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Innate Immunity in the Small Intestine of the Preterm Infant

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Abstract

The gastrointestinal tract comprises the largest surface area of the human body. This area is constantly exposed to myriad antigens as well as the large number of bacteria that coexist in the intestinal lumen. To protect against this exposure and help distinguish “self” from “foreign,” the intestinal tract has evolved a sophisticated barrier defense system that includes both innate and adaptive immune systems. However, infants who are born preterm do not have the benefit of an adequate immune response and, therefore, are more susceptible to bacterial injury, inflammation, and intestinal diseases such as necrotizing enterocolitis. In this review, we discuss the components of innate immunity that help to protect the small intestine as well as current knowledge about the role of these components in the pathophysiology of necrotizing enterocolitis.

Objectives

After completing this article, readers should be able to:

1. Understand the concept of two major sections of the small intestinal mucosa that constitute innate immunity.
2. Conceptualize the primary differences in timing between rodent and human gastrointestinal development.
3. Enumerate the major components of innate immunity in the epithelium and lamina propria of the small intestine.
4. Explain the critical role of innate immunity in intestinal diseases such as necrotizing enterocolitis.

Introduction

One of the key steps in early evolution was the development of a gastrointestinal tract. This innovative tube-within-a tube design allowed the growth of organism size and complexity from simple animals such as sponges and jellyfish to the complex animals seen today. However, to maintain the integrity of this inner tube and to protect it from the external environment, an intricate system of defense had to develop. This massive barrier must protect against the harsh acidic environment of the stomach, the digestive enzymes produced by the pancreas, and the at least 500 species of bacteria that outnumber the cells in human bodies 10 to 1 and synergistically coexist in the intestinal tract.

The newborn faces even greater challenges. After a relatively protective intrauterine environment, the newborn abruptly encounters an increasing array of antigens. In particular, infants born preterm face a hazardous combination of immature host defense and exposure

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to nonmaternal antigens in the intensive care setting. To protect the host from caustic luminal molecules, pathogenic microorganisms, and harmful inflammation, an intricate intestinal immune system developed, which can be divided into two sections: the outer epithelial layer and the inner lamina propria (Fig. 1). The primary component of the outer section is a single cell layer of intestinal epithelial cells (IECs). The IECs differentiate from a common progenitor stem cell into one of four types of cells: absorptive enterocytes, hormone-secreting enteroendocrine cells, mucus-secreting goblet cells, and antimicrobial-secreting Paneth cells. Interspersed between these IECs are intraepithelial lymphocytes (IELs) and the dendritic cell extensions. IELs are an important line of first defense that maintain the integrity of IECs; dendritic cells help to determine the type of immune response needed by sampling luminal antigens encountered by their extension. The second section of intestinal defense is located below the IELs in the lamina propria. This complex layer of immune cells includes the body of the dendritic cells, neutrophils, macrophages, immunoglobulin (Ig)A-producing plasma cells, natural killer (NK) cells, NK T-cells, conventional T-cells, and T-regulatory cells. This inner section of intestinal immunity is collectively known as gut-associated lymphoid tissue (GALT), which includes Peyer patches, isolated lymphoid follicles, and mesenteric lymph nodes. To cover all protective elements of the gastrointestinal tract is outside the scope of this article, which focuses on the role of the innate immunity of the small intestine throughout development as well as its potential roles in neonatal necrotizing enterocolitis (NEC).

Embryology

The embryogenesis of the gut is remarkably similar in all animals and is nearly identical in all vertebrates. In humans, by 4 weeks of gestation, the embryo has a single tube intestine that is relatively straight and uniform in its structure. Between the 10th and 12th weeks of gestation, villi, microvilli, and crypt structures begin to form, and by the end of the first trimester, Paneth cells begin to appear. By the 24th week of gestation, the fetus begins to have active digestive enzymes such as maltase and sucrase, and between the 32nd and 36th weeks, normal gastric emptying and suck-swallow coordination are achieved. Although the human digestive tract is considered to be structurally mature at birth, development of its mucosal barrier continues for the next 2 years. (1)

Almost all vertebrates follow this same pattern of intestinal tract development, but the timing of development can be markedly different. For example, in contrast to the full maturity of the human digestive tract at birth, the mouse does not obtain this same level of maturity until 4 weeks after birth (Fig. 2). In fact, at birth, the mouse has just developed villi-crypt structures, which is equivalent to a 10- to 12-weeks' gestation human fetus. Similarly, humans achieve enzyme production by 24 weeks of fetal gestation, but the mouse produces these same enzymes at 2 weeks of age. This difference has been invaluable in understanding the steps involved in gastrointestinal development, but it must also be taken into consideration when evaluating rodent models of neonatal gastrointestinal disease processes.

