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# The Role of Intestinal Barrier Function in Early Life in the Development of Colitis

R.C. Anderson<sup>1</sup>, J.E. Dalziel<sup>1</sup>, P.K. Gopal<sup>2</sup>,  
S. Bassett<sup>1</sup>, A. Ellis<sup>3</sup> and N.C. Roy<sup>1,3</sup>

<sup>1</sup>Food Nutrition & Health Team, AgResearch Grasslands

<sup>2</sup>Fonterra Co-operative Group Limited

<sup>3</sup>Riddet Institute, Massey University  
New Zealand

## 1. Introduction

The human intestine has the dual role of allowing absorption of nutrients while also acting as a barrier to prevent pathogens and toxins from entering the body and potentially causing disease. In the immature infant intestine this barrier is underdeveloped and large quantities of macromolecules cross the epithelium into systematic circulation. Consequently infants are susceptible to conditions such as infectious diarrhoea, necrotising enterocolitis and allergic gastroenteropathy (Schreiber & Walker, 1988). It is essential that the infant intestinal barrier matures appropriately because barrier dysfunction in adulthood is a critical factor in predisposition to intestinal diseases (Groschwitz & Hogan, 2009) and is associated with autoimmune diseases in other parts of the body (Cereijido et al., 2007).

Illnesses associated with intestinal barrier dysfunction are more common in adults that were formula-fed as infants than in those that were breast-fed (Verhasselt, 2010). This shows that breast milk promotes intestinal barrier maturation (Schreiber & Walker, 1988) and illustrates the need for “humanised” infant formulas so that infants that are not able to breast-feed still obtain the benefits associated with breast milk. However, to achieve this, more knowledge is required about intestinal barrier development and maturation, the roles of various breast milk components, and the mechanisms of action of active ingredients in infant formula.

This review describes the role of intestinal barrier function in the pathogenesis of a range of colitis types and discusses how maturation of the intestinal barrier in infants is critical to healthy intestinal function throughout life.

## 2. The intestinal barrier

The intestinal barrier, with a surface area of 300-400 m<sup>2</sup>, is the largest interface between the body and external environment. The intestinal barrier is a complex structure made up of four main components (Fig 1): the physical, chemical, immunological and microbiological barriers. The following sections describe the role of each barrier component in maintaining intestinal barrier function and discusses the link between motility and barrier function.

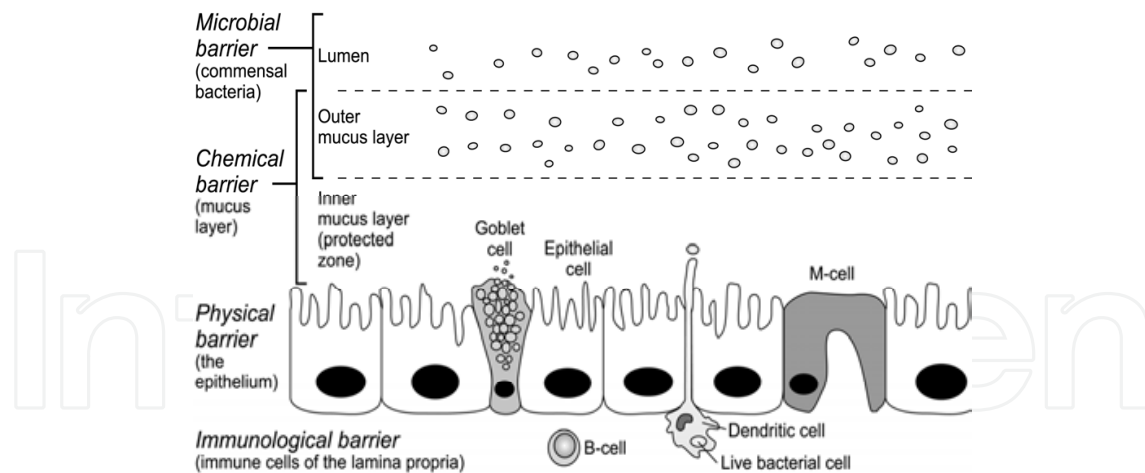


Fig. 1. Four components of the intestinal barrier.

## 2.1 Physical barrier

The physical barrier is made up of a layer of columnar epithelial cells that forms the first line of defence between the intestinal lumen and inner milieu. Of these cells, greater than 80% are enterocytes with the rest being enteroendocrine, goblet, and Paneth cells (Van Der Flier & Clevers, 2009). Between the epithelial cells are intercellular junctional complexes including tight junctions, adherens junctions, desmosomes and gap junctions (Fig 2) (Farquhar & Palade, 1963). These junctions allow the passage of fluids, electrolytes, and small macromolecules, but inhibit passage of larger molecules. Of the junctional complexes, tight junctions are the most apical and are primarily responsible for controlling permeability of the paracellular pathway. The adherens junctions and desmosomes are involved in cell-cell adhesion, whereas the gap junctions are involved in intracellular communication.

Tight junctions are formed by protein dimers that span the space between adjacent cell membranes (Fig 2). There are over 40 proteins with well recognised roles in tight junction formation. These proteins can be divided into three functional categories: 1) transmembrane proteins that form bridges between adjacent cell membranes; 2) scaffolding proteins that anchor transmembrane proteins to the actin cytoskeleton; and 3) dual location proteins that are not continuously associated with the tight junctions and also act as transcription factors.

## 2.2 Chemical barrier

The chemical barrier is primarily the layer of mucus that covers the intestinal epithelium. This mucus acts as a diffusion barrier against unwanted substances and also as a lubricant to minimise shear stress on the physical barrier. The main component of mucus are the secreted mucins, which are heavily glycosylated proteins. Mucins consist of a peptide backbone containing alternating glycosylated and nonglycosylated domains, with O-linked glycosylated regions comprising 70–80% of the polymer (Deplancke & Gaskins, 2001).

The mucus layer is a dynamic defence barrier containing antimicrobial peptides (immunological barrier) that helps prevent contact between bacteria and the epithelial layer. The outer loose mucus layer contains a limited number of intestinal microbes; whereas the inner adherent mucus layer contains very few microbes (Fig 1). Numerous studies show that mucin gene expression, mucus composition and secretion are altered by intestinal microbiota and host-derived inflammatory mediators (Deplancke & Gaskins, 2001).

