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Infectious Diseases

Probiotics and immunomodulation

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Summary:

The paper provides an overview of the present knowledge about biological mechanisms of probiotics' action. The data indicates that the effects of probiotics are strictly connected to the immunologic mechanisms. Probiotics are the immunomodulatiors, but the mechanisms of immunomodulation have not been fully elucidated yet.

Key words: probiotics, mechanisms of action, immunomodulation, cytokines

The positive role of lactic acid bacteria was defined for the first time by IlyaMechnikov over 100 years ago. Being the discoverer of phagocytosis, Mechnikov received Nobel Prize in 1908. He noted the good health of Bulgarian boys fed with fermented milk products. He accurately noticed that lactic acid bacteria cause higher immunity and good intestinal health.

His observations and publication on the subject in a French journal did not arouse adequate interest and only in the last 15 years studies on probiotics attained great dynamism in many countries around the world.

Nowadays probiotics have entered the arsenal of therapeutic and prophylactic means for many conditions e.g.:

- in allergic conditions affecting children, especially in atopic dermatitis
- in normalisation of bacterial flora of digestive tract after antibiotherapy
- Inflammatory boweldiseases
- in rotavirus diarrhoea
- in travellers' diarrhoea
- in radiation damage to the alimentary canal
- in eradication of Helicobacter pylori
- in tumour prophylaxis
- in surgical infections
- in urogenital infections

The impact mechanisms of probiotics are still the subject of intensive studies. It is well-known, that probiotics produce antibiotic substances. Circa 70 bacteriocins, which have antibiotic activity against various strains of bacteria, have been identified [22]. Probiotics produce also some amount of vitamins B in the large intestine, what is considered to be a very advantageous effect. It has been revealed that probiotics inhibit the activity of enzymes that stimulate carcinogenesis (beta-glucoronidase, azoreductase, nitroreductaseand beta-glucosidase) [7, 21].

A characteristic feature of probiotics is the production of short chain fatty acids such as acetic acid, propionic acid, butyric acid and lactic acid as the products of enzymatic degradation of polysaccharide ground [16]. Such body acidification inhibits the development of potentially pathogenic bacterial flora. It also favours better intestinal absorption of calcium, iron, phosphorus and milk proteins coming from milk or other products consumed simultaneously or in the meantime [6]. It is a well known fact that butyric acid is a perfect nutrient forcolonocytes. Thus, it has a crucial meaning for intestinal health and is a colorectal cancer prevention.

The competition for adhesion with mucous membrane between probiotics and pathogens is also

very important. The examples of such competition are well-known [4]. However, a special role in the mechanism of probiotics action should be attributed to their immunomodulatory properties [4, 9,16,23]. Gastrointestinal tract is the largest immunological organ. The immune system constitutes integrated system of cells and tissues, which role is to [18]:

- eliminate exogenous pathogens (bacterial and viral),
- eliminate tumour cells,
- keep the state of tolerance for:
  a) some environmental factors (inhibition of allergic reactions);
  b) some endogenous factors (blocking the autoimmune reactions).

Lymphocytes Tgrouped in Peyer's patches dominate in the gastrointestinal mucosa and in thesubmucous layer. These are mostly lymphocytes T , that belong to the subpopulation CD4 with immunological memory. Moreover, there are lymphocytes B and plasma cells, that produce antibodies. Within the layer ofthe intestinal epithelial cells macrophages, eozynophil granulocytes and mastocytes can be found. Throughout the intestinal crypts, numerous Peneth cells can be found, which secrete bacteriolytic enzymes (lysozyme) with capability for phagocytosis [8].

According to [8] immunological cells interact with each other through:

1) direct contact and cell adhesion molecules (CAM) on the cell surface,
2) cytokines (interleukins IL) as the soluble mediators and informative proteins. Nowadays over 20 IL have been identified,
3) NO, prostaglandins, leukotrienes and immunoglobulins.

