supported by a number of studies that demonstrate substantial differences in morbidity and mortality when breast-fed infants are compared with formula-fed control infants. The basis for this protective effect appears to be multifactorial. In light of substantial evidence in animal models linking the mammary glands with the respiratory- and gut-associated mucosal immune system, we review in this article the current state of knowledge of these related tissues and discuss the theories of how breast-feeding may impart its protective effects to the neonate.

THE MUCOSAL IMMUNE SYSTEM

The immune system is composed of lymphocytes and mononuclear accessory cells, their soluble products, and the epitheliolymphoid organs that form the distinct anatomic locations of lymphocyte maturation and differentiation. The complement proteins and polymorphonuclear cells of various types also play a critical role in immunity but will be considered to a lesser extent in this article. A variety of descriptive terms have been applied to the anatomic division of the lymphoid organs. In postnatal human life, the bone marrow and thymus function as the primary, maturation, or central lymphoid organs from which a circulating pool of lymphocytes is derived. This circulating pool populates the secondary or peripheral lymphoid organs, recentering the primary organs only to a limited degree.

Within the secondary lymphoid organs, it is now recognized that a further division exists, namely, the

Abbreviations used
- PP: Peyer's patches
- BALT: Bronchus-associated lymphoid tissue
- GALT: Gut-associated lymphoid tissue
- SIgA: Secretory IgA
- SIgM: Secretory IgM
- sIgA: Surface IgA
- SC: Secretory component
- HEV: High endothelial venules
- PLN: Peripheral lymph nodes
- BM: Breast milk
- PBL: Peripheral blood lymphocytes
- MLN: Mesenteric lymph nodes
- Mab: Monoclonal antibody
- FcR: Fc receptor
the mucosal portion of the immune system. This portion may be further subdivided along several lines. The term GALT refers to one large component of the mucosal immune system that is made up of PP, MLN, the appendix, and isolated microscopic lymphoid nodules within the intestinal mucosa. Current evidence suggests that the following components of the mucosal immune system are linked together into a network of shared immunologic response: GALT, lacrimal, and salivary glands; BALT and tonsils; and the mammary glands. This evidence has evolved along a number of separate lines of investigation.

**The secretory humoral immune response**

The concept of a mucosal immune system has its roots in the studies of the early 1900s in which a protective intestinal antibody response to orally presented killed *Shigella bacilli* was noted to precede and lack correlation with the serum antibody response. A similar phenomenon was recognized in rabbit studies in which pulmonary antibody response occurred without concomitant serum response after intranasal instillation of pneumococci. Looking from a different perspective, investigators such as Wells (in 1911) and Chase (in 1946) demonstrated actual inhibition of the systemic antibody response after mucosal exposure to certain antigens (the Sulzberger-Chase phenomenon). These and other investigations provided early evidence of a distinct network of immunologic responsiveness operating at the mucosal barrier. By 1959, there was evidence to suggest that the IgA class of proteins contained antibody activity against a number of enteric organisms, and in the early 1960s, several groups reported the substantial predominance of this immunoglobulin in secretory fluids. By 1965, it was established that IgA class antibodies existed preferentially in external secretions, and the concept of an immune system common to these secretions began to take shape.

The predominance of IgA in secretions is matched by a predominance of IgA-producing plasma cells in the submucosa in which they account for 49% to 84% of cells identified by immunohistochemical staining for intracytoplasmic immunoglobulin. The IgA found in secretions, termed SIgA, is dimeric or polymeric in contrast to the monomeric form of serum IgA. The polymerization of IgA is initiated by a 15.6 kd molecular weight polypeptide synthesized by plasma cells termed the J chain that covalently links two alpha (or mu) heavy chains together at their C-terminal cysteine residue. Dimeric IgA, produced in the submucosa by IgA plasma cells, is then actively transported via endocytosis from the basolateral to the mucosal surface of the mucosal epithelial cells where it is released into the secretions. This transport involves an integral membrane protein of the epithelial cells termed SC, which specifically binds J chain–linked IgA dimers and a portion of which remains covalently attached to the C-terminal end on release to form SIgA. A number of studies have confirmed that human SIgA is produced locally at the mucosal sites rather than being filtered from serum in which IgA exists as a minor constituent.