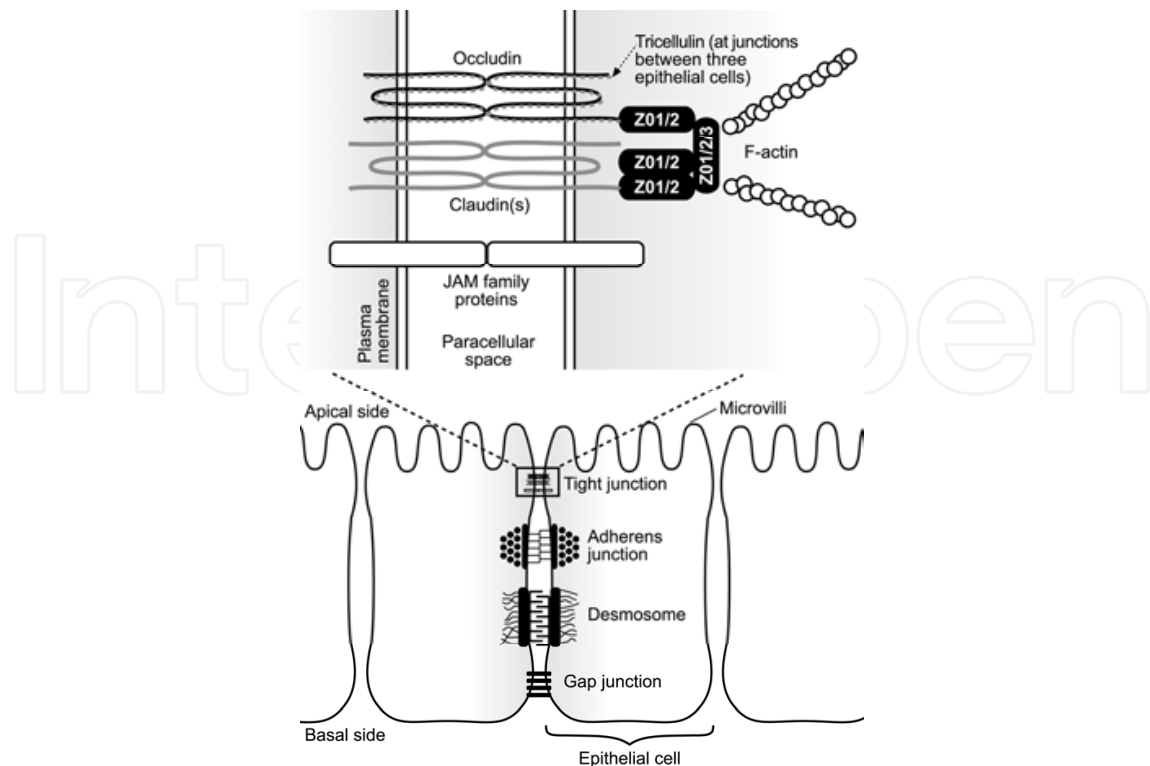


Fig. 2. The protein complexes between intestinal epithelial cells include tight junctions, adherens junctions, desmosomes and gap junctions. The tight junctions control paracellular permeability and consist of transmembrane (e.g., occludin, claudins and junctional adhesion molecules), scaffolding (e.g., zonula occludens, Crumbs group, Par group) and dual-location (e.g., cold shock domain protein A and cyclin-dependent kinase 4) proteins. Figure adapted from Ulluwishewa et al. (2011).

### 2.3 Immunological barrier

The immunological barrier's first line of defence is secretory IgA which binds to antigenic substances. These IgA-antigen complexes bind to IgA receptors on microfold M cells and the antigens are transferred to the lamina propria for presentation to dendritic cells. Antigen-presenting cells in the lamina propria receive immunostimulatory antigens from the lumen, which they process and present to T cells. The antigen-presenting cells also secrete interleukin (IL)-12 leading T cells to produce a  $T_H1$  immune response. This results in T cell secretion of interferon (IFN)- $\gamma$ , which in turn activates macrophages to secrete tumour necrosis factor (TNF)- $\alpha$ . IL-10 is also released from antigen-presenting cells, which feedbacks to limit the  $T_H1$  response.

The intestinal immune system must fulfil the dual tasks of tolerance to dietary antigens and immune defence (Rautava & Walker, 2008). To avoid reacting to dietary antigens and the intestinal microbiota, the mucosal immune system exists in a predominantly immune-suppressed (tolerant) state involving antigen-presenting dendritic cells and T cells (Bienenstock et al., 2010). Non-pathogenic bacteria, however, induce a mild immune reaction that contributes to a normal low level inflammation (defence) of the intestine (Bibiloni & Schiffrin, 2010).

## 2.4 Microbial barrier

The microbial barrier is an essential component of intestinal barrier function that influences epithelial metabolism, proliferation and survival (Neish, 2009). These symbiotic microbes limit pathogen colonisation by competing for adherence to epithelial surfaces, producing antimicrobial compounds, and stimulating increased mucin production. They can also secrete chemicals that allow communication between bacterial species, which can suppress pathogens by optimising the numbers of beneficial microbes (Neish, 2009). The intestinal microbiota provides other crucial functions for the host such as nutrient acquisition and energy regulation (Palmer et al., 2007), and influences processes such as predisposition to obesity, immune homeostasis, inflammation, repair and angiogenesis (Kelly et al., 2007).

The adult gastrointestinal tract is comprised of more than  $10^{14}$  microbes ranging from  $10^{11}$  cells/g content in the ascending colon to  $10^7 - 10^8$  cells/g content in the distal ileum and  $10^2 - 10^3$  cells/g content in the proximal ileum and jejunum. Comprised of 500-1000 species, the microbiota of each adult human colon is unique and remains stable over time (Eckburg et al., 2005). In contrast, the infant intestinal microbiota composition is variable and less stable over time (Palmer et al., 2007), rapidly expanding to over 300 species within the first postnatal week (Park et al., 2005).

The microbiota also produces metabolites such as short chain fatty acids (acetate, propionate and butyrate) that result from fermentation (Kien, 1996). As well as a major energy source for epithelial cells, butyrate affects cellular proliferation and differentiation, increases intestinal blood flow, and may also aid in the strengthening of tight junctions (Neu, 2007; Sanderson, 2004). In addition, butyrate increases intestinal motility (Fukumoto et al., 2003).

## 2.5 The role of motility in intestinal barrier function

Intestinal motility can influence intestinal barrier function in a number of ways (Fig 3). Motility is one of the most influential determinants of intestinal microbiota growth (Kim & Lin, 2007). In conjunction with fluid/mucus secretion it propels bacteria and toxins (DeMeo et al., 2002) through the lumen, maintaining turnover and providing another defence mechanism for the epithelial barrier. Conversely, the composition of the intestinal microbiota can influence colonic neuromotor function (Verdu, 2009) through release of substances that influence intestinal motility (Kim & Lin, 2007). For example, supernatant from the probiotic, *Escherichia coli* Nissle 1917 (Mutaflor – used in the treatment of colitis) can increase colonic motility in isolated muscle strips from humans (Bar et al., 2009).

There are many neuromodulators in the colon that affect motility, including neurotransmitters: adrenergic (-), cholinergic (+), serotonergic (+), dopaminergic, GABAergic, neuropeptides. These may be released from neurons or other cell types and act on receptors located on a variety of cells including smooth muscle and enteric neurons. Factors that affect neuromodulation can also affect smooth muscle contractility and hence affect transit (Kien, 1996). For example, butyrate produced by bacteria stimulates serotonin (5HT) release from enterochromaffin cells (Fukumoto et al., 2003). 5HT activates intrinsic primary afferent neurons (Fig 3) to initiate peristaltic reflexes (Hord, 2008) and has pro-inflammatory actions (Lakhan & Kirchgessner, 2010). 5HT receptor subtypes differ between animals and humans such that their function in peristalsis in humans is not fully determined (Wouters et al., 2007).