Secretory IgA

Newborns, whether term or preterm, lack secretory IgA (sIgA) at birth. High concentrations of IgA found in maternal colostrum and human milk help to compensate for this deficit. The concentrations of IgA, which represents 90% of all Igs in human milk, remain consistently high in human milk; other Igs such as IgM decrease over time while a mother is lactating. (2) Within 2 weeks after birth, the plasma cells that produce IgA begin to form in the Peyer patches and subsequently migrate to the lamina propria of the intestine. (3) Commensal bacterial flora are important to this process, as reflected in animals raised under germ-free

conditions showing underdevelopment of Peyer patches and an absence of IgA. (4) IgA is produced by plasma cells as dimers that are linked together by a 15-kDa polypeptide called the joining or “J” chain. (5) J chains are required for active transport of the IgA dimers to the mucosal surface by polymeric-Ig receptors. Once exported, the J chain is cleaved to release sIgA into the lumen of the intestine, where it plays multiple roles in innate immunity. The sIgA can bind to both luminal bacteria and to antigens to hinder microbial attachment to the epithelium, prevent microbial penetration, facilitate antigen sampling by M-cells, and entrap dietary antigens. In general, this promotes maintenance of bacterial flora. (6) In addition, the presecreted IgA dimers can promote clearance of microorganisms that have breached the epithelial layer either through transcytosis into the lumen or activation of effector immune cells. (7)(8)

Intestinal Mucins

A second predominant secretion of the small intestinal innate immune barrier is intestinal mucus. Mucins are large glycoproteins produced by goblet cells that are secreted to provide a physical barrier, facilitate removal of adherent bacteria, and concentrate enzymes near the epithelial surface to aid in host nutrient digestion. (9) The ileal portion of the human small intestine expresses multiple mucin genes, including *MUC1*, *MUC2*, *MUC3*, *MUC4*, *MUC13*, and *MUC17*. These genes produce the corresponding proteins that are synthesized in the endoplasmic reticulum and are glycosylated in the Golgi apparatus. *MUC1*, *3*, *4*, *13*, and *17* encode mucins that are anchored to the cell membrane by a transmembrane domain and a short cytoplasmic tail that associates with cell cytoskeleton proteins. (10)(11)(12) This is in contrast to the most abundant mucin in the small intestine, *MUC2*, which is packaged into storage granules and secreted into the lumen. (12) In humans, mucin genes are expressed early in development, reaching adult levels of expression by 27 weeks of gestation. (13) However, the mucus produced by the immature intestinal tract has different viscosity, (14) buoyancy, and carbohydrate composition (15) from mucus produced by adults.

MUC2 is secreted through two different mechanisms. The first is baseline secretion via exocytosis where mucins are not stored in the goblet cells but are instead exported into the lumen via microtubules and vesicular transport. (16) The second mechanism involves stimulated release of mucins that have been stored in the theca of goblet cells. This occurs through a number of mucin secretagogues that include inflammatory and neuro-endocrine mediators. (17) We have shown that tumor necrosis factor (TNF)- α concentrations not affecting mature intestine can cause an increase in mucus secretion in the immature ileum. (18) The secreted mucus forms two separate layers. (19) The lower layer of mucus is thin, unstirred, and discontinuous and covers the epithelium in the small intestine but is absent over small intestinal Peyer patches. This layer acts as a physical barrier and may play a significant role in cellular signaling in the event of epithelial damage. *MUC1* has been shown to bind with members of the ErbB family, (20) which affect cellular proliferation, migration, and apoptosis. It has also been shown to form complexes with active I κ B kinase complexes, thereby preventing nuclear factor (NF)- κ B activation and further downstream inflammatory responses. (21)

The outer layer of mucin acts as an additional barrier for the epithelium. The mucus layer contains saccharides that adherent bacteria can use as a nutrient source. (16) In this manner, peristalsis and removal of intestinal mucus can help to decrease bacterial loads. Further, mucin gels have the ability to capture and hold biologically active molecules. Excellent examples of this in the small intestine are the trefoil factors, a conserved family of peptides that are produced by intestinal epithelium and bound to mucins. They serve to increase mucus gel viscosity, promote wound healing, and decrease apoptosis. (22)