A further distinction between serum and SIgA is observed in the relative distribution of IgA subclasses. Although serum IgA is predominantly IgA1, IgA2 accounts for a more substantial proportion of the total IgA in external secretions. Immunofluorescence studies reveal that IgA2* plasma cells are increased in distal gut (50%), mammary glands (37%), and salivary glands (34%), as compared with spleen, PLNs, and tonsils (5% to 9%). The surface IgA2* cells identified in GALT tend to produce J chain with a higher frequency than SIgA1* cells, suggesting a difference in the regulatory events involved in terminal differentiation. IgM- and IgG-producing plasma cells are also found associated with mucosal surfaces, and these cells produce J chain with a higher frequency than PLN plasma cells. In selective IgA deficiency, SlgM appears to replace the missing SIgA. Selectively IgA-deficient individuals who fail to compensate with SlgM appear to have more frequent infections than individuals who make this compensation. There is little data to support a primary role for IgG at the mucosal barrier because IgG does not bind to SC or to J chain. The J chain synthesized by IgG producing plasma cells is degraded intracellularly. It has been noted, however, that IgG is the predominant isotype found in the tonsils and in the distal alveolar segments of the lung. These areas may represent an overlap between mucosal and peripheral immunity. It has also been noted that IgG4 is the predominant IgG subclass found at various mucosal surfaces, and may act either as a reaginic antibody or as a mast cell blocking antibody in allergic individuals.

The antibody activity of SIgA is unique in several respects. Unlike IgM and IgG, SIgA is unable to initiate complement activation except by the alternative pathway and then only when it is aggregated. Consequently, SIgA is not bactericidal and does not promote the formation of opsonic complement subfragments. It also generally lacks direct opsonic activity, although IgA-mediated antibody-dependent cellular cytotoxicity has been demonstrated in both rabbits and humans. The primary function of SIgA appears to be the blocking of adhesion to mucosal epithelial cells by potential pathogens. SIgA antibodies have
been isolated that are specific for a multitude of potentially pathogenic enteric bacteria that elaborate special adhesive structures (adhesins) capable of interacting with complementary epithelial cell-surface receptors. These pathogens are effectively neutralized by adhesin-specific SIgA.

### Lymphocyte migration

A further understanding of mucosal immunity comes from the study of lymphocyte migration. The delineation of migration patterns began with the study of lymph node entry sites, which are now recognized as segments of postcapillary venules, HEV. With an in vitro technique with frozen tissue sections, it was found that lymphocytes isolated from the thoracic duct bind preferentially to the HEV of GALT, whereas lymphocytes obtained from peripheral lymphatic tissue bind preferentially to sections of PLN. To some extent these patterns of preferential binding may be an epiphenomenon in the sense that B-lymphocytes have been demonstrated to bind preferentially to GALT and T cells to PLNs regardless of their tissue of origin. Thus, after some period of time, each cell type might accumulate at the preferred site of exit, and a migratory loop would become more apparent. Subsets of mouse lymphocytes have also been demonstrated to exhibit binding specificities with Lyt-2- (helper/inducer T) cells, demonstrating preference for PP and Lyt-2+ (suppressor/cytotoxic T) cells demonstrating preference for PLN. The role of HEV-type interactions in regulating lymphocyte localization within the gut mucosa is incompletely understood. Although HEV has been demonstrated in the interfollicular areas of PP, it is not found in the specific, diffuse mucosal sites where T- and B-lymphocytes eventually come to reside.