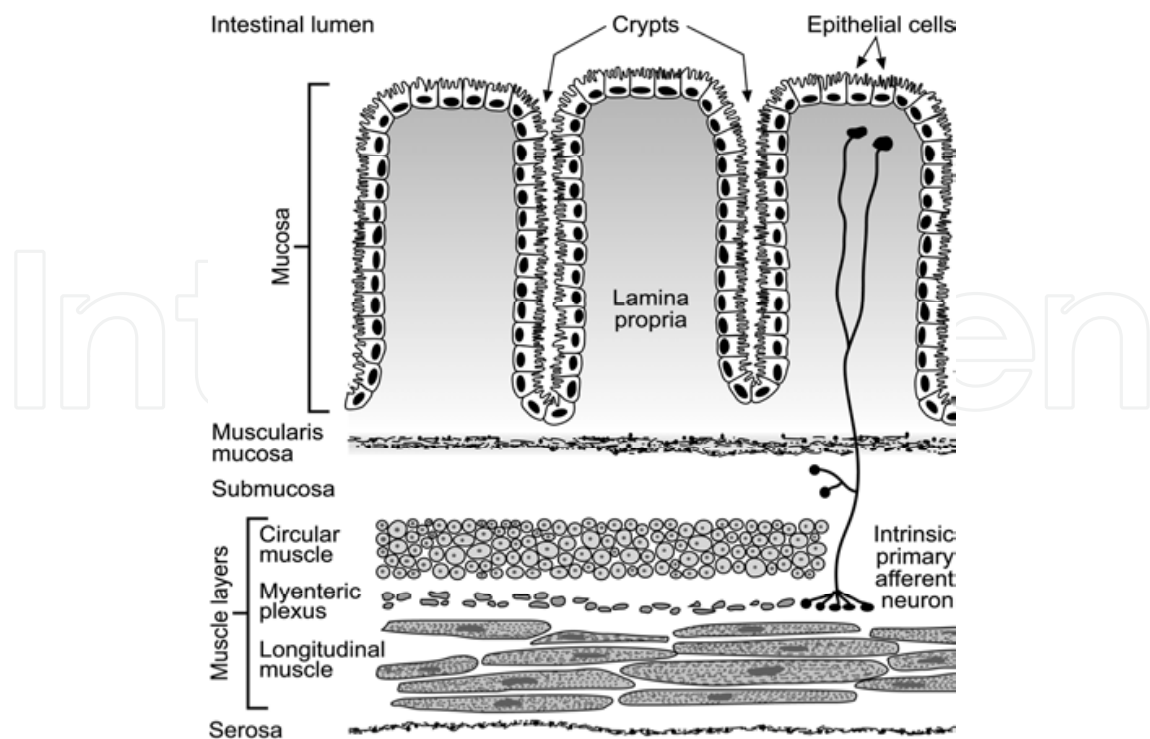


Fig. 3. Intestinal barrier and muscle layers in the colon.

Sympathetic nerves release norepinephrine which inhibits acetylcholine release from motor neurons and relaxes smooth muscle, decreasing gastrointestinal motility. Another enteric neurotransmitter is dopamine. Although the function of dopaminergic neurons is unclear, mice lacking the  $D_2$  dopamine receptor subtype (present in smooth muscle from stomach to distal colon) have increased intestinal motility and stool water content and frequency (Zhi et al., 2006). Expression of most dopamine receptor subunits was detected in submucosal and myenteric neurons (Zhi et al., 2006). Since dopaminergic gene expression begins early at embryonic day 10 in the foetal intestines, prior to the appearance of neurons, it is possible that dopamine affects enteric nervous system development (Zhi et al., 2006).

### 3. Development and maturation of the intestinal barrier

The complexity of the intestinal barrier develops over time from early gestation through to childhood. The intestine undergoes incredible growth, elongating 1000-fold from 5-40 weeks gestation, to reach a mean length at birth of 275 cm (Neu, 2007). While growth occurs most rapidly during gestation, the intestine continues to lengthen until 3 to 4 years of age (Newell, 2000). The following sections describe the development and maturation of the intestinal barrier and the role of breast milk in these processes.

#### 3.1 Maturation of the intestinal barrier in infants

The physical barrier begins developing from conception; its basic structure is formed by the end of the first trimester, and by week 22 of gestation the absorptive epithelial cells resemble those of the adult intestine (Montgomery et al., 1999). Initially, the absorptive lining of the intestine is stratified (Fig 4A) but soon becomes a single layer of columnar cells (Fig 4B). Simultaneously, structural differentiation begins with establishment of the crypt-villus axis.

Villi form by week 8 of gestation, beginning in the small intestine and progressing to the colon by week 10-12 with crypts developing throughout the intestine between weeks 12-19 (Fig 4C) (Maheshwari & Zemlin, 2009; Montgomery et al., 1999; Polak-Charcon et al., 1980). However, villi disappear from the colon at 30 weeks of gestation as the adult-type crypt epithelium is established (Fig 4D). Epithelial cells with microvilli, goblet and enteroendocrine cells, all derived from the same undifferentiated stem cells, appear by week 8 of gestation (Louis & Lin, 2009) and tight junctions are detected from week 10 (Fig 4B).

Many of the protective aspects of the foetal intestine are evident early in gestation and continue to mature throughout pregnancy (Louis & Lin, 2009). The goblet cells, responsible for producing the chemical barrier, start producing mucin by week 12 of gestation (Fig 4B)(Montgomery et al., 1999). The protective secretory cells of the innate immunological barrier are also formed early in gestation. For example, Paneth cells appear by the week 12 of gestation and begin to produce defensins by week 13 and lysozyme by week 20 with their number per crypt increasing with maturation until adulthood (Fig 4C-F) (Louis & Lin, 2009; Maheshwari & Zemlin, 2009; Rumbo & Schiffrin, 2005). M cells, specialised for antigen sampling, are first observed at week 17 of gestation, and distinct T cell zones and B cell follicles containing follicular dendritic cells, both associated with Peyer's patches, appear by week 19 (Fig 4C). All major components of the intestinal immune apparatus are identifiable by week 29 of gestation (Fig 4D) (Maheshwari & Zemlin, 2009).

Luminal factors play a crucial role in intestinal development. By week 16, the foetus begins to ingest amniotic fluid, which provides essential growth and trophic factors, such as epidermal growth factor and polyamines, that stimulate intestinal differentiation and growth (Pácha, 2000; Rumbo & Schiffrin, 2005). Other cytokines and growth factors necessary for maturation are provided by the systemic circulation and interstitial fluid (Harada et al., 1997; Hirai et al., 2002; Montgomery et al., 1999).

While the foetal intestinal mucosa is permeable to intact macromolecules allowing an exchange between amniotic fluid and foetal serum (Harada et al., 1997), "gut closure", or membrane closure, occurs during the first postnatal week. Any delay or change to these processes, particularly in pre-term or small-for-date infants, predisposes the infant to infection, inflammatory states and allergic sensitisation (Maheshwari & Zemlin, 2009). The gut closure process is mediated by human milk hormones and growth factors that play a crucial role in stimulating intestinal epithelial growth and maturation (Cummins & Thompson, 2002). These are described in more detail in section 3.2.

Formation of the microbial barrier is also crucial during this time. Unlike the adult intestinal tract, the newborn gastrointestinal tract was thought to be essentially sterile. However, recent discoveries point to pregnancy as the beginning of intestinal colonisation of the developing foetus (Jiménez et al., 2008) with a temporal progression towards an adult microbiota profile by the end of the first year of life (Fig 4E-F) (Palmer et al., 2007; Round & Mazmanian, 2009). Many factors contribute to the acquisition of intestinal microbiota including mode of delivery, gestational age, exposure to antibiotics (in either the mother or the infant), feeding (i.e. breast milk or formula, introduction of solids), and other environmental exposures. The first bacteria to colonise the intestine are facultative aerobes (such as *Staphylococcus*, *Streptococcus* and *Enterococcus*) while anaerobic bacteria such as eubacteria and clostridia appear later (Palmer et al., 2007).

