

Enteral feeding and its impact on the gut immune system and intestinal mucosal barrier

Jarosław Szefel^{1,2}, Wiesław J. Kruszewski^{1,2}, Tomasz Buczek²

¹Department of Propaedeutic Oncology, Faculty of Health Sciences, Medical University of Gdansk, Gdansk, Poland

²Department of Surgical Oncology, Gdynia Oncology Centre, PCK Maritime Hospital, Gdynia, Poland

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Address for correspondence: Jarosław Szefel MD, PhD, Department of Surgical Oncology, Gdynia Oncology Centre, PCK's Maritime Hospital, 1 Powstania Styczniowego St, 81-519 Gdynia, Poland, phone: +48 58 726 02 50, fax: +48 58 726 03 07, e-mail: jaszefel@mp.pl

Abstract

Enteral feeding is the preferred method of nutritional therapy. Mucosal lack of contact with nutrients leads to lymphoid tissue atrophy, immune system functional decline, and intensification in bacterial translocation. Currently, it is assumed that microbiome is one of the body organs that has a significant impact on health. The composition of microbiome is not affected by age, sex, or place of residence, although it changes rapidly after diet modification. The composition of the microbiome is determined by enterotype, which is specific for each organism. It has a significant impact on the risk of diabetes, cancer, atherosclerosis, and other diseases. This review gathers data on interaction between gut-associated lymphoid tissue, mucosa-associated lymphoid tissue, microbiome, and the intestinal mucosal barrier. Usually, the information on the aforementioned is scattered in specialist-subject magazines such as gastroenterology, microbiology, genetics, biochemistry, and others.

Introduction

The introduction of Parenteral Nutrition into clinical practice in the United States in the 1960s was a giant step forward in the development of nutritional therapy. It took many years to prove that enteral nutrition (EN) causes fewer complications, is cheaper, and is as effective as parenteral nutrition (PN).

Clinical practice often entails situations in which the underlying disease and its complications interfere with nutrient absorption and intestinal peristalsis. Persistence of these disorders leads to malnutrition, impaired immunological response, and many other negative effects. These are the reasons why patients with intestinal failure require the implementation of EN, PN, or concomitant use of both methods of nutrition therapy.

The condition for the maintenance of gut-associated lymphoid tissue (GALT) and mucosa-associated lymphoid tissue (MALT) in the state of full efficiency is the use of EN, because the mucosal lack of contact with nutrients and inhabiting microbiome inhibits the development of neonatal GALT and in mature individuals causes its atrophy.

This review gathers data on the mechanisms that influence the effectiveness of nutritional therapy in order to facilitate rational planning and its implementation individually adapted to the needs and condition of each patient.

Microbiome

GI mucosa is in permanent contact with the microbiota and its genome, which together is called the microbiome. The composition of the microbiome in humans is different. For this reason there are enterotypes, which are named after the dominant type of bacteria. Based on this principle, there are the following enterotypes: *Bacteroides*, *Prevotella* and *Ruminococcus*, and others. Diet affects changes in enterotype, but age, sex, and body mass index (BMI) do not. Wu *et al.* proved that a change in diet from high-fat to low-fibre and from low-fat to high-fibre changes the microbiome within 24 h and the enterotype after a longer period of time [1].

A landmark step towards the knowledge of the relationship between the host and the microbiota is the research conducted since 2007 as part of the Human Microbiome Project (HMP). At this stage, they rely on the

analysis of 16S rRNA gene microbiota. Comparison of the nucleotide sequence in a particular gene with data stored in the HMP enables microorganism identification without the need for bacterial culture. DNA analysis provides more information than RNA analysis because 80% of the gene encodes a protein. Moreover, it determines the type of microorganism and its phenotype.

The initial colonisation of the mucous membranes occurs during childbirth – this is why the composition of the microbiome of infants born from caesarean section is different than the ones born from natural childbirth [2]. Neonatal nutrition determines their immune profile and susceptibility to diseases in adulthood [3]. The composition of the child microbiome is already set at the age of 1 year and is basically unchanged for the rest of its life [4].