Lymphocyte migration appears to be directed by cell-surface molecules termed "homing receptors" that interact selectively with molecules on the HEV to capture the lymphocytes at particular lymphoid organs. Subsequent entry of the cells into the nodes may require further chemotactic or chemokinetic signals. The receptor-HEV interaction appears to involve the binding of carbohydrate moieties. The most recent evidence suggests that the lymphocyte-bound receptor for PLNs is a ubiquitin-containing branched-chain polypeptide, a portion of which exhibits calcium-dependent binding specificity for phosphomannosyl residues. Site specificity of the homing receptors has been demonstrated through blocking experiments with Mabs. These Mabs appear to discriminate between an epitope on the lymphocyte receptor for PLN-HEV surface molecules (Mel-14) and an epitope for PP-HEV (1B.2). It is not yet clear where circulating lymphocytes develop their homing receptors. There is evidence to suggest that murine T cells may acquire them during maturation in the thymus in which 1% to 3% of cortical lymphocytes and 80% of exiting (postthymic) lymphocytes express PLN receptors. The relationship between this finding and the finding that antigen-exposed lymphocytes from sheep Peyer's patches circulate back through the thymus is unclear.

On the basis of the clonal selection theory of antibody response in which random rearrangements of immunoglobulin variable region genes provide a vast repertoire of antigen-binding specificities (idiotypes), it is logical to assume that lymphocytes would migrate until they contacted the antigen for which they display specificity. The evidence to date is in many ways consistent with this hypothesis. It is known that the progeny of these idiotype-committed immature B cells retain the potential to express multiple heavy chain isotypes. These virgin B-lymphocytes have been demonstrated to migrate, but to a lesser extent, than primary antigen-exposed B cells. Exposure to antigen affects the receptors in the sense that B and T cells have been noted to transiently down regulate receptor expression after antigen exposure. Lymphocyte traffic through primary antigen-exposed PLNs occurs at the same rate as through nonexposed nodes, but the antigen-specific lymphocytes may selectively accumulate there. Although GALT-derived, antigen-sensitized lymphocytes will home to antigen-free intestinal transplants, lungs, salivary, and mammary glands, the ultimate retention and expansion of cells previously exposed to antigen is probably dependent on reexposure to the antigen. This would explain the observations that lymphocytes derived from lung, small intestine, and colon tend to return precisely to the organ of origin. A sharing of antigens between lung or salivary gland and gut is easily imagined, since respiratory and oral secretions are swallowed regularly, and this may explain to some extent the sharing of immunologic responses between these sites. It does not explain the localization of IgA-producing plasma cells in the mammary gland, however.

### Functional activities of mucosal lymphocytes

Lymphocytes are generally considered in terms of the functions that they display or mediate. To some extent, these are reflected in cell-surface antigens that are recognized in increasing numbers through the application of Mab technology. The functional attributes of mucosa-associated lymphocytes vary according to their location, which itself may be determined in part
by their functional potential at any particular stage of differentiation (see above). Lymphocytes constitute 15% of the cells found in the intraepithelial compartment. In mice, >90% of large intraepithelial lymphocytes express a unique surface antigen recognized by a newly described Mab termed F3.85.6.54 Lymphocytes derived from spleen, thymus, PP, and MLN, as well as lipopolysaccharide-induced splenic blasts are largely unreactive with this Mab. It is not clear whether the antigen recognized by F3.85.6 is responsible for localization to the intraepithelial compartment or whether it is elaborated as a result of interactions with the intraepithelial environment. The lymphocytes found in this compartment display various functions. A minority population of natural killer-like cytotoxic cells has been demonstrated in mice with the capacity to protect the murine intestine from coronavirus.55 Cytotoxic T cell precursors, identified phenotypically as Thy-1.2*, Lyt-1.1*, and Lyt-2.1*, have also been found in the murine intraepithelial compartment. In humans, cytotoxic or suppressor T cells predominate.56 By contrast, the activity of lamina propria T cells is characterized predominantly by help for antibody synthesis.57 The response to mitogens differs also, with peripheral circulating lymphocytes and lamina propria lymphocytes responding well, whereas intraepithelial lymphocytes respond poorly.58 Similar differences in response are observed in the mixed lymphocyte reaction.59

