[haematologica reports]
2006;2(10):18-26

Ontogeny of the intestinal immune system

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A B S T R A C T

All major components of the gut immune apparatus including the (1) epithelial barrier (2) mononuclear leukocytes in the lamina propria, and (3) organized gut-associated lymphoid tissue are anatomically identifiable in the fetus by 200 days of gestation. However, the functional maturation of this mucosal immune system is completed only in the postnatal period following introduction of enteral feeds and colonization with commensal bacterial flora. In the premature or sick newborn infant, this process of maturation might be delayed or altered and may in turn predispose the infant to infection, inflammatory states such as necrotizing enterocolitis, and allergic sensitization.

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The newborn infant faces a major antigenic challenge following introduction of oral feeds and microbial colonization of the gastrointestinal mucosa.[1-3] The mucosal immune system in the intestine has a complex role, in protecting the host from potentially harmful pathogens while at the same time 'tolerating' other resident microbes and dietary macromolecules to allow absorption and utilization of nutrients.[4,5] In this review, we outline the ontogeny of the intestinal immune system and analyze possible relationships between abnormal maturation of the mucosal immune response in premature/sick infants and various pathophysiological states. The emphasis is on human intestinal development, and corroborating evidence from experimental animals has been appropriately qualified in the text.

Ontogeny of the intestinal immune system

Intestinal epithelium and its immune functions

Structural differentiation of the mucosal epithelium starts with establishment of the crypt-villus axis. Villus formation progresses from the proximal intestine at about 8 weeks gestation to the colon by 10-12 weeks.[6] Crypt differentiation follows, occurring at 12-19 weeks.[7,8] By week 9, mucosal cells differentiate into primitive enterocytes, goblet cells and enterochromaffin cells.[9-11] Intercellular tight junctions appear from week 10 and form the anatomical basis for an epithelial barrier.[7]

Epithelial maturation continues during late gestation and infancy. This process is modulated by various cytokines and growth factors present in the systemic circulation, interstitial fluid, and ingested amniotic fluid and human milk.[7,12-14] A detailed description of these peptides is available elsewhere.[15] Mucosal growth involves fission and deepening of crypts, increase in villus width and number, and appearance of submucosal folds. A second phase of epithelial hyperplasia is observed at the time of weaning.[16]

Intestinal epithelial cells (IECs) play a key role in mucosal immunity. These cells express HLA-I and HLA-DR by 18-22 weeks, and can serve, at least *in vitro*, as non-professional antigen-presenting cells.[15,17-20] IECs can also express a variety of non-classical MHC class I molecules, which may have a role in antigen presentation, as co-stimulatory molecules, or as intercellular adhesion molecules.[21] Besides a possible role in antigen presentation or processing, IEC HLA-DR expression may also be important in the maturation and selection of intra-epithelial lymphocyte clones.[22]

Fetal/neonatal IECs express various innate response receptors and can produce a significant local acute inflammatory response. Fetal IECs produce more interleukin-8 (IL-8 or CXCL8) upon exposure to lipopolysaccharide (LPS) or IL-1 than ileal/colonic epithelial cells from adult subjects (Figure 1).[23-27] Epithelial-derived IL-8

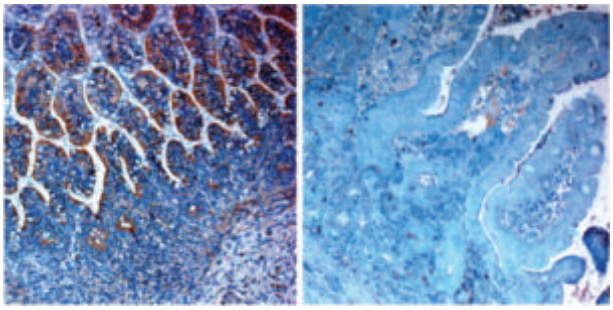

Figure 1. Immunohistochemistry for interleukin-8 (diaminobenzidine, brown) in sections from (A) human fetal intestine (22 week gestation) and (B) duodenal biopsy from an adult subject. In contrast to adult intestinal epithelial cells, fetal epithelial cells display strong immunoreactivity for IL-8. Magnification: 400x. *(Data from Maheshwari et al. 2004).*