The development of surgical techniques and transplantation has made intestine transplantation possible. A fistula created during these operations to graft control allows the determination of changes in the composition of the microbiome caused by an anaerobic environment change into the oxygen environment. Hartman *et al.* noted that oxygen supply to the gut through the fistula vitally reduces the ratio of anaerobic bacteria to aerobic, and the closure of the fistula restores the original microbiome composition [5]. Drugs such as antibiotics and chemotherapy also affect changes in the microbiome composition. Chemotherapy in children with acute myeloid leukaemia causes a 100-fold decrease in the total number of bacteria. This is a result of the 10,000-fold decrease in the number of anaerobic bacteria and 100-fold increase in the number of streptococci [6]. Zwieler *et al.* showed a decrease in the number of enteral bacteria after one chemotherapy course and a restoration to baseline after a few days of its completion [7]. Benus *et al.* observed a change in the number of certain bacteria strains and a ten-fold quantity increase of short chain fatty acid (SCFA) synthesis due to consuming a fibre-rich diet for 2 weeks [8].

A beneficial effect of synbiotics on health was the stimulus for the development of research on microbiome and its interactive relation with its host. Their findings led to attempts at faeces transplantation, an organ treated as obtained from a healthy individual, transplanted to a patient [9, 10]. The idea of this original method of therapy was the change the microbiome together with its microenvironment, instead of changing single strains of probiotic bacteria.

Colitis is a common complication of antibiotic treatment caused by *Clostridium difficile*. Unfortunately, the sole withdrawal of the antibiotic and administration of the vancomycin with metronidazole is not as effective as a graft stool collected from a healthy donor.

The change in the microbiome by a faecal transplantation improves the efficiency of the immune system, and increases the effectiveness of *Clostridium difficile* elimination and lowers the risk of reinfection [11]. Although the faecal transplantation is an effective method of treatment for *Clostridium difficile* infection, it is a rather unappealing technique. It exposes the patient to complications such as perforation, bleeding, bacteria translocation, sepsis, and septic shock. Furthermore, it was found that stool collected from donors with type 1 diabetes, and breast or liver cancer markedly increases the risk of developing these diseases in transplant recipients [12, 13].

Intestinal mucosal barrier

Mucosa protects the organism very efficiently against invasion of pathogens and harmful dietary elements. Moreover, they are involved in the excretion of metabolic products and communication between the enteric nervous system (ENS), GALT, and microbiome. The apical junctional complex (AJC) is located between the epithelial cells covering the intestinal mucous membranes. It is formed of specific construction protein complexes and functions differently. These include tight junctions (TJs), adherens junctions (AJs), and desmosomes located on the top of the side surface of epithelial cells. They mediate in the substance exchange between the organism and the environment. It is estimated that approximately 85% of dietary components penetrate epithelium by diffusion and the remaining 15% by transcytosis. Diffusion loses its selective character in the course of viral, bacterial, and inflammatory bowel disease [14]. TJs and AJs permeability is highly selective due claudin, which barrier properties support occludin and immunoglobulins [15] (Figure 1).

The functions of these proteins are modulated by growth factors (EGF, HGF, VEGF, FGF; transforming growth factor β (TGF- β)), cytokines, hormones, and certain drugs [16, 17].

In patients with protective ileostomy, mucosal lack of contact with the ingest leads to atrophy, and the absorption and motility of the distal intestine decreases [18]. The closure of the fistula restores intestinal passage to the original state after 6 months on average [19]. Williams *et al.* showed that 34 weeks after creating protective ileostomy, the force of contraction and quiescent voltage decreased significantly in the distal loop. The index of villous atrophy decreased twice, although the depth of the intestinal crypts did not change [20]. Brinkman *et al.* analysed the impact of TPN, EN, and glucagon-like peptide-2 (GLP-2), administered in various combinations, on weight gain and regeneration of the mucosa in patients with short bowel syndrome (SBS)