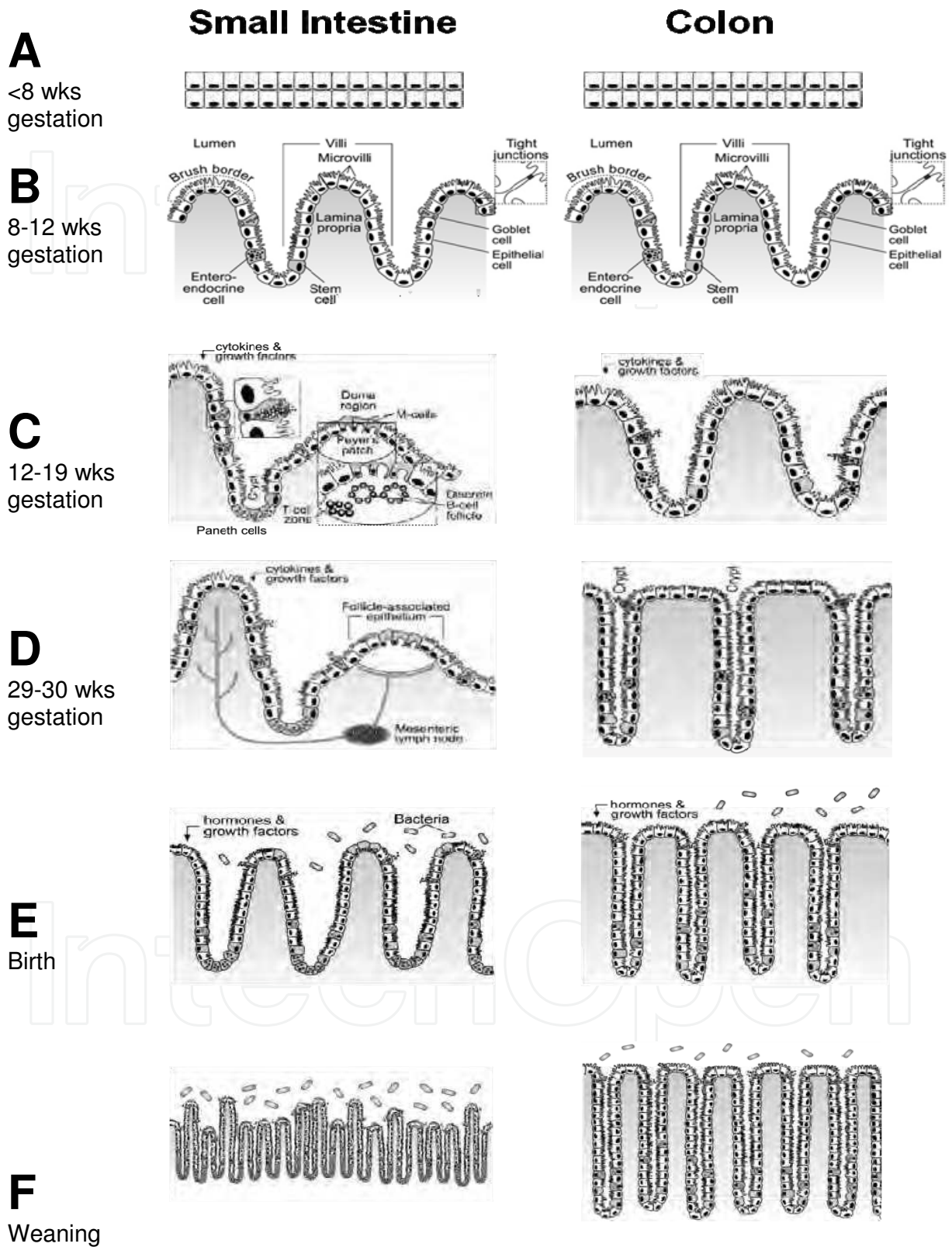


Fig. 4. Development and maturation of the intestinal barrier from conception to weaning.



Intestinal microbiota is necessary for both morphological and immunological maturation of the intestinal barrier (Hooper, 2004). For example, germ-free mice have hypoplastic villi that normalise when colonised with commensal bacteria (Louis & Lin, 2009). Other examples include bacterial-induced expression of the microbiocidal protein angiogenin-4 (Ang4) by paneth cells (Hooper et al., 2003), and induction of the development of networks of blood vessels in the villi (Stappenbeck et al., 2002).

The intestinal mucosal barrier continues to grow in a process that involves fission and deepening of crypts, increase in villus width and number, and appearance of submucosal folds (Cummins & Thompson, 2002). In the early postnatal period, development of intestinal mucosa is associated with profound tissue remodelling and modification of intestinal digestive and absorptive functions. An increase in the number of epithelial cells is also observed at the time of weaning; this involves a shift in the equilibrium between mitosis and apoptosis that is vital for maturation (Zabielski et al., 2008). Because the sIgA system is not fully mature until 4 years of age, it has been postulated that the intestinal barrier is in itself not fully mature until this time (Mayer, 2003).

### **3.2 Role of breast milk in intestinal barrier maturation**

Human breast milk provides all the necessary ingredients for a newborn to make an optimal transition from intrauterine to extrauterine life. Breast milk contains numerous bioactive proteins, lipids and complex carbohydrates, including immune factors and growth factors that play roles in healthy structural and functional postnatal development of the intestinal barrier of the human infant. Although full-term infants are born with sufficiently developed absorptive and digestive function, the gastrointestinal tract undergoes significant postnatal development in the first year of life. The components in human breast milk that compensate for the developmental immaturity of the intestinal barrier include sIgA, lactoferrin, lysozyme, platelet activating factor-acetylhydrolase and cytokines.

Several studies have indicated that human breast milk decreases intestinal permeability and therefore enhances the physical barrier. Since the intestinal barrier is underdeveloped in pre-term babies, the influence of breast milk is particularly important. A study on pre-term infants in the first month post-birth found that those predominately fed human milk demonstrated lower intestinal permeability when compared with those fed minimal or no human milk (Taylor et al., 2009). A similar effect of breast feeding on intestinal permeability has also been reported for full-term babies (Catassi et al., 1995). The effect of formula-feeding on permeability appears to be related to the protein content: in a study using piglets, those fed a high-protein formula had increased intestinal permeability compared with those fed an adequate-protein formula (protein concentration the same as sows milk) and others fed by their mothers (Boudry et al., 2011). However, due to the complex composition of human breast milk and the interplay among its components, it has been difficult to delineate the roles of individual components on intestinal development.

## **4. Importance of the intestinal barrier in health and wellness**

The controlled regulation of the intestinal barrier in the healthy intestine leads to antigenic tolerance. However, disruption of the intestinal barrier, in particular the tight junctions of the physical barrier, results in increased permeability (Fig 5). This allows direct access of

antigens to the dendritic cells in the lamina propria, as opposed to the dendritic cells sampling the lumen, and results in an aberrant immune response that can target any organ or tissue in genetically predisposed individuals. As discussed in the following sections, this can lead to inflammatory and autoimmune diseases both during infancy and adulthood.

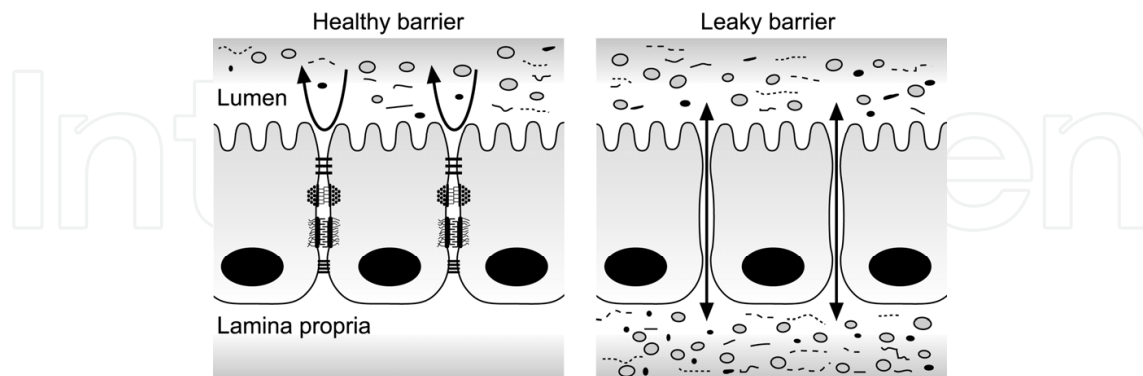


Fig. 5. When the intestinal barrier is functioning correctly, luminal bacteria and antigens are unlikely to pass across the epithelium into the lamina propria. In contrast, when the intestinal barrier is dysfunctional, paracellular permeability is increased.