In the healthy gut, the combined actions of peristalsis, mucous production, and ciliary motion form a relatively effective barrier to bacterial adhesion, preventing subsequent bacterial invasion. Intraepithelial effector T cells appear to complement this barrier in preventing viral invasion. Humoral immune responses to enteric antigens are complex and involve both systemic suppression of the IgG response as well as induction of the mucosal IgA response.60 Cholera toxin appears to be unique in overcoming or bypassing this systemic suppression.61 Several lines of evidence support the hypothesis that the primary activation signals for gut B cell differentiation occur in the lymphoid follicles, which are devoid of goblet cells and villi on their luminal surface, being covered instead with columnar epithelium interspersed with M-cells.62 The M-cells are highly specialized epithelial cells that pinocytose antigens and present them to cells at the basal surface. In the initial steps of B cell activation, HLA class II (HLA-D/DR) antigens mediate the signals required for mitogenesis. Once the activation cascade has been initiated, HLA-D/DR antigens are no longer necessary.63 Intestinal epithelial cell HLA-D/DR expression has been found to be restricted primarily to the dome-corona and T cell areas overlying lymphoid nodules.64 The distribution of antigen-presenting accessory cells further supports a primary role for PP in B cell activation. Macrophages are only occasionally found in the mucosal intraepithelial compartment,56 whereas in PP they constitute 5% to 10% of the total number of cells.57 With special techniques for isolating these macrophages, they have been demonstrated to be capable of functioning as antigen-presenting cells to antigen-primed T cells.65 The T cells in PP are predominantly of the helper phenotype and are presumed to be necessary for triggering T cell-dependent B cell activation.66 The ratio of helpers to suppressors in the laminal propria is 2:1, similar to that in peripheral blood.66 By contrast, the helper:suppressor ratio in the intraepithelial lymphocyte compartment is 0.06 to 0.14.58 Perhaps the strongest argument is provided by the study of sheep PP in which metaphase-arrest studies have demonstrated that only 5% of the lymphocytes produced there ever leave. When they do leave, they migrate quickly to the lamina propria in which within 24 hours they become plasma cells.57 These observations may relate to antibody affinity maturation after antigen exposure.

The predominance of IgA antibodies in the secretions is accomplished by a complex network of cellular interactions. It is not yet clear how various cell types come to reside initially in GALT, although it is known that PP develop in utero before antigen exposure. Craig et al.67 found that repopulation of irradiated mice with lymphocytes derived from GALT led to selective repopulation of the gut and preferential IgA production, whereas repopulation with PLN-derived lymphocytes led to IgG production and poor gut repopulation. Taking their experimental observations together with emerging data on B cell immunoglobulin gene rearrangements, they proposed the hypothesis that IgA expression would be driven by persistent B cell antigen exposure such as would occur in the PP.68 Subsequent information has led to a revision of this B cell-focused hypothesis to include a primary role for regulatory T cells. The rapid emigration of B cells away from PP after antigen exposure argues against the concept of prolonged antigen exposure driving the cells toward IgA expression.69 Furthermore, mapping of the human Ig heavy chain genes has demonstrated that stepwise 3' deletions of genes would obviate the production of IgA1, since it is located 5' to the γ2, γ4, ε, and α2 heavy chain genes.69 Direct evidence for the involvement of T cells in IgA expression comes from the studies of Elson et al.69 These investigators demonstrated that mitogen-induced suppressor T cells from mouse spleens inhibited synthesis of all isotypes by indicator B cell
cultures, whereas similarly treated T cells from PP inhibited IgG and IgM but actually enhanced IgA synthesis. These findings are consistent with earlier evidence that T cells are involved in the regulation of IgG subclass secretion. More detailed studies by Kawanishi et al. revealed that cloned PP T cells are capable of inducing a phenotypic change from sIgM+ to sIgA+, but not IgG+ to IgA+. This phenotypic change was not associated with immunoglobulin secretion, leading to the concept of an isotype-specific switch T cell that effects regulation at the level of gene transcription. In the murine system, this cell type appears to be activated by autologous cells bearing Ia determinants after the latter have been activated by antigen or polyclonal stimulator. In this sense the cells are not antigen specific. The switch signal appears to be delivered shortly after the B cell has received its initial antigenic signal for activation.