Antimicrobial Peptides

A third prominent secretion involved in small intestinal innate immunity is the group of antimicrobial peptides (AMPs). AMPs are commonly found in nature and play an important role in innate immunity for plants, insects, and vertebrates. In the human small intestine, AMPs are produced by Paneth cells, the pyramidal-shaped columnar exocrine cells located in the crypt base of small intestinal villi that are found as early as the first trimester of gestation. (23) These cells are significant for their apical granules that contain lysozyme, α -defensins, secretory phospholipase A2, Reg3 γ , and TNF- α , among others. Unlike IgA, Paneth cell development is not dependent on the microbial flora, and concentrations of AMPs have been shown to be similar in germ-free and conventionally reared mice. (23) Under physiologic conditions, AMPs are constitutively released to control the microenvironment of the intestinal crypt, where intestinal epithelial stem cells are located. Disruption of Paneth cells prevents clearance of pathogenic bacteria such as *Escherichia coli*. (24) However, in the presence of inflammatory or cholinergic agents, AMPs also are secreted into the lumen to support defense of the epithelial layer.

Paneth cells produce many AMPs such as phospholipase A2, which cleaves phospholipids, and Reg3 γ , which is active against gram-positive bacteria. However, the two most significant AMPs produced by Paneth cells for neonates are α -defensin and lysozyme. Defensins are small cationic peptides characterized by three intramolecular disulphide bridges that have the capacity to kill or inactivate bacteria, fungi, protozoa, and viruses. (25) The α -defensins are constitutively secreted by Paneth cells, but an increase in their secretion can be induced by lipopolysaccharide (LPS) (endotoxin), inflammatory mediators, and cholinergic agonists. Secretion of α -defensins helps to regulate the microbial density of the small intestine, protect neighboring stem cells in the crypts, and defend the epithelial layer against pathogens. (25) In contrast to α -defensins, β -defensins are found constitutively in epithelial cells and are most abundant in the colon and stomach. Like α -defensins, β -defensins are secreted into the mucus layer and serve to defend against bacterial invasion. (26)

Another well-conserved antimicrobial peptide secreted by Paneth cells is lysozyme, a polypeptide containing four cysteine residues forming disulfide bridges. It is produced in macrophages and Paneth cells in the small intestine and, when secreted, localizes near the mucosal surface. Unlike defensins, lysozyme concentrations have been shown to decrease during inflammation and to correlate with the severity of inflammatory insult. (27) This has specifically been shown in infants who had NEC and demonstrated a depletion of Paneth cell lysozyme. (28)

An additional AMP found in the small intestine is LL-37, the only human member of the cathelicidin family. Cathelicidins are synthesized as large precursor peptides that are cleaved to yield several peptides with antimicrobial activity. In the small intestine, LL-37 is constitutively expressed primarily in the Brunner glands of the duodenum. The role of cathelicidins includes antimicrobial activity against both gram-positive and gram-negative bacteria and chemotaxis for monocytes, macrophages, and T-cells. (29) In addition, LL-37 has been shown to bind to and neutralize LPS, activate monocytes, and alter dendritic cell function. (25)

Pathogen-recognition Receptors

Below the secreted portion of intestinal innate immunity, the next layer of defense encountered by invading pathogens is the group of structural factors located on the epithelial surface. These include the pathogen-recognition receptors (PRRs) and the tight junction (TJ) complexes holding together the epithelial cells. PRRs are a series of conserved receptors

located on the epithelial surface that recognize pathogen-associated molecular patterns and initiate immune responses. These PRRs include the membrane-bound toll-like receptors (TLRs) and the cytoplasmic Nod-like receptors (NLRs).

TLRs are transmembrane proteins found on the cell surfaces of immune cells such as lymphocytes and phagocytes but also on the surfaces of IECs and in their endosomes. Of the 10 known human TLRs, TLR 1 to 5 and TLR9 have all been detected in the human small intestine and act as sentinels for the presence of pathogens. (30) TLR 2, 4, 5, and 9 recognize common bacterial and fungal structures such as LPS (TLR4), and flagellin (TLR5); TLR 3 primarily detects double-stranded DNA from viruses. (31) Once bound, TLRs recruit adapter proteins such as MyD88, MAL, TRIF, and TRAM to form a complex with the C-terminal domain of the TLRs. (32) This complex activates mitogen-activated protein kinases, leading to activation of nuclear translocation of NF- κ B and further production of inflammatory cytokines and chemokines. Activation of TLRs is key to many intestinal processes, including IEC proliferation, maintenance of TJs, IgA production, AMP expression, (33) and healing of injured intestinal epithelium. (34)