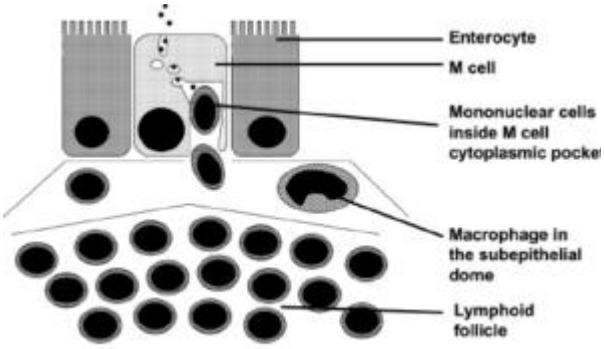

Figure 2. Schematic diagram showing the relationship of M cells with the subepithelial dome and the lymphoid follicle. The M cell shows an active transcytotic pathway which transfers antigenic particles from the intestinal lumen (top) to the basolateral 'pocket' domain. Mononuclear cells, which apparently cross through the relatively porous basal lamina, enter the M-cell pocket to receive these antigens. Lymphocytes, macrophages and dendritic cells are present in the subepithelial dome, which is a cap-like structure overlying a lymphoid follicle.

may serve an important role in host defense as this chemokine can recruit and activate both neutrophils as well as mononuclear phagocytes.[28-30] Fetal IECs also produce tumor necrosis factor (TNF)-α, IL-1, IL-6, IL-8, and platelet-activating factor (PAF).[31] The ability of fetal IECs to respond to LPS points towards a functional Toll-like receptor 4 pathway, which activates nuclear factor kappa B (NF-κB)-mediated gene transcription.[8]

An intact NF-κB pathway may be of teleological advantage during the fetal period. We have shown that NF-κB may block the apoptotic effects of TNF-α by activating IL-8 production.[23] Since reduction in apoptosis is important for the exponential increase in cell numbers during mucosal growth,[32] an active NF-κB pathway may be conducive for intestinal organogenesis. The hyper-responsiveness of fetal enterocytes to LPS is due to lower levels of inhibitor of κB (IÎB).[33] NF-κB signals are downregulated after birth, perhaps as an adaptive mechanism to prevent inflammation from bacterial colonization. In neonatal (as compared to fetal) mice, IECs develop a post-transcriptional down-regulation of IRAK-1, a key intermediate in LPS-induced signaling.[34]

Enterocytes have also an important role in immunoglobulin (Ig) transport. Polymeric Ig receptor (pIgR) expression has been observed in the fetal intestine by 12-15 weeks, and the protein can be demonstrated by immunofluorescence by 28 weeks.[17,35,36] pIgR allows the uptake of polymeric Ig at the basolateral surface, which is then translocated to the luminal surface. Fetal/neonatal enterocytes also express the neonatal Fc receptor (FcRn) from 18-22 weeks, which allows for bidirectional Ig transport across the intestinal epithelium.[37,38] FcRn facilitates the passage of antibodies to the lumen or the uptake of immune complexes or breastmilk antibodies from the lumen.[8,37,39]

Besides enterocytes, other epithelial cells also play an important role in host defense. Goblet cells start producing mucus by week 12.[7] Paneth cells also appear at this time, and these cells produce antibacterial proteins such as lysozyme and α-defensins. The number of Paneth cells per crypt is developmentally regulated and increases with maturation until adulthood.[40]

Follicle-associated epithelium (FAE)

The epithelium overlying the lymphoid follicles and Peyer's patches is uniquely adapted to sample luminal antigens for transfer to the subjacent immune cells. The FAE includes the so-called M cells ('membranous,' or 'microfold' cells), which are specialized for the uptake and transcytosis of macromolecules.[41-45] M cells have epithelial characteristics such as polarization and tight junctions, but instead of a brush border typical of enterocytes, have small microfolds on the apical surface.[42,46-52] In addition, the basolateral membrane is invaginated to form a cytoplasmic 'pocket' that typically contains lymphocytes, and occasionally macrophages or other cells (Figure 2).[53-55] M cells have been demonstrated in the human fetus as early as 17 weeks.[11,18,42,56,57] The M-cell population expands rapidly in the first postnatal week in various animal models, but these changes have not been studied in the human neonate.[49,58,59]

Perinatal closure of mucus membranes

During the immediate neonatal period, particularly in the preterm or small-for-date infant, the intestinal mucosa remains permeable to intact macromolecules

Table 1. Development of Peyer's patches (PP) in the human fetus.