#### 4.1 Intestinal barrier dysfunction in infants

Dysfunction of intercellular junctions is a key factor in pathogenesis of several early infancy autoimmune diseases, including necrotising enterocolitis and allergic gastro-enteropathy, and may also play a role in the pathogenesis of infectious diarrhoea. The following sections look at consequences of intestinal barrier dysfunction in the human infant.

##### 4.1.1 Necrotising enterocolitis

Necrotising enterocolitis (NEC) is an inflammatory bowel necrosis that primarily afflicts the terminal ileum and proximal colon in pre-term infants (Caplan & MacKendrick, 1993). Although full-term infants can also develop NEC, there is usually an underlying cause such as birth asphyxia. Immaturity of intestinal barrier function may be a major risk factor for pre-term babies developing NEC. This includes: 1) an underdeveloped physical barrier with incomplete development of tight junctions; 2) a lack of proper chemical barrier due to lower gastric acid and mucin production, immature proteolytic enzyme activity (Udall, 1990), and deficiency of bacteriostatic proteins such as defensins (Salzman et al., 1998); and 3) a poor immunological barrier due to an under developed mucosal immune system.

In addition, the peristaltic muscle contractions can also be abnormal in pre-term infants, which can lead to increased bacterial adhesion, that in turn allows for bacterial overgrowth that could increase endotoxin exposure and predispose to NEC (Beeby & Jeffery, 1992). Pre-term infants have increased intestinal permeability and infants with NEC have even greater permeability (Neu, 2005). Thus any abnormality in maturation of the components of the intestinal barrier can predispose the neonatal intestine to insult by pathogenic or non-pathogenic invasion leading to tissue inflammation.

No case of NEC has been described *in utero*, supporting the importance of bacterial colonisation in the NEC pathophysiology. Most cases of NEC are sporadic, hence a specific

infectious agent is not suspected. It is more likely that abnormal colonisation of the gastrointestinal tract with an unfavourable balance between desirable and undesirable microbes plays a significant role in the pathogenesis of NEC. In the case of a normal vaginal birth the infant first comes in contact with microbiota from the mother; whereas, in the case of caesarean birth it is the environment of the hospital or neonatal intensive care unit that provides the first bacterial exposure to the newborn. Indeed, there is evidence of abnormal colonisation in very low birth weight infants (Hoy et al., 2000).

Human breast milk contains a large amount of oligosaccharides that may promote growth of desirable bacteria. Studies have shown differences in the composition of microbiota between breast-fed and formula-fed babies (Rubaltelli et al., 1998; Wold & Adlerberth, 2000). This lack of human milk oligosaccharides in formula-fed pre-term babies may also contribute to NEC pathogenesis. Although the role of enteric bacteria is unclear, studies suggest that early colonisation with probiotics reduces the risk of NEC (Hoyos, 1999).

The likely common pathway in pathogenesis of NEC is the pro-inflammatory cascade initiated by bacteria, bacterial products and other antigens that gain access through a leaky intestinal barrier (Lin & Stoll, 2006). Inflammatory mediators implicated in NEC pathogenesis include platelet-activating factor (PAF), tumour necrosis factor (TNF- $\alpha$ ) and pro-inflammatory cytokines such as IL-6, IL-8 and IL-12 (Edelson et al., 1999).

The definitive pathogenesis of NEC remains poorly understood. Hopefully, future research on the maturation of the intestinal barrier, role of probiotics and understanding of genetic predisposition will lead to better preventative and treatment strategies for this disease.

#### 4.1.2 Infectious diarrhoea

Infectious diarrhoea is another disease where intestinal barrier dysfunction plays a role. It is defined as diarrhoea due to bacterial, viral or parasitic infection of the gastrointestinal tract that results in more than three bowel motions in a day with an excessive amount of watery stools. Diarrhoeal episodes are a major health problem in children worldwide and the global incidence of diarrhoeal disease has remained unchanged over the last decade; about 3.2 episodes per child per year (Kosek et al., 2003). In developing countries diarrhoeal illnesses are associated with a high risk of mortality and thus are a major concern.

Rotavirus infection is the single greatest cause of infectious diarrhoea in children worldwide (Dennehy, 2000). Rotavirus disrupts absorptive function by the selective invasion of mature enterocytes by the invading pathogen, resulting in osmolar diarrhoea. Rotavirus acts on epithelial cells by altering protein trafficking, disrupting cell-cell interactions, and damaging tight junctions, thereby increasing paracellular permeability (Obert et al., 2000). The toxic rotavirus unstructured protein-4 induces age- and calcium ion-dependent chloride secretion and disrupts sodium-dependent glucose transporter-1 mediated reabsorption of water (Ball et al., 2005).

There are a number of other pathogens that are responsible for infectious diarrhoea. The prevalence and type of individual pathogen varies widely between geographies and age groups. Common bacteria responsible for infectious diarrhoea include *Campylobacter*, *Salmonella*, *Clostridium*, *Shigella*, and *E. coli*; whereas *Giardia* and *Cryptosporidium* are among the most common parasites. The mechanisms by which these enteropathogens cause

diarrhoea are highly variable, and include crypt cell proliferation, cellular invasion, production of enterotoxins or cytotoxins, and enteroadhesion. Infectious agents usually induce diarrhoea by directly damaging epithelial barrier function. For example, the *Vibrio cholera* zonula occludens toxin acts by disrupting tight junctions leading to fluid secretion into the lumen (Fasano et al., 1991). Others affect ionic permeability, for example, enterotoxins produced by bacterial pathogens selectively and specifically increase either cyclic adenosine monophosphate (e.g., heat labile *E. coli* toxin) or cyclic guanosine monophosphate (e.g., enterotoxigenic *E. coli*, or *Klebsiella* heat stable toxin – Sta), resulting in the opening of Cl channels in the luminal membrane.

One of the most rapidly expanding areas in prevention and treatment of diarrhoeal diseases is the use of probiotics. A growing number of rigorous meta-analyses show the efficacy of probiotics in prevention of acute infectious diarrhoea in children (Guandalini 2006). Analysis shows that probiotics may shorten the duration and severity of diarrhoea, particularly in young children. Some evidence suggests that probiotics may improve intestinal barrier function (Anderson et al., 2010a; Anderson et al., 2010b). This will be discussed further in Section 5.1.

#### 4.1.3 Allergic gastroenteropathy

Allergic gastroenteropathy is a term that describes an immune-mediated process that can affect any area of the gastrointestinal tract and may include classic allergic reaction, protein losing enteropathy, malabsorption syndrome and post-enteritis milk protein intolerance (Moon & Kleinman, 1995). The features of enteropathy may include lymphocyte and plasma cell infiltration, epithelial abnormality, or crypt hyperplastic villus atrophy and impaired absorption. Allergic gastroenteropathy is more common in infants, but may occur at any age.

The pathophysiologic basis of allergic gastroenteropathy remains elusive and the primary treatment is the elimination of offending antigens. An elemental diet may prove beneficial in many patients, but the process of identifying causal allergens is time-consuming and often frustrating. The onset of symptoms after the addition of a problematic food may be delayed, adding to the diagnostic difficulties. Cows' milk-sensitive enteropathy is the most common food allergic gastroenteropathy (Walker-Smith et al., 1978).

The most common type of eosinophilic gastroenteropathy, and most difficult to diagnose and manage, is allergic eosinophilic esophagitis. This disorder is particularly challenging to diagnose because the symptoms overlap those of gastroesophageal reflux (Sicherer, 2003).

#### 4.2 Life-long impact of intestinal barrier dysfunction

Intestinal barrier dysfunction in infancy underlies predisposition to and exacerbation of various autoimmune and inflammatory diseases. In addition, compromised tight junctions are involved in cancer development, infections, and allergies (Fasano, 2011; Groschwitz & Hogan, 2009). The following sections highlight the life-long impact of intestinal barrier dysfunction.