Proliferation and terminal differentiation into immunoglobulin-producing plasma cells occur subsequently under the influence of T cell-derived B cell growth and differentiation factors. These T cells appear to reside primarily in the MLN, although their precursors are present in PP. The factors have been demonstrated to derive from clones of IgA FcR+ T cells, implying that T cell regulatory activity in the terminal stages of B cell differentiation may be class specific. There is also evidence of class nonspecificity, and the relative importance of the two phenomena is open to debate. Class-specific suppression of IgA is also known to occur and has been demonstrated in cases of selective IgA deficiency. The cells mediating this suppression are also IgA FcR+ T cells that elaborate IgA binding factors in response to IgA itself. Taken together with evidence that IgA can enhance its own secretion, there is good reason to suspect that IgA is involved in regulating its own production.

IMMUNOLOGY OF BREAST MILK
Nonspecific antiinfective properties

With the exception of SlgA, the activity of most of the anti-infective factors in BM has been demonstrated only in vitro. This has been recently reviewed elsewhere and include both antimicrobial factors (GM 1-like gangliosides, glycoproteins, carbohydrates, and lipids) and antiviral factors (c-macroglobulin-like protein, ribonuclease, and polyunsaturated fatty acids). Milk lipases have been demonstrated to inactivate a variety of protozoan parasites as well.

Breast milk antibodies

The repertoire of antibodies found in human milk is extensive, with more than 20 viral, bacterial, and toxin-specific antibodies identified to date. The precise nature of the milk-antibody response is complex, and under experimental conditions, the isotype and magnitude of the response varies considerably as a function of the antigens used for oral immunizations. The presence of SlgA antibodies directed against enteric pathogens is believed to result from migration of gut-derived lymphocytes to the mammary tissues. Knowing that lymphocyte homing to GALT occurs in germ-free mice and in antigen-free ectopic grafts of fetal gut, the accumulation of GALT-derived lymphocytes in the lactating mammary gland may be viewed in the context of site-specific ligands recognized by homing receptors on the GALT-derived lymphocytes. Indeed, the demonstrated transfer of immunologic responsiveness from both BALB and GALT to the mammary glands supports the concept of a common mucosal immune system, although certain patterns of lymphocyte migration may be species specific. The mammary gland remains unique among these tissues, however, in terms of antigen exposure, and it is not clear why B cells terminally differentiate into IgA-producing plasma cells at this site. The role of milk factors that are selectively chemotactic for SlgA+ and slgG+ B cells of GALT origin is currently under investigation.

Although SC-bound, J chain–linked IgA dimers resist nonspecific proteolytic degradation in the gut, a number of pathogenic organisms have evolved the capacity to degrade IgA1 through elaboration of an IgA1-specific protease. This threat is countered by antiprotease antibodies of the IgA isotype found in human colostrum and milk. A deletion in the hinge region of IgA2 removes the site of IgA protease cleavage, and this may explain in a teleologic sense the relatively high percentage of IgA2-producing cells found at mucosal sites.

Breast milk lymphocytes

The variety of cells found in human colostrum and BM has been well described. Most cells are neutrophilic granulocytes and macrophages, with the percentage of each varying according to the amount of nursing. Lymphocytes account for 10% to 20% of the cells and include T cells, B cells, and various T cell subsets. The number of T cells decreases rapidly in the first week post partum and continues to steadily decline over time. Functional assays have demonstrated that BM T-lymphocytes are generally hyporesponsive but respond to mitogens in vitro and display in vitro evidence of delayed hypersensitivity responses, respond to foreign transplantation antigens in a mixed lymphocyte reaction, and produce macrophage chemotactic factor. The ability of BM lymphocytes to mediate antibody-dependent cellular cy-
The concept of BM T-lymphocytes represent a select population of immunocompetent cells is suggested by the striking lack of correlation between milk and blood T cell functional responses in the same individual. The lack of antigen trapping at the breast could also account in theory for this lack of correlation. For example, studies with polio vaccination demonstrate that boosting seropositive women by the oral route leads to decreases in their milk antipolio antibody titers, whereas boosting via the subcutaneous route leads to transient increases in antipolio milk SIgA. The possibility exists that oral boosting leads to antigen trapping of migratory polio-specific lymphocytes in the gut mucosa, thus "draining" the breast of these cells.