11 wks gestation	PP anlagen with HLA-DR+ CD4+ lymphoid cells
16 wks gestation	Appearance of T and B cells First appearance of CD8+ cells* B cell maturation with appearance of surface IgM and IgD
16-18 wks gestation	Appearance of CD5+ B-1 cells Surface IgA on B cells
18-20 wks gestation	Appearance of PP zonation into B and T cell areas
24 wks gestation	PP are macroscopically identifiable
0-4 wks post-natal	Germinal center formation

**Fetal Peyer's patch T cells are predominantly of the CD4+ phenotype.*

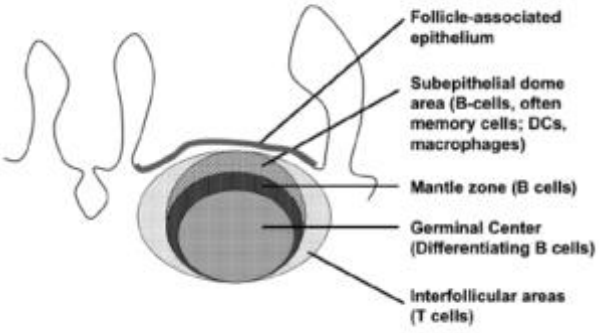

Figure 3. Organization of a Peyer' patch. Peyer's patches appear as lymphocyte clusters at 100-110 days of gestation. Discrete B cell follicles and T cell zones, a dome region, and the FAE are observed at 130-140 days. Germinal centers develop after birth following antigenic stimulation.

and bacteria.[60] This increased permeability may be related to increased transcytosis and/or higher paracellular permeability due to immature tight junctions.[61] Mucosal permeability can be indirectly measured as urinary lactulose and mannitol ratio following oral administration of a measured load of both sugars. There is a rapid reduction in sugar permeability over the first postnatal week, resembling the pattern of *gut closure* in experimental animals.[62] A similar reduction in permeability is also seen at other mucosal sites and therefore disappearance of IgG from saliva can also be used to study these maturational changes.[63]

The mucosal *hyper-permeability* may by teleologically advantageous *in utero* by allowing a bidirectional exchange of bioactive molecules between amniotic fluid and fetal serum.[64,65] However, in the postnatal period, timely and efficient membrane closure is essential for survival.[60] Colostrum/breastmilk feeds, in contrast to infant formula, enhance the maturational process.[62] Similarly, initial colonization with lactobacilli or bifidobacteria, as against coliforms, facilitates the normal reduction in mucosal permeability.[66,67]

Lymphoid tissue

Peyer's patches and other organized lymphoid tissue

Peyer's patch become identifiable in fetal ileum at 11 weeks as aggregates of HLA-DR$^+$, CD4$^+$ lymphoid cells.[68,69] Major events in Peyer's patch development have been summarized in Figure 3 and Table 1.[19,69,70] At birth, the organized lymphoid compartment is naïve but structurally complete, and the predominant activity involves proliferative expansion (rather than primary lymphopoiesis).[70] The number of PP increases from about 60 at birth to over 200 by 12–14 years.[71] In the vermiform appendix, the development of lymphoid structures lags behind the Peyer's patches.[72] Appendiceal lymphoid follicles enlarge rapidly after birth following bacterial colonization and translocation.[73] The first IgA$^+$ plasma cells appear at 2 weeks after birth and then increase to adult levels at 4-5 months.

Lymphocytes in Lamina propria and intra-epithelial compartments

Scattered B cells are first observed in the lamina propria at 14 weeks gestation.[69] The fetal intestinal B cell population consists of two distinct cell types. The first population of large, dividing, mature B cells shares morphologic and phenotypic (CD20$^+$IgM$^+$IgD$^+$light chain$^+$) features with the thymic B cells. These are large-sized cells with extensive cytoplasmic processes, which are in contact with adjacent T cells. A second population of smaller pre-B cells (IgM$^+$ light chain-CD20$^-$) has also been identified, suggesting the presence of local B cell development.[74] As extrathymic T cell development occurs in human fetal intestine (vide infra), it has been hypothesized that as in the thymus, the B cells may play a role in the development and selection of the T cells.