##### 4.2.1 Inflammatory bowel diseases

Inflammatory bowel disease (IBD) is a collection of conditions characterised by chronic and relapsing inflammation of the gastrointestinal tract, and includes Crohn's disease and

ulcerative colitis. The exact etiology and pathogenesis of IBD is still unclear, although there is strong evidence for a genetic contribution to disease susceptibility, with more than 40 IBD loci identified (Frank et al., 2011). IBD is considered to involve overly aggressive acquired (T cell) responses to a subset of intestinal microbiota that develop in genetically susceptible individuals where environmental factors precipitate the onset or reactivation of the disease (Sartor, 2006).

The immune-pathogenesis of IBD occurs in three distinct stages: 1) barrier defects allow luminal contents to penetrate the underlying tissues; 2) clearing of foreign material from the intestinal wall is impaired; and 3) a compensatory immune response, leading to the production of pro-inflammatory cytokines, perpetuates the increased intestinal permeability by re-organising the tight junction proteins (Fasano & Shea-Donohue, 2005; Matricon et al., 2010). This results in a vicious cycle in which barrier dysfunction allows further leakage of luminal contents, thereby triggering an immune response that in turn promotes further leakiness.

Although the intestinal microbiota has been shown to play a role in the development of IBD, specific contributions are undefined due to the complexity of this microbial community. *IL10*-gene-deficient mice that develop colitis in response to colonisation by enteric bacteria, but not under germ-free conditions, demonstrate that bacteria are required to initiate IBD (Hoffmann et al., 2011). However, studies of IBD patients have shown that while there are significant shifts in the composition of the microbiota, there is no consistent microbial profile associated with IBD (Frank et al., 2007; Frank et al., 2011), nor in chronic IBD (Nell et al., 2010). Toll-like receptors, which recognise conserved microbial molecules, and regulatory T cells have an important role in maintaining tolerance and immune homeostasis to prevent chronic inflammation (Levin & Shibolet, 2008; Nell et al., 2010). Likewise, NOD2, which plays an important part in the detection and elimination of intracellular pathogens, is also a recognised risk allele for Crohn's disease (Nell et al., 2010).

Receptors associated with colitis suggest targets for modulation by beneficial bacteria or functional foods to strengthen barrier integrity, immune tolerance and defence. An example is the intermediate conductance K<sup>+</sup> ion channel (IK, KCNN4) for which a gene variant has been implicated in Crohn's disease in an Australia/New Zealand cohort in which IK mRNA expression is significantly reduced (Simms et al., 2010). Decreased IK expression would limit its role in colonic anion secretion (Barmeyer et al., 2010) and positive modulation of motility (Wang et al., 2010), which would affect the microbiota environment. Since IK is also expressed in the colon and lamina propria and modulates T cell activation and cytokine production (Logsdon et al., 1997), reduced expression might impact immune function.

#### 4.2.2 Celiac disease

Celiac disease is an autoimmune disorder of the small intestine that occurs in genetically predisposed individuals. It is caused by a reaction to gliadin, a prolamins component of gluten found in wheat, and similar proteins found in other cereals within the grass genus *Triticum*, such as barley and rye. Symptoms include chronic diarrhoea, failure to thrive and fatigue. Some patients also experience lactose intolerance due to the decrease in intestinal surface and reduced production of lactase but this is usually resolved once the condition is treated. Currently, the only known effective treatment for Celiac disease is a lifelong gluten-

free diet. However, enhanced intestinal permeability persists even in asymptomatic patients while on a gluten-free diet (Chahine & Bahna, 2010; Schulzke et al., 1998).

Normally, gliadin is prevented from crossing the intestinal barrier by the intercellular tight junctions. However, in susceptible individuals, interplay between gliadin and the intestinal cells triggers tight junction disassembly. Gliadin causes a reorganisation of actin filaments and altered expression of the tight junction proteins occludin, claudin-3 and claudin-4, the tight junction-associated protein ZO-1 and the adherens junction protein E-cadherin resulting in increased intestinal permeability (Sander et al., 2005). This is thought to precede gliadin-induced immune events that eventually lead to Celiac disease (Schuppan, 2000).

Following tight junction disassembly, gliadin peptides can cross the epithelium and reach the lamina propria where they are recognised by antigen presenting cells. This triggers an inflammatory reaction; the body produces antibodies which damage the villi lining the small intestine and make it difficult for the body to absorb vitamins, minerals and other nutrients (Clemente et al., 2003; Fasano, 2011). Exercise can contribute to the disease by increasing intestinal permeability (Chahine & Bahna, 2010).

#### 4.2.3 Irritable bowel syndrome

Irritable bowel syndrome (IBS) is characterised by abdominal pain and cramping, discomfort, bloating, and changes in bowel movements. Diarrhoea or constipation may predominate, or they may alternate, classified as IBS-D, IBS-C or IBS-A, respectively. While IBS is a common malady, the mechanisms by which the symptoms arise are poorly understood. IBS is associated with psychological disturbance (Drossman et al., 1999), food intolerance (Atkinson et al., 2004; Francis & Whorwell, 1994), and prior gastroenteritis (Dunlop et al., 2006; Spiller, 2003). The psychological aspect of this disease is not surprising given that stress is a well-documented inducer of intestinal permeability (Söderholm & Perdue, 2001).

Growing evidence suggests that patients with IBS have decreased intestinal barrier function and that some forms of IBS are associated with low-grade intestinal inflammation (Collins et al., 2001). Permeability of colonic biopsies is significantly higher in patients with IBS compared with healthy subjects (Piche et al., 2009). Furthermore, intestinal permeability profiles differ among IBS subtypes with increased small bowel permeability both in post infectious-IBS and IBS-D without an infectious onset when compared with both controls and IBS-C (Dunlop et al., 2006).

A number of other IBS-like intestinal disorders are associated with increased intestinal permeability. For instance, chronic alcohol consumption leads to enhanced translocation of endotoxins from the intestine to other organs resulting in inflammation and tissue damage (Groschwitz & Hogan, 2009). Non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin, also promote altered intestinal barrier dysfunction and hypermotility (Sigthorsson et al., 1998), as do the enterotoxins produced by bacterial pathogens such as *Vibrio cholerae*, and enteropathogenic *E. coli* (Fasano et al., 1991; Groschwitz & Hogan, 2009). The inflammatory responses elicited by bacteria and bacterial toxins due to changes in the integrity of the intestinal barrier have also been shown to enhance cancer progression (Fukata & Abreu, 2008). In some studies of IBD, the degree and prolongation of the duration of ulcerative colitis were recognised as factors leading to increased risk of gastrointestinal

cancer development (McConnell & Yang, 2009; Tlaskalová-Hogenová et al., 2011), although the mechanisms involved are not fully understood.

Stress induced in early life by neonatal maternal separation may affect colonic permeability and motility (Bian et al., 2010; Coutinho et al., 2002; Gareau et al., 2007). When this condition is mimicked in a rat model of IBS, colonic smooth muscle contraction amplitude is increased and this is associated with an increased expression of L-type calcium ion channels in colonic smooth muscle, as the level of calcium in smooth muscle cells increased in response to L-type calcium ion channel activation (Zhang et al., 2010).