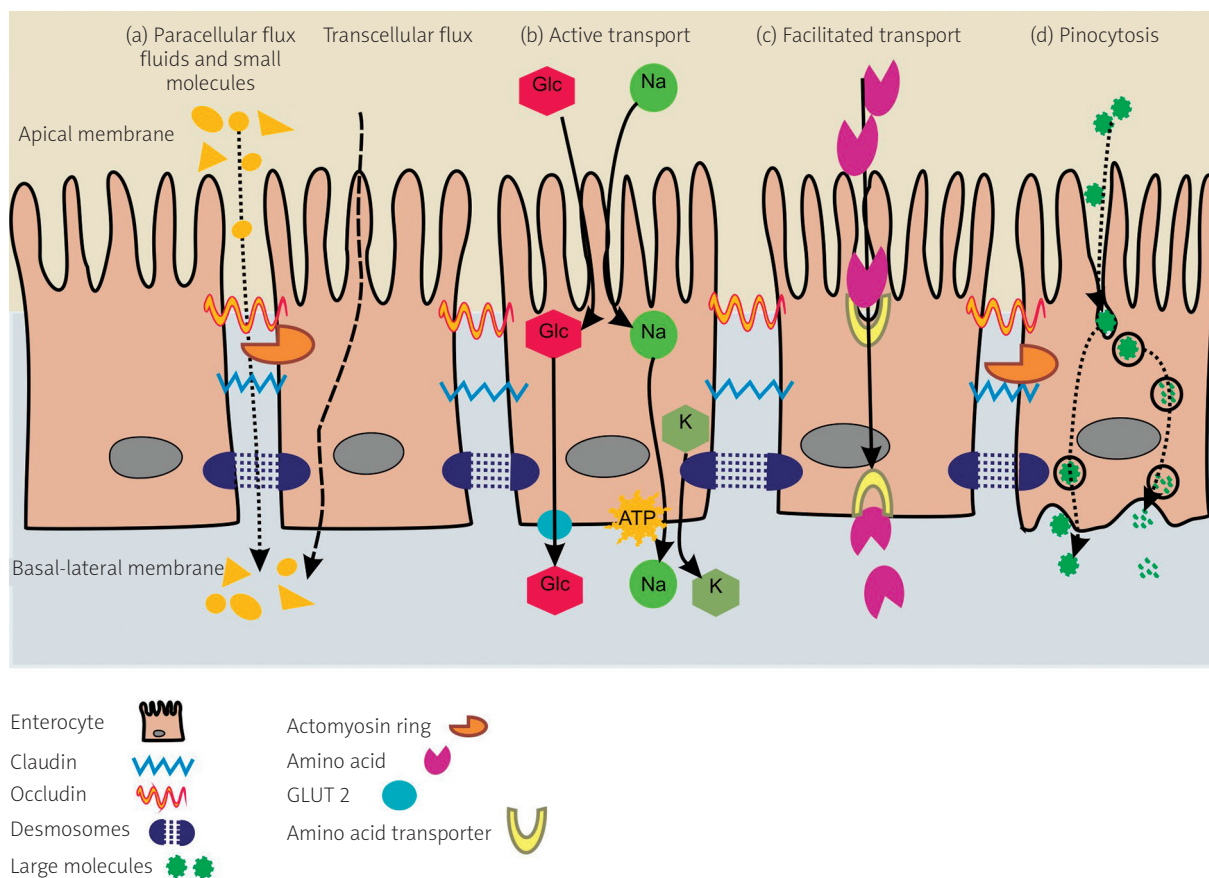


Figure 1. Mechanisms of nutrient absorption. Nutrients are absorbed into enterocytes by diffusion through paracellular flux, and through transcellular flux by active transport, facilitated transport, and by pinocytosis. (a) Some substances, such as water and small molecules, cross membranes freely. (b) Active transport requires energy expenditure. The energy is supplied by ATP and Na⁺/K⁺ pump. (c) Other compounds cannot cross cell membranes without a specific carrier, which affects the permeability of the membrane. Facilitated diffusion, like simple diffusion, allows on equalisation of the substance on both sides of the membrane. (d) Some large molecules are moved into the cell via engulfment of the cell membrane

[21]. It appeared that after massive intestinal resection the adaptation to the new conditions of the rest of the small intestine occurred solely in the group receiving EN and GLP-2 simultaneously.

The increase in permeability of the intestinal mucosal barrier, called leaky gut syndrome, often occurs in the course of inflammatory bowel disease [22]. It has been proven that, contrary to widespread opinion, oral administration of fluids to patients not only protects from fluid loss, but allows for reduction in the volume of infusion [23].

Mucositis occurs in about 40% of patients receiving standard chemotherapy and in 100% of patients after haematopoietic stem cell transplantation receiving high doses of chemotherapy. Keefe *et al.* found that the chemotherapy combined with autologous stem cell transplantation increases the apoptosis of epithelial

cells sevenfold, resulting in a 25% reduction in the area of the intestinal villi after one day [24]. The Mucositis Study Group of the Multinational Association of Supportive Care in Cancer (MASCC) recommends the oral administration of palifermin, a humanised recombinant keratinocyte growth factor (rHuKGF), before each cycle of chemotherapy due to oral cancers. It causes proliferative capacity recovery of intestinal epithelial cells, reduced apoptosis rate and a reduction in the number of inflammatory cytokines synthesised [25].