The B cell population in the fetal intestine comprises IgM$^+$ and IgG$^+$ cells.[17] The fetal intestinal B cell repertoire is similar to B cells in circulation or other organs, but differs significantly from plasma cells in postnatal intestine.[74] After birth, the IgM$^+$ plasma cell population expands faster than IgG$^+$ cells, and at the same time microbial stimulation induces B cells to undergo

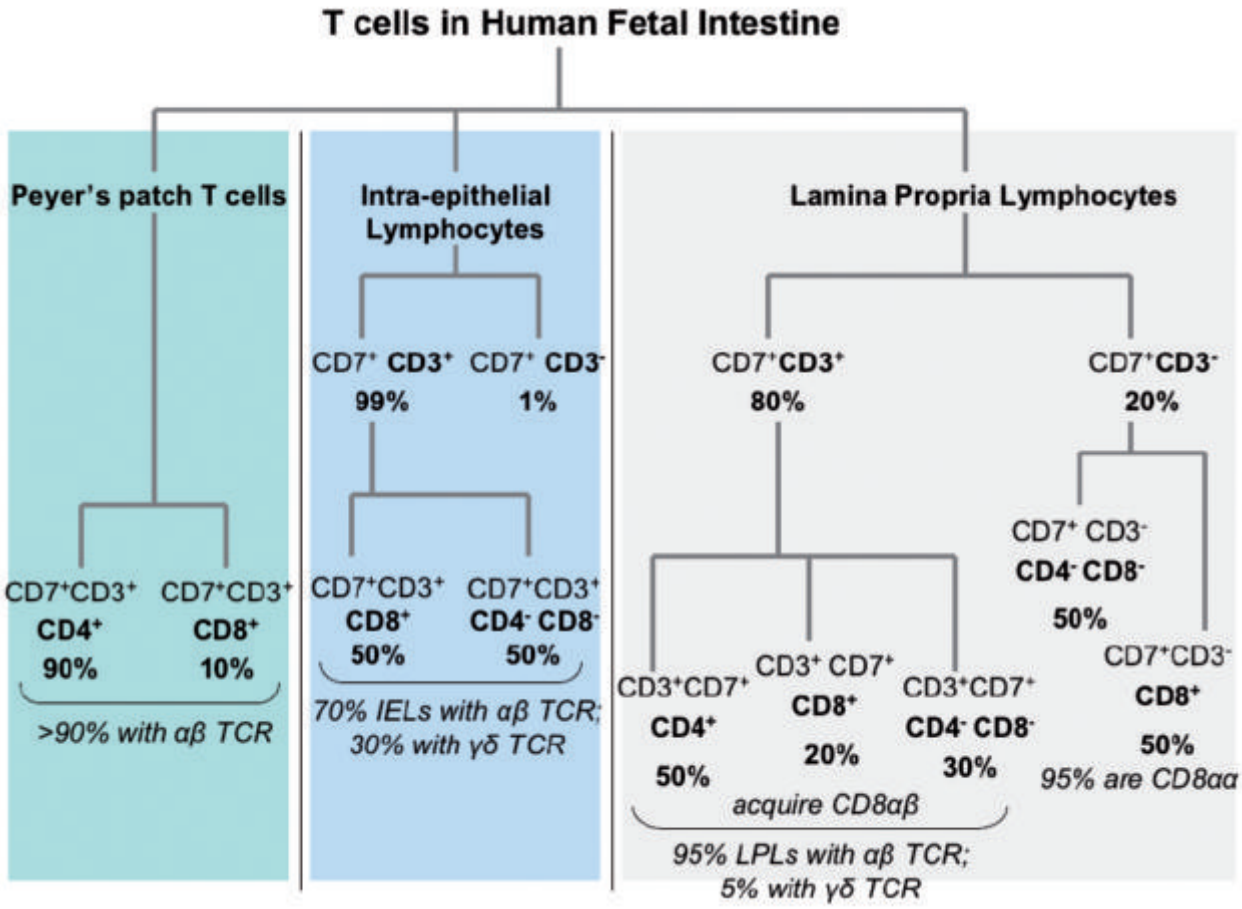

Figure 4. T cell populations in the human fetal intestine. Intestinal T cells are distributed in the Peyer's patch interfollicular zone, intra-epithelial paracellular spaces, and in the lamina propria. In fetal Peyer's patches, majority of the T cells are of the CD4$^+$ helper/inducer phenotype. Intra-epithelial lymphocytes are predominantly CD3$^+$, but include equal numbers of CD8$^+$ cytotoxic/suppressor and CD4$^-$ CD8$^-$ double negative cells. In the lamina propria, majority of the cells are CD3$^+$ with a CD4$^+$ helper/inducer phenotype. However, nearly 20% cells are CD3$^-$ with a CD8$^+$ or double negative phenotype. Unlike CD8$^+$ cells elsewhere in the gut, these CD3$^-$ CD8$^+$ cells may carry an atypical CD8^{--} homodimer. The presence of various immature T cell populations suggests that fetal intestine may serve as an extra-thymic site of T lymphocyte differentiation.

IgA class switch in both lamina propria and organized lymphoid tissue.[75] IgA$^+$ plasma cells are first seen in the lamina propria during the second postnatal week.[76-78] The number of IgA$^+$ cells in the mucosa reach adult levels at 2 years, although serum IgA concentrations reach adult levels only during the second decade.[19]

Intestinal T cells can be identified from 12-14 weeks of gestation.[79] Outside the organized lymphoid tissue, intestinal T cells are distributed as intra-epithelial (IELs) and lamina propria lymphocytes (LPLs). The fetal gut has a small number of IELs (3-5 CD3$^+$ IEL/100 IECs compared to 6-27 cells/100 IECs in older children), which expand rapidly after birth (a 10-fold expansion of the $\alpha\beta$ T cells and a 2-3 fold increase in the $\gamma\delta$ cells, *vide infra*).[19,80] In contrast, LPLs continue to expand during fetal period and have a density similar to the postnatal intestine by 19-27 weeks gestation.[79]