#### 4.2.4 Non-intestinal disorders

There is increasing evidence to suggest intestinal barrier dysfunction results in immune responses that can target any organ or tissue in genetically predisposed individuals (Fasano & Shea-Donohue, 2005; Fasano, 2011), such as the skeletal system (ankylosing spondylitis, rheumatoid arthritis: Edwards, 2008), pancreas (type 1 diabetes: (Carratù et al., 1999), kidney (IgA nephropathy: Davin et al., 1988), liver (nonalcoholic steatohepatitis: Wigg et al., 2001), and brain (multiple sclerosis; Yacyshyn et al., 1996). Barrier dysfunction can also result in an aberrant or exaggerated inflammatory response to the intestinal microbiota. This has been implicated in a wide range of diseases such as cardiovascular disease, neoplastic diseases, diabetes and obesity (Chahine & Bahna, 2010). Intestinal microbiota and increased intestinal permeability have also been linked to atopic diseases such as eczema and dermatitis (Penna et al., 2008).

### 5. Improving intestinal barrier function

Ingestion of specific foods or bacteria to reverse barrier dysfunction has the potential to break the vicious cycle that occurs in colitis, that is, to improve physical barrier integrity and to maintain an immune homeostasis. Food and probiotics are intricately linked in their effects on colitis. In addition to the direct effects of food on intestinal barrier growth and survival, many food components are prebiotics, promoting the growth of beneficial bacteria. While effects of food components are generally studied in isolation it is the net effect of these interactions with the intestinal barrier that will determine their impact in colitis.

#### 5.1 Probiotic bacteria that enhance intestinal barrier function

Probiotics are microorganisms that when ingested transiently occupy the gastrointestinal tract to confer health benefits (Saavedra, 2007). *Lactobacillus*, *Bifidobacterium* and *Streptococcus* species are widely used in foods for fermentation, and some strains are probiotic in that they help maintain intestinal barrier and immune functions (Saavedra, 2007). Multiple mechanisms have been implicated in beneficial probiotic modes of action. These include immune modulation of the host, production of substances that inhibit pathogens or toxins, competition with and therefore inhibition of pathogen growth, mucosal barrier repair (decrease permeability) (Penna et al., 2008), increased mucus secretion (Saavedra, 2007), and altered motility (Verdu, 2009). More specifically, probiotics have been reported to exert beneficial effects including altered cytokine secretion (particularly to down-regulate inflammation in infants), to affect T cell differentiation, and to increase macrophage activation (Saavedra, 2007).

Some probiotic bacteria, such as *Lactobacillus plantarum* (Anderson et al., 2010a; Anderson et al., 2010b), can improve tight junction integrity (physical barrier). For a recent review see Ulluwishewa et al. (2011). Probiotic bacteria may also enhance mucin production (chemical barrier). For example, a probiotic formula composed of *Lactobacillus*, *Bifidobacterium*, and *Streptococcus* species induces mucin gene expression and secretion in colonic epithelial cells (Caballero-Franco et al., 2007). Additionally, some probiotic bacteria can reduce the risk of infection (immunological barrier), for example, non-pathogenic *E. coli* have been shown to protect pre-term infants from infection (and reduce allergy) (Candy et al., 2008). Supplementation with probiotic bacteria can also alter the microbiota composition (microbial barrier). For example, when pre-term formula-fed infants are supplemented with bifidobacteria, their microbiota composition more closely resembles that of breast milk-fed infants (Saavedra, 2007).

Finally, probiotics can alter intestinal motility, which in turn can affect intestinal barrier function as discussed in Section 2.4. Probiotics that increase motility can also have the benefit of reducing constipation; whereas those that decrease motility may reduce diarrhoea (permeability changes are also relevant). Some *Lactobacillus*, *Bifidobacterium* and *Streptococcus* species increase intestinal motility *in vitro* (Massi et al., 2006; Wang et al., 2010) and *in vivo* (Ohashi et al., 2001) and reduce transit times from approximately 4 to 3 days in patients with chronic constipation (Krammer et al., 2011).

## 5.2 Foods that enhance intestinal barrier function

The most common way to alter intestinal barrier function using dietary intervention is via modification of the intestinal microbiota composition (microbial barrier). A prebiotic is a non-digestible ingredient that results in activity of the intestinal microbiota that is beneficial to the host (Roberfroid et al., 2010). The main substrates for bacterial growth are dietary non-digestible carbohydrates (e.g. pectins), non-digestible oligosaccharides (e.g. galactins), undigested disaccharide components (lactose), and sugar alcohols (Scheppach et al., 1996). Many of these are fermented by colonic bacteria to short chain fatty acids, which are also beneficial in that they acidify the lumen suppressing pathogen growth, and alter motility as described in Section 2.4 (Yajima, 1985). Short chain oligosaccharide fermentation increases bifidobacteria concentrations in adult faecal samples *in vitro* (Hernot et al., 2009). Although promotion of bifidobacteria concentration has been demonstrated in a number of infant studies (Rautava & Walker, 2008), few reports exist on the clinical benefits of dietary oligosaccharides in infants (Roberfroid et al., 2010). In pre-term infants, an oligosaccharide mix did not enhance the postnatal decrease in intestinal permeability (Westerbeek et al., 2010). However, treatment of healthy pre-term formula-fed infants with oligosaccharides has been shown to speed gastric emptying by 30% (Indrio et al., 2009). This is consistent with clinical studies on the effects of galacto-oligosaccharides reported for adults and the elderly that increase motility (Niittynen et al., 2007). The relatively slow mode of action of prebiotics in promoting bacterial growth is reflected in studies which demonstrate its effectiveness in prophylaxis rather than treatment (Roberfroid et al., 2010). Prebiotic supplementation to formula-fed infants increased bifidobacteria counts and reduced the occurrence of diarrhoea four-fold (Rao et al., 2009).



Some food components can improve tight junction integrity (physical barrier). For example: green pepper, nutmeg, and bay leaf extracts (Hashimoto et al., 1997), star anise, black tea (Konishi, 2003), and the flavonoid quercetin (Amasheh et al., 2008; Suzuki & Hara, 2009). Curcumin, a polyphenolic from turmeric, reduced inflammation in a mouse model of colonic inflammation (Nones et al., 2009). Black tea has multiple effects on physical aspects of the intestinal barrier in that it can improve tight junction integrity and speed gastrointestinal transit (Chaudhuri et al., 2000; Hashimoto et al., 1997). Some polyunsaturated fatty acids (PUFAs) are able to decrease intestinal permeability (Vine et al., 2002) and reduce intestinal inflammation (Knoch et al., 2009). Some dairy compounds can also enhance barrier function, for example,  $\beta$ -lactoglobulin (Hashimoto et al., 1995) and the casein peptide Asn-Pro-Trp-Asp-Gln (Yasumatsu & Tanabe, 2010) improve tight junction integrity. Bovine colostrum and goat milk powder were shown to reduce heat-induced intestinal hyperpermeability in a rat model (Prosser et al., 2004).

Additionally, food components can promote immune system development and homeostasis (immunological barrier). For example, lectin from kidney beans can accelerate the process of intestinal mucosa maturation in piglets (Zabielski et al., 2008). Bovine milk is a rich source of proteins and peptides that are important in immune system development and function. For example, glycomacropeptide derived from kappa casein, has anti-inflammatory activity in a rat model of colitis, suggesting potential for IBD treatment (Daddaoua et al., 2005). Oligosaccharides from goat milk have been shown to enhance recovery from colonic inflammatory damage in a rat model of colitis and may therefore also be useful for treatment of IBD (Daddaoua et al., 2006).

## 6. Delivering ingredients to infants

The delivery of required nutrients during the neonatal period is critical to later health outcomes. It is therefore essential that when breast feeding is not possible, steps are taken to incorporate functional ingredients suitable for infants into appropriate food systems, and deliver them to the required areas of the body. Infants can only ingest foods in liquid form until they are 4-6 months old, after which formulas and more structured food matrices, such as puréed/semi-solid foods can be introduced to their diet. The addition of functional ingredients can cause a range of adverse effects such as changes in stability, appearance and taste of the product. Additionally, the effects of processing, lack of bio-accessibility, or interaction with the food matrix may reduce the activity of the functional ingredient (Patel & Velikov, 2011).