A second group of PRRs are the NLRs, which recognize pathogen-associated molecular patterns in the cytoplasm. The best-known NLRs are Nod1 and Nod2. Nod1 is expressed by IECs and is required for recognition of invasive gram-negative bacteria through binding of bacterial peptidoglycan. Once activated, Nod1 elicits an immune response through the GALT and especially the Peyer patches in the small intestine. Nod2, which is highly expressed in monocytes, dendritic cells, and Paneth cells, recognizes the C-terminal caspase-recruitment domain 15, which is found in both gram-positive and gram-negative organisms. Activation of Nod2 mediates release of cryptidins and proinflammatory cytokines. (33) Work by Kobayashi and associates (35) and Maeda and colleagues (36) showed that Nod2 is a key component to the intestinal defense provided by macrophages, dendritic cells, and Paneth cells, and defects in Nod2 result in decreased bacterial clearance.

Junctional Proteins

In addition to providing innate immunity through receptors and secretions, the epithelial layer itself acts as part of the immune barrier. This is accomplished, in large part, through the system of junctional proteins that cement the epithelial cells together and act as gatekeepers for transcellular transport. The junctional proteins can be grouped into two structural categories: the TJs, which bind the cells together at their apical surfaces, and the adherens junctions (AJs), which bind the cells at their lateral surfaces. TJs are located at the apical surface of epithelial cells and define the boundary between the apical and lateral cellular surfaces. These multiprotein complexes are composed of transmembrane proteins and intracellular scaffold proteins that function to regulate selective permeability of the epithelium. These proteins act to anchor the TJ to the actin cytoskeleton, help to cluster the transmembrane proteins, and may play a role in helping to regulate TJ dynamics.

The transmembrane portion of the TJ is made up of three types of proteins: occludin, the claudin families, and the junctional adhesion molecules (JAMs). Occludin was the first identified transmembrane protein component and is almost universally present in all TJs. Despite finding occludin first, its role in the TJ complex is still not well understood. Occludin knockout mice have structurally normal TJs, (37) although occludin has recently been shown to play an important role in regulation of macromolecule flux. (38) Unlike occludin, the claudin family of proteins shows great variability in their distribution in TJs. The claudin family includes at least 24 members that have tissue- and organ-specific distribution. (39)(40) Claudins form pores across the TJ that contain charged loops of amino acids in their structure. These loops regulate the size, strength, and specificity of the ions

that are allowed through the junction and are believed to be the key reason why different epithelia have different permeabilities. The JAMs consist of five members of an IgG-like family of proteins found at TJs as well as on circulating lymphocytes. JAM-A is found at inter-cellular contacts, and although it does not participate in formation of TJ strands, its loss has been shown to alter cellular polarity and permeability. (41)

While TJ proteins are primarily involved creating the “gate” and “fence” functions involved in the selective porosity of the epithelial barrier, the AJ acts to cement adjacent cells together and serve as a site of intracellular signaling. This is accomplished through the nectin-afadin and cadherin-catenin complexes. These complexes are located just below the TJ and serve to connect adjacent cells and link into the cellular actin assembly. Loss of these connections disrupts cell polarization and differentiation and leads to premature apoptosis. (42)

Cellular Innate Immune Response

Based on T-cell receptor (TCR) domain structures, intestinal epithelial lymphocyte T-cells can be divided into TCR $\alpha\beta$ T-cells and TCR $\gamma\delta$ T-cells. T-cells expressing $\alpha\beta$ TCR are primarily responsible for antigen-specific cellular immunity, whereas TCR $\gamma\delta$ T-cells typically are considered part of the innate immune responses because they do not require antigen processing. (43) TCR $\gamma\delta$ T-cells are predominantly interspersed between the IECs. In mice, TCR $\gamma\delta$ T-cells are the first T-cells to colonize the epithelium during embryogenesis, and their origin can be thymic or extrathymic. It has been hypothesized that TCR $\gamma\delta$ T-cells contribute disproportionately to early life immunity because they are found in human fetal liver as early as 6 weeks' gestation. (44) In fact, neonatal TCR $\gamma\delta$ T-cells are likely a critical source for immunoprotective and immunoregulatory activities in the perinatal period when conventional TCR $\alpha\beta$ T-cell responses are not yet fully mature. (45) In older children and adults, TCR $\gamma\delta$ T-cells represent 1% to 5% of circulating T-cells but approximately 10% to 20% of IELs in the small intestine. (46) In contrast, we detected a much higher proportion (40% to 50%) of TCR $\gamma\delta$ T-cells within the ileum IEL in the first 6 postnatal months (personal communication, J. Weitkamp, June 2011). Although the precise role of TCR $\gamma\delta$ T-cells is not yet clearly defined, they appear to be critical for the maintenance of epithelial integrity through antibacterial defense, TJ preservation, recognition of epithelial stress, regulation of inflammatory responses, and epithelial growth factor production. (47)