Acute radiation toxicity (ART) includes diarrhoea and abdominal pain. The pathophysiology includes enterocytes apoptosis, mucosal barrier injury, and dysbiosis. Diabetes, hypertension, and atherosclerosis reduce visceral blood flow and, therefore, increase the risk of radiation enteritis [26]. Chronic radiation syndrome symptoms appear 6–12 months after radiotherapy, or

Table I. Features of acute and chronic radiation toxicity

Parameter	Acute radiation toxicity	Chronic radiation toxicity
Effects	Cells with high proliferation rate (stem cells, Paneth cells, enteroendocrine cells, etc.)	Mostly fibroblasts
Pathogenesis	Inhibition of stem cell proliferation and differentiation. Intensification of apoptosis and intestinal epithelial stem cell impairment	Fibroblast stimulation to proliferation and accumulation in the submucosa. Submucosal fibrosis is related to increase of collagen synthesis. Increase in secretion of hepatocyte growth factor (HGF), transforming growth factor β (TGF- β 1), and cytokines. Mesenteric thrombosis and vasculitis leads to intestinal ischaemia
Time since start of radiotherapy to onset of symptoms	2–4 weeks	Months – years
Symptoms and complications	Nausea, vomiting, diarrhoea, water and electrolyte disturbances, mucositis, dysbiosis	Ileus, fistulas, bleeding, ulceration, perforations
Treatment	Conservative	Mainly surgical
Disease course	Acute – resolves spontaneously after radiotherapy	Chronic, irreversible. Natural mechanisms are not able to repair the damage

even later. The pathophysiology includes intestinal wall fibrosis and blood vessels damage by radicals formed by the photons of radioactive energy. They interfere with the stability of the genome, causing DNA strand breakage and increase in the synthesis of TGF- β [27, 28]. As a result of fibrosis the intestinal motility weakens and Auerbach's plexus neurons undergo a compensatory hypertrophy. Due to anal sphincter muscle fibrosis, 1/5 of patients after radiotherapy suffer faecal incontinence [29] (Table I).

A treatment method of radiation-induced fibrosis has not yet been developed, but its effects can be reduced by administering pentoxifylline with high doses of vitamin E [30]. The combined administration of the two antioxidants may partially reverse the fibrosis. Attempts at radiation-induced fibrosis treatment with anti-TGF, anti-platelet-derived growth factor (PDGF), and statins are promising for the future [31].

The intestinal immune system

Toll-like receptors are located on the apical surface of the intestinal epithelium. They collect pathogen-associated molecular patterns and transfer them to antigen-presenting cells. On the basis of obtained information, GALT differentiates commensal bacteria from pathogenic and either tolerates or destroys them. Gut-associated lymphoid tissue is composed of lymphoid aggregates, Peyer's patches, isolated lymphoid follicles diffusely distributed along the lamina propria, and intraepithelial lymphocytes. It is estimated that

GALT contains approximately 70% of total immune system cells. Malnutrition and chronic inflammatory bowel disease cause lymphocyte apoptosis and inhibition of thymocyte proliferation [32]. The fact that the thymus regenerates and cellular immunity normalises as nutritional status improves shows that those reactions are reversible [33]. As well as recognition and neutralisation of harmful antigens, GALT is responsible for oral tolerance, which in essence is the lack of hypersensitivity reactions to harmless food and bacterial antigens [34]. Dendritic cells (DC) play an important role in forming the oral tolerance. It migrates from lamina propria to GALT and transmits the information to regulatory lymphocytes (Treg) on the emergence of a specific antigen. The essence of tolerance is the elimination of the antigen by sensitised lymphocytes via clonal anergy, clonal deletion, sequestration, antigen ignorance, or preventing lymphocytes from contact with the antigen [35].

Dendritic cells identifies antigens collected from the intestinal lumen or from the M cells. Then DC migrates to the mesenteric lymph nodes, where antigens are processed and presented to effector lymphocytes. Besides DC, M cells (microfold cells) are involved in the antigen transport. M cells are mostly localised close to follicle-associated epithelium. M cells, like DC, migrate and present antigens to lymphocytes, although their main function is transcytosis [36]. M cells are able to carry (apart from antigens) bacteria, viruses, and other particles into the subepithelial space without changing their morphology or features. This feature is used by a few microorganisms to invade the organism. This