### 6.1 Delivering probiotic bacteria to infants

Since probiotics do not colonise the intestines, they must be continually supplemented via food products to be of benefit. Probiotics are now added to many established infant formula ranges (e.g., Nestle-Nan Pro Gold, Danone-Aptamil and Nutirica-Karicare). The main difficulty associated with the incorporation of probiotics into foods is ensuring that the bacteria are both viable (at quantities sufficient enough to show an effect) and functional when they are delivered to the intestine. The three main obstacles to viability and functionality are the effects of processing, storage, and transition through the gastrointestinal tract. Industrial preparations of various probiotic strains can be bought in a

number of forms (e.g. spray- and freeze-dried). A solution to delivering probiotic bacteria through the gastrointestinal tract is encapsulation. Matrices that can be used for probiotics have been comprehensively reviewed (Anal & Singh, 2007). It is important to understand the possible effects of the protective matrix on intestinal barrier function. For example, the food grade polymer chitosan, used in encapsulation matrices, can itself increase tight junction permeability (Sadeghi et al., 2008). Such particles are used in the drug/medical industry to help open tight junctions to allow particles through (targeted drug delivery).

The composition of the food matrix used to deliver the probiotic bacteria, including its pH, water activity, dissolved oxygen level and storage temperature, can affect viability. The pH of a fruit juice system for example will be low (3-4), and therefore this factor along with the organic acids present can cause a decrease in viability of most probiotic strains over storage time (Saarela et al., 2006). Researchers have found that milk-based systems perform well as delivery systems for probiotics due to the buffering capacity and pH of the milk, which can protect the bacterial strain from detrimental effects of gastric acid (Ranadheera et al., 2010). The amount and type of fat present in yoghurts can have an effect, with lower levels of fat showing greater probiotic viability for certain strains (Vinderola et al., 2000).

The delivery matrix can also have a significant effect on probiotic functionality due to positive or negative interactions. The response of probiotics to their surrounding environment could affect the level of organic acid produced, and therefore limit the extent of health benefit conferred. Interactions between probiotics and macromolecules in the matrix are also important. For example, a probiotic strain of *Lactobacillus reuteri* interacts preferentially with the fat globule membrane in dairy products (Brisson et al., 2010).

The survival of probiotics can also be enhanced by the addition of prebiotics, which are now added in varying quantities to food systems such as infant formulas (Boehmm G., 2007). For example, fructo and galacto-oligosaccharides have been found to promote the growth rate of bifidobacteria (Siggers et al., 2011).

## 6.2 Delivery of food components to infants

Peptides that play a role in promoting intestinal barrier function can be released from bovine milk proteins, casein ( $\beta$ - and  $\alpha$ -) and whey ( $\beta$ -lactalbumin and  $\alpha$ -lactoglobulin) (Yasumatsu & Tanabe, 2010), through commercial processing and gastric digestion. A number of factors can affect peptide activity, such as processing, shelf life of the product and the food system in which they are delivered to the body. An example of how both the intrinsic properties of the peptides and external factors can affect bioactivity was described in a recent study (Dupont et al., 2010). It was found that casein fractions ( $\kappa$ - and  $\alpha_{s2}$ ) were more resistant to infant digestion, due to both hydrophobic areas on the protein at pH 3 and heat processes during preparation of the product. This resistance to hydrolysis within the intestine may also be attributed partially to interactions with whey protein, which may protect the casein fractions to an extent. Conversely, a casein hydrolysate was found that can withstand manufacturing processes (atomisation, homogenisation, pasteurisation) and storage for a considerable time without any significant effect on its activity (Contreras et al., 2011). Recently a few studies have focused on assessing the effect of digestion on various peptides such as caseinophosphopeptides (García-Nebot et al., 2010). Further hydrolysis can occur as the peptides move through the stomach that may not always be desirable as it may

reduce bioactivity within the body (Kamau et al., 2010). The effect of high temperatures on amino peptides and lipids during processing in the presence of reducing sugars can lead to the formation of advanced glycation end products (AGEs). While these milk fractions may have been placed in the food system to potentially decrease intestinal permeability, the formation of AGEs can actually have the opposite effect (Rapin & Wiernsperger, 2010). Therefore it is of vital importance that the properties of the bioactive ingredients are considered, along with the composition of the food matrix and changes that occur to the product during processing and storage.

As with probiotics, there are many limitations that prevent the delivery of functional food components to the required site in the body. Encapsulation and protection have been identified as critical to the incorporation and delivery of biologically active ingredients to infants. The reasons are varied; from protection of the ingredient against processing conditions as discussed above, to masking of taste and also providing protection between the ingredient and the surrounding environment (gastric acid). The site of release is also important in order for these ingredients to confer a health benefit. Some peptides have been found to give a bitter taste, therefore effects on the organoleptic properties of food products are also a concern. This bitterness has been attributed to the hydrophobic nature of their amino acid side chains. Both the hydrophobicity and bitterness of milk peptides have led to the use of encapsulation as a means to incorporate these ingredients into food systems. Methods such as spray drying have been recently used to try and reduce the extent of the bitterness of a casein hydrolysate (Favaro-Trindade et al., 2010). Mixtures of soy protein isolate and gelatin as carriers for the peptide helped to mask the adverse effects of the powdered samples.

## 7. Conclusions

It is well-established that intestinal barrier dysfunction can lead to gastrointestinal illness in infants and is a risk factor for inflammatory and autoimmune disease during adulthood. Since it is difficult to permanently alter intestinal barrier integrity in adults, greater success may be achieved by intervening in early-life to ensure the intestinal barrier matures appropriately, improving health both during infancy and adulthood.

Breast feeding is the most beneficial way to feed an infant and promote intestinal barrier maturation; however, this may not always be possible. Many infants, even while being breast-fed, also receive formula in order to meet their nutritional needs. Therefore, the optimisation of infant formulas and foods with ingredients that enhance intestinal barrier function is necessary to promote life-long wellness. However, more research is needed to fully understand how the intestinal barrier develops and the mechanisms by which food ingredients may enhance this process. In addition, there are still challenges in delivering ingredients to ensure that functional food ingredients maintain their activity throughout production, storage, and digestion.

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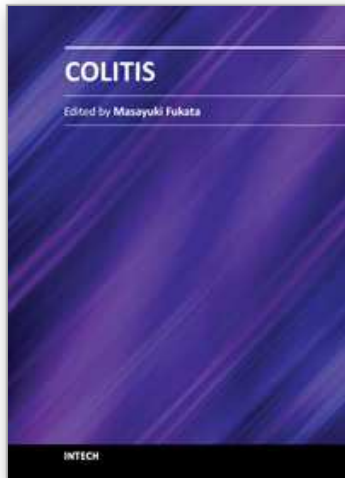
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Inflammation of the colon is collectively called "Colitis". Since a variety of conditions may cause colitis and its manifestations are similar among the causes, selection of the right treatment based on the correct diagnosis is important in the management of this group of illnesses. Over the last few decades, a major shift has been observed in the clinical attention to the pathogenesis of colitis from infectious to idiopathic inflammatory bowel diseases. Colitis cases that are associated with chemical therapeutics and specific pathogens such as amoeba, have become prominent in hospitalized individuals and immune deficient patients, respectively. In addition, a great deal of progress has been made in colitis research triggering the need for updating our knowledge about colitis. This book Colitis provides comprehensive information on the pathogenesis, mechanism of resolution, and treatment strategies of colitis.

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Unit 405, Office Block, Hotel Equatorial Shanghai  
No.65, Yan An Road (West), Shanghai, 200040, China  
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元  
Phone: +86-21-62489820  
Fax: +86-21-62489821

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