Located below the epithelial layer is the lamina propria. This thin layer of loose connective tissue contains capillaries, lymphatic vessels, and the GALT. Although much of the GALT is dedicated to adaptive immunity (B-cells and T-cells), it also plays a role in innate immunity through both phagocytosis and maintenance of homeostasis of the innate immune barrier.

Macrophages located in the lamina propria become activated after exposure to LPS and interferon- γ . After activation, these cells release proinflammatory cytokines and nitric oxide, both of which are important for effective immune responses but also contribute to epithelial injury. (48) To prevent excessive mucosal damage, the cytokine expression of intestinal macrophages is normally suppressed through a tumor growth factor- β mechanism. However, such suppression appears to be incomplete in the preterm intestine. (49)

In addition to macrophages, the lamina propria has both NK cells that are cytotoxic lymphocytes and NK T-cells that are T-cell lymphocytes that share properties of both T-cells and NK cells. NK T-cells differ from many other T-cells by responding within minutes after antigen recognition. This immediate immune response makes NK T-cells ideal sentinels for invading pathogens. NK T-cells, NK cells, and TCR $\gamma\delta$ T-cells are important

sources of interleukin (IL)-17, a critical cytokine for protective immunity in the mucosa, (50) although their role in the small intestine in preterm infants is not yet well defined.

Intestinal innate immune responses are critical to prevent invasion of pathogenic bacteria, but the same mechanism may also contribute to inflammatory injury. In fact, despite deficiencies in innate immune defense, the preterm neonate, in particular, may be predisposed to intestinal inflammation. For example, compared with adult intestinal epithelial cells, human fetal intestinal epithelial cells exhibit exaggerated production of inflammatory cytokines in response to both pathogenic and commensal bacteria as well as to endogenous inflammatory mediators such as TNF and IL-1 β . (51) T-cell-mediated suppression of the early innate immune response is required to prevent death from acute infection. (52) Such inhibition is primarily mediated by regulatory and naive T-cells through cell-cell contact with effector cells and by suppressing TNF production from various immune cells. In the intestinal tract, FOXP3-expressing T-regulatory (Treg) cells are critical for immune homeostasis, especially in the face of rapidly increasing antigenic challenge in the neonate. (53) Treg cells not only counterbalance intestinal inflammation but also contribute to host defense by promoting microbiota antigen-specific IgA responses. (54) Treg cells can be detected in the human fetal thymus at 13 weeks of gestation, approximately 4 weeks after the first appearance of adaptive T-and B-cells, which suggests an important role in tolerance to maternal antigens. (55)(56) Treg cells enter the fetal lymph nodes, spleen, liver, and bone marrow by 14 to 17 weeks' gestation, and intestinal Treg cells are present as early as 23 weeks' gestation in humans. (56)

Relevance to NEC

Despite these innate defenses, preterm infants remain predisposed to developing NEC, the leading cause of gastrointestinal mortality and morbidity in preterm infants. In the United States, NEC affects 7% of all infants whose birthweights are less than 1,500 g and causes the death of approximately 16% to 42% of such infants, depending on their birthweight. (57) The incidence and mortality rates of NEC are inversely related to birthweight and gestational age, although NEC typically does not affect infants immediately at birth. Instead, the disease develops over days to weeks, suggesting that changes in gut development regulate susceptibility to NEC. (58)(59) The exact pathophysiology of NEC remains unclear, but immaturity of the barrier functions coupled with an exaggerated inflammatory response mounted by the immature intestinal epithelium in response to injury is the leading hypothesis. (51)(59) Compared with term infants, preterm infants have looser TJs, thinner goblet cell secretions, fewer Paneth cells, and decreased IgA concentrations. (60) However, the exact role of these barrier components is still not clear.