Several early lineage T cell populations can be seen in the fetal intestine, suggesting that T cells may develop locally in an extra-thymic pathway.[69,70,79,81-86] These immature T cell lineages have been shown in Figure 4. Whereas most immature LPLs differentiate rapidly after birth, the differentiation of IELs is slower and continues through infancy.[87] In addition to phenotypic changes, intestinal T cells also continue to undergo functional maturation during infancy and childhood. The TCR β-chain repertoire is polyclonal during fetal period and infancy and gradually becomes restricted to the oligoclonal pattern characteristic of adults. This restriction is likely due to expansion of a few dominant clones specific for the commensal bacterial flora.[87]

In the fetal intestine, about 10-30% IELs express the $\gamma\delta$ T cell receptor.[69] Rodent studies suggest that $\gamma\delta$ cells

may regulate IEC function, display cytotoxic activity, and may promote antimicrobial immunity.[88-90] Similar to αβ T cells, the fetal/neonatal γδ repertoire is also polyclonal.[91]

Intestinal macrophages and dendritic cells (DCS)

Many macrophage-like CD45+, HLA-DR+, CD4+ cells are seen in the lamina propria even before 11 weeks, but the relationship of these primitive cells with mature macrophages and/or DCs is unclear.[18] In fetal rats and non-human primates, a small CD68+ macrophage population is seen sparsely scattered in the lamina propria. These cells expand rapidly in the early neonatal period.[92,93] Recent studies on the mouse fetus are consistent with the observations in human adults that intestinal macrophages lack various innate immune receptors such as CD14, CD89, FcγR I–III (CD64, CD32, CD16), CD11a, CD11b, CD11c, and CD18.[34,94] This *inflammatory anergy* of intestinal macrophages is likely an adaptive mechanism to minimize inflammation in the normal intestinal mucosa despite close proximity to immunostimulatory bacteria.