The functional capabilities of BM B cells remain an area of debate. Using several experimental techniques, Moro et al. reported that lymphocytes did not stain for intracytoplasmic IgA or IgM and that plasma cells were not observed. In a subsequent study, this group found that colostral lymphocytes did not elaborate immunoglobulin in response to stimulation with pokeweed mitogen or Epstein-Barr virus. On the basis of these findings, it has been suggested that, in contrast to the T cells in BM, B cells represent a discarded and nonfunctional subset of lymphocytes. Evidence from other laboratories raises the possibility that BM B cells may retain functional capabilities similar to the T cells. Ahlstedt et al. reported that puromycin-sensitive plaque-forming cells (plasma cells) can be found in human milk. Also, Epstein-Barr virus transformed lymphoblastoid cell lines, selectively producing and secreting IgA, have been established from human Colostral cells. Selective synthesis of IgA in vitro has been demonstrated in other experimental settings as well.

**Immunologic advantages of breast-feeding**

Multiple advantages of breast-feeding over formula feeding have been advanced from a variety of disciplines. In the context of this article, the advantages of interest relate to allergy and infections. A large number of studies have been published and reviewed regarding the potential benefit of breast-feeding in prevention of atopic dermatitis and/or asthma. Opinion appears to remain divided, with equally well-performed studies demonstrating beneficial effects and a lack thereof. The current recommendation as outlined by the American Academy of Allergy and Immunology committee on Adverse Reactions to Foods takes the stand that breast-feeding may avoid the introduction of food allergens.

There is considerably less controversy regarding nursing and infections. From the study of the immunologic components of BM and with an understanding of mucosal immunity, it is reasonable to put forward several hypotheses regarding the observed protective effects of BM. The activity of the immunologic components has been well studied in vitro, and the potential for in vivo effectiveness should not be underestimated. However, despite the arsenal of anti-infective components contained in the milk, the feces of infants are by no means sterile. An early observation of neonatal gut flora was that bifidobacteria predominated over potential gut pathogens in breast-fed infants. This led to the hypothesis that direct modulation of the flora was of primary importance. However, recent studies have demonstrated that colonization with particular flora may be more dependent on environmental factors than on diet, and furthermore, a great variety of potential enteric pathogens do exist in the feces of breast-fed infants.

Even after antigenic stimulation begins, it takes several weeks to months after birth before SIgA can be detected in human saliva. This delay is also observed systemically in the failure of infants to make type-specific antibody in response to infection. Current theories regard SIgA as the primary protective factor contained in the milk. There does not appear to be a specific mechanism designed for transporting this ingested SIgA into the infant’s circulation. Although individual variability exists, it has been found that serum IgA levels actually drop over time when breast-feeding is initiated within the first 6 hours post partum, implying a role for BM in gut closure to macromolecules. In the rodent model, transport of immunoglobulin across the gut epithelium is specifically limited to ingested IgG. IgA is found in the feces of breast-fed infants by the second day of life, whereas only 30% of formula-fed infants demonstrate any IgA in the feces by 1 month of age. Therefore, it appears unlikely that ingested SIgA could directly effect protection of the lower respiratory tract except as it may bind to potential pathogens in the oropharynx. It has been suggested that aspiration of BM would explain the respiratory protection, although this mode appears contrary to normal physiology. There is evidence from studies of necrotizing enterocolitis in rats that cellular components in milk play a critical role in protection against that disease, since breast-feeding was found to be protective only when cell-containing milk was ingested. The influence of breast-feeding in preventing human necrotizing enterocolitis has also been reported.