A separate group of cytokines is constituted by a growth factor and interferons. Most cytokines posses topical activity, whereas some actsystemically e.g. IL-1 and IL-6 [12].

Immunomodulatory properties of probiotics bacteria:

- induction of moderate proliferation of CD4+ lymphocytes T, what manifests as lymphocytes B stimulation
- synthesis of cytokines IL-10 blocking pro-inflammatory reactions
- synthesis of antibacterial and antiviral cytokines (TNF-alpha)
- stimulation of IgA production (mainly secretory antibodies in saliva, tears, intestinal mucosa, nose and respiratory tract
- stimulation of IFN-gamma production in healthy patients increases the humoral immunity and ensures better protection during infections

Interactions between probiotics and GALT cells (Gut-associated lymphoid tissue) have not been fully elucidated [1, 8].

It has been proved that probiotics stimulate the increase of the cell number, that produce IgA as the main secretory antibodies, what is significant in treatment of bacterial and viral diarrhoea especially those affecting children [8]. The increase in the number of cytokines TNF-alpha, IFN-gamma and IL-10 has been observed and this fact has a beneficial effect in the treatment of gastrointestinal tract infections [8,21].

Prophylactic and medicinal effect of probiotics administration was confirmed in allergic children especially with atopic dermatitis.

The authors confirmed significantly higher immunological response from the Th1 helper cells in comparison with Th2 lymphocytes [11, 14, 24]. Th1 lymphocytes are considered to be antiallergic, whereas Th2 are thought to be proallergic. The imbalance between Th1 and Th2 is crucial in very first months and years of life and fosters bronchial asthma in adult patients.

The prevalence of allergic diseases in developed countries is being explained by so-called hygiene hypothesis, which states that insufficient stimulation of environmental bacterial antigens affects the lack of balance of immunological response [2, 3, 13].

It should be noticed that probiotics are important remedy and prophylactic measures in the treatment of allergic diseases affecting children especially with atopic dermatitis [11, 17]

Studies revealed that probiotics may exhibit side effects especially after their administration to children with impaired immunity as well as premature neonates exhibit increased risk of sepsis i.e. a systemic inflammation [5, 15]

It was also confirmed, that bifidobacteriainhibit the production of pro-inflammatory IL-8 by Helicobacter pylori and therefore they suppress inflammatory changes in the cells of the host. It is likely that this inflammatory reaction is mediated by nuclear factor kappa B (Nf-kB) [19].

The well-known fact is, that Helicobacter pylori inflammation is the main aetiological factor that contributes to gastric ulcer formation and the eradication of this pathogen is required to treat the disease. This is an oncogenic bacterium.

Probiotics were used in the treatment of autoimmune diseases of central nervous system i.e. in the treatment of multiple sclerosis (encephalomyelitis). Some improvement of health status is identified with

the indirect action of IL-10 dependant probiotics, produced by Th2, monocytes and macrophages [8].

Probiotic lactobacillus acidophilus induce a production of interferon IFN in healthy humans, what causes better protection when organism is being infected.It may be recognized as an effectiveness marker of probiotics for the immunological response. The authors have concluded, that a yoghurt may be used in treating malnutrition and anorexia nervosa. The positive effect has been observed after 10 weeks of treatment. Various strains of probiotics demonstrated to have diversified effects on cytokines production, what was dependant on the level of expression of Bcl2 encoding protein in the intestine epithelial immune cells. Oral administration lasted from 2–7 days [16].

In conclusion, it should be highlighted, that probiotics bacteria constitute a part of commensal bacterial microflora. For this reason, symptoms of significant systemic response (cellular and humoral) should not be expected after oral administration.

Selection of specified strains of bacteria (with well-known immune system modulation profile) may be useful in restoring disturbed immune functions:

- after antibiotherapy
- in the infections of gastrointestinal tract
- after radiotherapy
- in some immunodeficiencies
- in some allergic diseases especially in children
- in the improvement of lactose intolerance.

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