We have shown recently that intestinal macrophages are derived from blood monocytes, which are recruited under the influence of extra-cellular matrix products such as IL-8 and transforming growth factor (TGF)-β.[28] In the lamina propria, newly recruited monocytes acquire the unique phenotypic and functional properties of intestinal macrophages under the influence of TGF-β.[94]

There is very limited data on fetal intestinal DCs.[95] HLA-DR+ DC-like cells have been reported in both the lamina propria as well as Peyer's patches after 14 weeks, but these cells could not be clearly differentiated from lamina propria macrophages.[96] In rats and non-human primates, DCs have been noted in the fetal lamina propria as well in Peyer's patches.[92,97] The significance of early colonization by DCs is not clear.

Secretory immunoglobulins

Secretory immunoglobulins, IgA and IgM, play an important role in mucosal defense. Secretory IgA (sIgA) can be detected in mucosal secretions as early as 1-8 weeks after birth.[63,98-100] sIgM, on the other hand, appears transiently during early infancy.[63]

sIgA levels rise during neonatal period to reach an initial peak (as measured in saliva) at 4-6 weeks. In premature infants, sIgA appears in secretions at a similar chronological age as in full term infants, although sIgA concentrations may be lower than full term neonates. If chronological age is corrected for prematurity, sIgA concentrations then become similar to matched full term infants.[101,102] Salivary IgA levels continue to rise up to 18 months of age.[102] A transient nadir in sIgA has been inconsistently[100,103] recorded at 3-6 months.[63,104]

Secreted immunoglobulins also change qualitatively during the first year. There is a switch from monomeric IgA to polymeric sIgA sometime during the first year, indicating maturation of the secretory immune system,[105] or alternatively, increasing exposure to exogenous antigens.[106] The relative amounts of IgA subclasses in mucosal secretions also changes during infancy. At birth, sIgA1 is the dominant subclass but sIgA2 increases rapidly by 6 months of age.[103]

Specific sIgA responses appear to be related more to the timing and quantum of the antigenic stimulus than to developmental factors during infancy. sIgA antibodies to E. coli somatic antigens appear in neonates within a few weeks after timed exposure and colonization.[107] The strength of the stimulus also has an effect: earlier, and stronger, specific sIgA responses are seen in neonates born in areas endemic for a pathogen as compared to infants in the developed world.[105,108]

During the neonatal period, colostrum provides an important alternative source of sIgA.[109] Milk antibodies, amounting to about 0.5-1 g/day throughout lactation (comparable to the 2.5 g/day being produced by a 65 kg adult), are directed against antigens present in the environment shared by the mother-infant dyad.[110] The presence of 'enteromammary' and 'bronchomammary' pathways allow immune cells stimulated by antigens in the maternal intestine and bronchial mucosa to migrate to the mammary gland.[109,111-113] Interestingly, sIgA levels have been reported to be higher in colostrum and milk of mothers of preterm neonates.[114]

Clinical relevance of delayed/altered maturation of the mucosal immune system

Bacterial translocation

The high permeability of the neonatal mucus membranes may place the premature or sick neonate at risk of systemic infection. Bacterial translocation, defined as the passage of both viable/nonviable microbes and microbial products of the flora across the intestinal mucosal barrier, has been extensively studied in rodent models.[73,115-118]

Premature neonates often have multiple risk factors for bacterial overgrowth and translocation: delayed initiation of enteral feedings, frequent use of histamine receptor (H2) blockers, ileus secondary to opiate sedatives, and the acquisition of coliform bacteria as the initial microbial colonizers may all increase the risk of bacterial translocation.[3,110,119-127] Indeed, there is increasing indirect evidence to suggest that bacterial translocation plays a role in neonatal sepsis: (1) reported isolation of identical bacterial ribotypes from blood

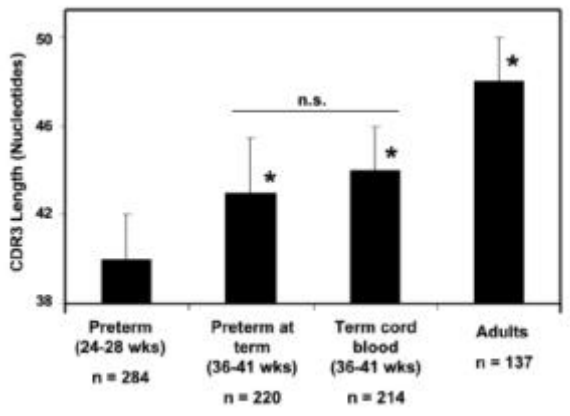

Figure 5. Developmental changes in immunoglobulin heavy chain CDR3 lengths. Premature infants have a significantly shorter CDR3-region as compared to premature infants at term post-conceptional age, newborn term infants, and adults (p<0.05). The implications of short CDR3 lengths in premature neonates include a smaller antibody repertoire, which may increase the chances of antigen exposure and sensitization, and antigen-binding sites that favor peptides with allergenic potential. *(Data from Zemlin et al. 2001, Bauer et al., 2002).*