IgA, which is a key component of the immunologic properties of human milk, has been tried as a preventive measure for NEC but has had little to no benefit, (61) and a recent report has shown that immune globulin intravenous use is associated with an increase in the incidence of NEC. (62) Although the role of intestinal mucins in NEC is largely unknown, TNF-induced inflammation causes depletion of intestinal MUC2 in immature but not mature ileum, (18) and MUC2 is lost in animal models of NEC. (63) In addition to loss of MUC2, newborn rats in NEC models also have increased paracellular permeability and altered TJ expression, (63) all of which predispose the epithelial layer to microbial invasion. Lastly, Paneth cell dysfunction may be associated with NEC. Lysozyme is depleted in infants who have NEC, (18)(28) and selective Paneth cell ablation results in NEC-like pathology in the immature intestine. (24)

Once bacteria breach the intestinal defenses and make contact with the epithelial layer, they are sensed by the PRRs. Both cow milk feeding and NEC increase small intestinal

expression of TLRs. (64) In particular, TLR4 and TLR9 have been associated with the pathophysiology of NEC. Absence of TLR4 is protective in experimental NEC models. (65) (66) In addition, TLR4 activation increases apoptosis and reduces enterocyte proliferation and migration. (67)(68)(69) Enterocyte apoptosis, which is one of the first histopathologic events in experimental models of NEC, (70) is caused by TLR4 activation in immature small intestinal tissue but not in immature colonic or adult small intestinal tissues. (67) This upregulation of TLR4 in NEC models can be reduced experimentally both by polyunsaturated fatty acids (71) and through activation of TLR9. (72)

As part of the epithelial defense, TCR $\gamma\delta$ T-cells are significantly diminished in surgical NEC (personal communication, T. Weitkamp, June 2011). Because the total number of T-cells in surgical NEC tissue is not affected, the specific depletion of the TCR $\gamma\delta$ IELs implies a possible role in NEC pathogenesis. Interestingly, the concentration of TCR $\gamma\delta$ T-cells in human milk is about threefold higher than in peripheral blood, and V δ 1 T-cells, which are the predominant IEL, are overrepresented in human milk compared with blood. (73) This increase in TCR $\gamma\delta$ T-cells in human milk may be an important source for TCR $\gamma\delta$ T-cells in neonates and could confer one mechanism for the protective effects of human milk against NEC.

NEC not only affects the epithelium but also is associated with changes in the entire mucosal immune response. For example, relative lack of tumor growth factor- β may lead to both reduced suppression of macrophage activation and reduced proportions of lamina propria Treg cells (personal communication, T. Weitkamp, June 2011). (49)(56) This combination may further reduce epithelial integrity through inflammatory injury. Because several proinflammatory cytokines impair Treg cell induction, the inflammatory cascade observed in NEC may result in a vicious circle in which uncontrolled host responses cause much of the morbidity and mortality associated with this disease.

Conclusions

It is easy to see the important role of the innate immune barrier in protection from bacterial invasion and immune homeostasis. However, this host defense and immuno-regulatory network is not yet fully intact in preterm infants. Such immunologic immaturity coupled with an abnormal nosocomial microbiome may predispose pre-term infants to further barrier dysregulation and eventually to development of devastating consequences, such as NEC.

Abbreviations

AJ	adherens junction
AMP	antimicrobial peptide
GALT	gut-associated lymphoid tissue
IEC	intestinal epithelial cell
IEL	intraepithelial lymphocyte
Ig	immunoglobulin
IL	interleukin
JAM	junctional adhesion molecule
LPS	lipopolysaccharide
NEC	necrotizing enterocolitis

NF	nuclear factor
NK	natural killer
NLR	Nod-like receptor
PRR	pathogen-recognition receptor
sIgA	secretory immunoglobulin A
TCR	T-cell receptor
TJ	tight junction
TLR	toll-like receptor
TNF	tumor necrosis factor
Treg	T-regulatory

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American Board of Pediatrics Neonatal-Perinatal Medicine Content Specifications

- Know the two types of host defense mechanisms (innate and acquired immunity) and understand their role and interrelationship in normal development of the immune system.
- Know the origins and functions of natural killer cells in the lymphocyte system.
- Know the normal development and function of monocytes and macrophages.
- Know the contribution of increased cytokine production to the pathogenesis of neonatal disorders such as NEC, chronic lung disease, periventricular leukomalacia, and retinopathy of prematurity.
- Know the role of cytokines and chemokines in inflammation.
- Recognize the immaturity of the immune function of the GI tract during development.
- Know the pathophysiology and prevention of NEC.

Figure 1.
Components of innate immunity in the immature small intestine.

Figure 2.
Conserved development between humans and mice.