Table II. Characteristics of intestinal mucosal cells

Cell type	Function	Specific products
Dendritic cells	Antigen absorption from the intestinal lumen and mucosal lamina propria. Antigen-presenting cell. Cell maturation after contact with antigen and migration to lymph nodes and spleen	IL-12, IFN- α , IL-1, IL-6, IL-7, IL-10, IL-15
Paneth cells	Innate, non-specific immunity. Substance synthesis that coats and disables pathogens and diet antigens. Impact on the maintenance of intestinal microbiota. Stem cell protection	α -Defensin-5 HD5 and HD6, secreted phospholipase A ₂ (sPLA ₂)
Stem cells	Differentiate into intestinal epithelial cells	
M (microfold) cells	Macromolecules transcytosis (pathogens, commensal microorganisms, and antigens) from intestinal lumen to submucosa	
Enteroendocrine cells	Hormones synthesis and secretion	5-HT, somatostatin, peptide YY, GLP-1, glicentine, oxyntomoduline, glucose-dependent insulinotropic hormone (GIP)
Goblet cells	Innate immunity component. Secreted mucus is the first line of defence against pathogens	Mucin 2, trefoil factor 3 (TFF3) and resistin-like molecule β (Relm β)
Enterocytes	Nutrients absorption. Induction of immune tolerance of protein intake. Induction of oral tolerance contributes to the formation of the microenvironment. Maintaining balance between antigen tolerance and inflammation	
B Cells	Antigen-presenting cell via Toll-like receptor, homing to lymph nodes and conversion to plasmocytes, which return intestinal mucosa and produce antibodies	IgA, IgM
Macrophages	The first phagocytic cells of innate immunity that microorganisms come into contact with after passing through the intestinal epithelium. Phagocytosis, bactericidal, and bacteriostatic properties without inducing an inflammatory reaction	IL-10, TNF- α , IL-1, IL-6, nitric oxide, reactive oxygen intermediates, cathepsins and metalloproteases

specific feature of M cells is the reason for their use as a means of transport for some vaccines and drugs into the organism. Its advantage is the ability of drugs and vaccines to be administered in an oral, non-invasive, safe way and at low-cost (Table II).

Gut-associated lymphoid tissue defence functions support the innate immune components, such as low gastric pH, bile acids, mucus, lysozyme, and defensins. A secretory immunoglobulin A2 (sIgA) is the first line of immune defence of the organism against harmful agents. The contact of B cells with antigen triggers the synthesis of sIgA. Sensitised B cells proliferate and differentiate into plasmocytes. This process is coordinated by T helper cells, TGF- β , and IL-10. sIgA is secreted by plasma cells as a dimer, which, after binding to the polymeric immunoglobulin receptor (pIgR), is transmitted via transcytosis by the M cells to mucosal surfaces [37]. sIgA

causes agglutination and inhibits bacterial adhesion to epithelium. It absorbs antigens and deactivates viruses, toxins, and enzymes produced by microorganisms. As sIgA is resistant to proteolytic enzymes, as much as 40% of anaerobic bacteria excreted with the faeces is covered with it. sIgA, unlike other immunoglobulins, does not activate, complement, or cause the inflammatory response due to contact with an antigen. This phenomenon is called an "immune exclusion" (Figure 2).

Conclusions

Although the introduction of PN into medical practice has allowed many patients to return to an active lifestyle, it deprives the organism of the many benefits resulting from EN. For this reason, decision-making on the implementation of PN requires consideration of the possibility of administration, at least partially, of EN.