and pharynx/rectum in septic neonates;[128,129] (2) frequent isolation of gut-derived (endogenous) organisms in bloodstream infections in neonates receiving parenteral nutrition;[127,130] (3) reduction in incidence of necrotizing enterocolitis-related deaths by using oral antibiotics;[131,132] the investigators hypothesized that bacterial translocation is a graded phenomenon, is more likely if enteric bacteria exceed a critical population level ($>10^{9-10}$/g of stool in an animal model), and is a key component of the pathophysiology of NEC;[131,133] and (4) lower incidence of sepsis in breastfed neonates; breastfeeding may alter the pattern of microbial colonization, improve gut barrier function, and provide antibacterial and immune factors.[134,135]

Viral infections

The high mucosal permeability of the neonatal intestine to macromolecules as well as intact leukocytes is likely to be an important factor in vertical and breastfeeding-related HIV transmission.[136] In a recent study on breastmilk-related HIV transmission, each 10-fold increase in cell-free or cell-associated virus was associated with a 3-fold increase in viral transmission after adjusting for maternal CD4 cell counts and disease stage.[137]

Neonatal monocytes, due to higher proliferative activity, are more permissive to infection with HIV-1 as compared to monocytes from adult subjects.[138] Furthermore, developmental characteristics of neonatal lymphocytes such as suppression of interferon-α and -γ responses by HIV proteins and relatively deficient cytotoxic activity may prevent early elimination of virus-infected cells.[139-141]

Necrotizing enterocolitis

The developing intestine has a pro-inflammatory bias and is predisposed to conditions such as necrotizing enterocolitis. Neonatal enterocytes have a higher propensity to bind pathogenic gram-negative bacteria due to the presence of sialic acid and N-acetylglucosamine residues in the membrane glycocalyx.[3] These cells respond strongly to bacterial products such as LPS, and a highly active NF-κB pathway increases the epithelial inflammatory response with various mediators such as TNF-α, IL-1, IL-6, IL-8, and PAF.[31]

Allergic sensitization

Premature infants lack the intrinsic protective mechanisms of the adult intestinal mucosa that prevent sensitization against luminal constituents: a strong physical barrier, luminal enzymes that can alter ingested antigens, presence of regulatory T cells, and the production of sIgA.[142] The risk of sensitization is further increased due to several developmental deficiencies within primary immune cells: (1) specific antibody responses in premature infants are abnormal due to reduced antigen affinity, increased polyreactivity, and autoreactivity;[143,144] (2) the lengths of immunoglobulin heavy chain third complementarity determining regions (CDR3) are almost 3 amino acids shorter in the fetus/premature infant than adults (Figure 5).[145] This reduces the potential antibody diversity available to the fetus/preterm neonate by about 20^3 (= 8000) fold.[145] Moreover, antigen binding sites with short CDR3 regions, due to their tertiary structure, are more likely to bind to peptides such as allergens;[146] and (3) the the short CDR3 regions of fetal $CD5^+$ B1 cells share characteristics with variable regions of IgE heavy chains.[147,148] These observations have led to the hypothesis that B1 cells may contribute to the repertoire of allergen specific IgE^+ plasma cells, and that premature exposure of the immature intestinal B cell repertoire to allergens may influence the risk of sensitization.[148]

Acknowledgments: supported in part by NIH/NIAID Center for HIV AIDS Vaccine Immunology (A.M.), American Gastroenterological Association/Foundation for Digestive Health and Nutrition Research Scholar Award (A.M.), American Heart Association BGIA 0665155B (A.M.), the Children's Center for Research and Innovation/The Children's Hospital of Alabama (A.M.), and the Deutsche Forschungsgemeinschaft TR22, TPA17 (M.Z.).

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