The protective role played by BM polymorphonuclear granulocytes is uncertain, since they appear to be "down regulated." Although they contain ingested IgA, they do not release it during phagocytosis of latex particles. Phagocytosis, respiratory burst, and killing activities of these BM granulocytes are diminish-
ished compared with allogeneic peripheral blood neutrophils.\textsuperscript{137, 138} These phenomena are believed to be due to a suppressor factor or factors elaborated by either the BM macrophages or lymphocytes.\textsuperscript{139} Similar suppressive effects by BM cell culture supernatant fractions have been noted on both natural killer activity and immunoglobulin production by allogeneic PBL.\textsuperscript{141}

In contrast with the BM granulocytes above, colostral macrophages, also demonstrated to contain ingested IgA, release it while they are phagocytosing opsonized bacteria or latex particles.\textsuperscript{140} Surface-membrane stimulation of BM leukocytes also leads to the release of IgA through a mechanism that could be blocked by inhibitors of actin filaments.\textsuperscript{136} These findings suggest a role for BM macrophages in releasing their intracellular store of IgA on contact with enteric pathogens.\textsuperscript{141} Another possibility is that these cells may be armed with FcRs for cytophilic IgA antibody, allowing for antigen binding even at low antigen concentrations. In this respect they could function as accessory cells in the activation of antigen-specific T cells.

A protective role for BM lymphocytes has recently been suggested by the finding that, in animal models, these cells actually gain entry into the GALT of the nursing neonate. Puente et al.\textsuperscript{142} found that T- and B-lymphocytes harvested from rat GALT and injected into the tail vein of syngeneic lactating female rats are carried into the intestinal lumen of suckling pups in which they exhibit transepithelial migration to arrive in the GALT. Several studies by independent investigators have demonstrated similar transepithelial migration of ingested milk leukocytes in rats, newborn calves, and newborn lambs.\textsuperscript{143-146} It is as yet unclear whether these cells gain entry by virtue of being trapped in the mucin and are processed as antigens or if they use receptor-ligand interactions as described above. It appears that, although all BM cell types gain entry, lymphocytes may predominate.\textsuperscript{143} It has been suggested that BM macrophages might play a role in supporting the defective neonatal alveolar macrophage compartment if entry could be gained.\textsuperscript{141} There could well be a mucosal homing system similar to lymphocytes operative with these cells, as evidenced by the unique surface antigens expressed by human BM and alveolar macrophages.\textsuperscript{144}

There appears to be a definite role played by BM T cells in the induction of immunologic tolerance. This phenomenon has been observed in both animal and in human studies.\textsuperscript{105, 148-150} It remains a matter of speculation whether BM T cells could modulate the development of the neonatal IgA system at the mucosal level. The same speculation might be applied to BM B cells, since it has recently been suggested that B cells play a role in the normal development of T cells in the human system.\textsuperscript{151}

A final consideration is the role played by soluble immunoregulatory factors either contained in milk or elaborated by BM cells. A number of studies have indicated that unfractionated supernates of BM cell cultures will selectively stimulate IgA production by PBL\textsuperscript{152-155} and cord blood lymphocytes.\textsuperscript{156} Recently, it has been demonstrated that cell-free, defatted, filtered human colostrum stimulates murine splenic B-lymphocytes to produce significant quantities of immunoglobulin, as compared with controls where cow’s milk formula or late human milk was studied.\textsuperscript{157} These findings again raise the possibility that cellular or soluble components in the milk may modulate the immunologic maturation of the neonatal IgA system. In a fascinating study of the immune responsiveness of rabbits to bovine serum albumin, it was demonstrated that oral immunization of the pregnant dams with this antigen led to antigen-specific systemic hyporesponsiveness in the suckling kits. This phenomenon was not attributable to placental or milk transfer of antibody or antigen and was believed to be secondary to the products of dam suppressor T-lymphocytes transmitted via the placenta, the milk, or both.\textsuperscript{158} The identification of epidermal growth factor in milk suggests that factors may also be present that support the anatomic integrity of the mucosal barrier.\textsuperscript{159}

CONCLUSIONS

The immunology of BM appears to be intimately related to mucosal immunity in general. Although this may be due to the relationship between mammary tissues and other secretory mucosal sites, the possibility exists that breast-feeding may impart specific immunologic advantages to the neonate through enhancement or induction of the still developing neonatal immune system. Although several preliminary studies support this hypothesis,\textsuperscript{160-161} a great deal remains to be learned about the basis for the observation that breast-fed infants tend to remain healthier than their bottle-fed cohort.

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