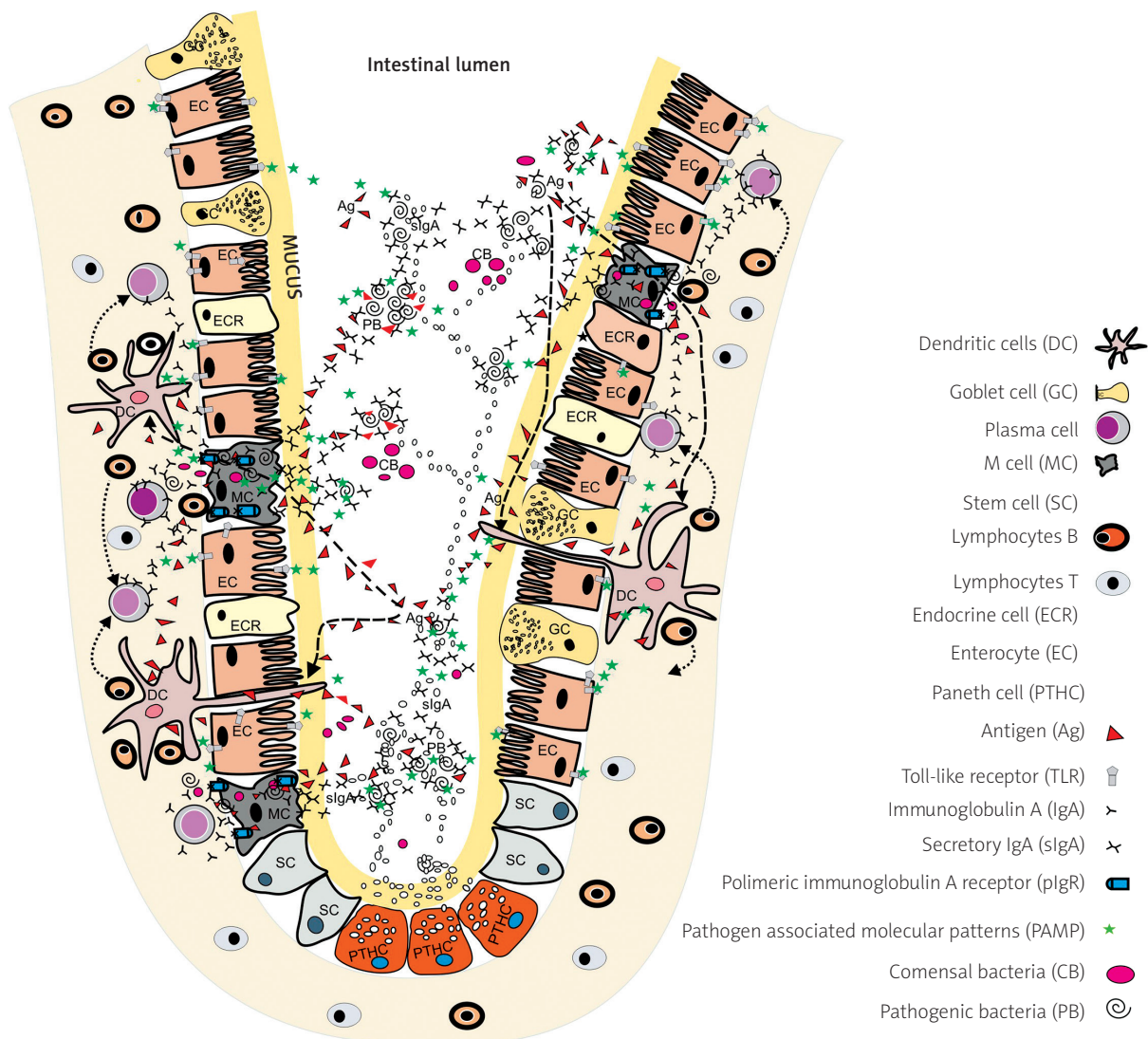


Figure 2. The mechanisms of human immune defence system against pathogen invasion through the intestinal mucosa. (a) The antigens penetrate from the intestinal lumen into the epithelium via M-cell transcytosis, or are transported by dendritic cell veils (DC). Dendritic cell and B cells are activated by antigens and migrate to lymph nodes. In lymph nodes, B cells convert to plasmocytes. Dendritic cell matures, which results in their loss of the ability to present antigens. Plasmocytes and mature DC return to intestinal mucosa lamina propria, where they start to secrete immunoglobulin A and many inflammatory cytokines. IgA is polymerised and then combined with the polymeric immunoglobulin A receptor (pIgR). These complexes are transferred through transcytosis. When sIgA reaches the apical cell side it is secreted into intestinal lumen, where it binds to the pathogens. (b) Pathogen-associated molecular patterns (PAMP) bind to pattern recognition receptors (PRR), which include Toll-like receptors (mainly in the intestine: TLR3, 4 and 5) and Nod-like receptors. These complexes trigger a cascade reaction that leads to NF- κ B activation and transport to the nucleus, as well as increased expression of genes encoding inflammatory cytokines. Toll-like receptors (TLR) are expressed mostly on the surface of antigen-presenting cells (APC) – dendritic cells, macrophages, and B cells. Regulatory T cells, the main function of which is to maintain tolerance to self-antigens, also express TLR. (c) Paneth cells, located in the mucosa, synthesise and secrete antimicrobial peptides into the lumen. They present antibacterial, antiviral, as well as antifungal and anti-parasitic activity. These include α human defensins 5 and 6 (HD5,6) and human β -defensin 1-3 (HBD1-3). The mechanism of their antimicrobial activity involves binding defensins to the targeted cell membrane followed by endocytosis and the triggering of metabolic processes that lead to cell apoptosis

Conflict of interest

The authors declare no conflict of interest.

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