Review paper

Therapeutic applicability of helminths in autoimmune diseases – literature overview

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Abstract

This paper presents an overview of published studies conducted on helminths – parasites of the human gastrointestinal tract. Making use of their ability for immunomodulation may lead to the introduction of effective therapies for autoimmune diseases. This paper presents chronologically attempts to treat autoimmune diseases not only of the gastrointestinal tract, but also of the nervous and endocrine systems, which have been undertaken for decades. The overview of analysed reports demonstrates that as medical knowledge on the cells and mediators participating actively in inflammatory processes accumulates, clinical trials focus on ever more specific areas concerning the pathomechanisms of autoimmune diseases. The outcomes of clinical trials conducted both on animals and humans give reasons to assume that the modification of the human intestinal microflora may be the key to fighting against these diseases.

Helminths, parasites residing in the digestive system in mammals, exemplify immunomodulation in order to freely inhabit the host organism. This group of invertebrate worm-like parasites includes flatworms (tapeworms and flukes) and roundworms. All of them inhabit different host organs, especially the intestines. In natural conditions they are a big threat to public health and life. At the same time, it seems that the ability of helminths to reduce immune response could be made use of in therapies of diseases caused by an overactive immune system. For several decades researchers have investigated the applicability of helminths to treat autoimmune diseases such as multiple sclerosis, Crohn's disease, ulcerative colitis, allergy, asthma, and – most recently – diabetes.

In the 1970s the relationship between living conditions and the prevalence of allergies was noticed. It was documented that the prevalence of allergic diseases was greater among communities living in highly developed urban areas as compared to populations inhabiting rural areas [1]. Observations made in the following years led Strachan to formulate a hypothesis according to which the precise immune response depends on the organism training, whereas this training is influenced by everyday contact to pathogens. Thus, a smaller exposure to infectious diseases in early childhood increases the risk of allergy in later years [2]. Further epidemiological studies revealed the relationship between intestinal microbiota and the propensity to allergic reactions and autoimmune diseases [3]. The gastrointestinal tract plays a major role in shaping the immune response because the intestine is the location where the majority of antigens a human being is exposed to come into contact with the host organism. The intestinal immune system – gut-associated lymphoid tissue (GALT) – is responsible for recognising a given antigen, direct defence against it, and the generation of the immune response. GALT contains most of the organism's lymphocytes (70%), plasma cells (80%), and tissue macrophages [4]. The intestine is constantly exposed to an immense

number of bacteria, viruses, fungi, and protozoa, whereas 500 million people are or have been colonised by helminths [5, 6]. It is estimated that annually more than 130,000 people die of the complications [7]. Different 'residents' of the intestinal microbiota generate different immune responses in the host. The helminth colonisation of the gastrointestinal tract provokes the immune response involving the largest activity of type 2 T helper cells (Th2) and regulatory T cells (Treg), along with the secretion of cytokines, mainly interleukins: IL-4, IL-5, IL-13, and IL-10, transforming growth factor β (TGF-β), and IgG1, IgG4, and IgE antibodies [8–10]. This response is generated via proteins secreted by worms. Thus far, more than 1000 of such proteins have been identified. Interestingly, during their evolution, particular worm species have individually developed different immunomodulation paths. Substances secreted by various species have different target points, ranging from the aforementioned T cells and B cells, through natural killer cells (NK) and dendritic cells (DC), to neutrophils, eosinophils, basophils, and mastocytes [11]. However, the common effect of various reactions is the increased production of mucus by goblet cells, increased intestinal motility, increased enterocyte proliferation, and synthesis of substances that induce healing. Multigenerational evolution of helminths in concert with mammals has led to the achievement of immune balance between the host and the parasite [12]. Rook, the author of the 'old friends' hypothesis as developing Strachan's suggestion, believes that the precision in the T-cell activity results, among other factors, from a specific training in response to the stimulation caused by microorganisms and parasites of low pathogenicity, whereas their removal from the gastrointestinal tract can have a harmful effect [13]. This is evident in African countries where the percentage of allergy patients increased following deworming actions [14].

Because helminths modify types of immune response typically disturbed in autoimmune diseases, therapeutic applications of worms have been considered. The first step was extracting proper organisms with low risk of health complications for the humans. Two species: *Trichuris suis* and *Necator americanus* were chosen. *T. suis* applied intestinally does not cause long term colonisation, whereas larvae of *N. americanus*, having migrated from the skin (place of application) through the lungs to the small intestine, can inhabit the host organism asymptomatically for a long time [14, 15]. Studies on the therapeutic use of helminths concern mainly chronic inflammatory bowel diseases (IBD): Crohn's disease, ulcerative colitis, and celiac disease. The outcomes of studies on multiple sclerosis and other systemic diseases: type 1 diabetes, rheumatoid arthritis, systemic lupus erythematosus, and psoriasis, are also promising [16, 17]. The first stage of research into therapeutic applications of the parasites was to confirm the hypothesis concerning the effectiveness of helminthic therapy in animal models. The effectiveness of exposure to helminths or their eggs has been best documented for inflammatory bowel diseases. Numerous studies have reported a decrease in the severity of induced active bowel inflammation in mice [18–24]. Additionally, evidence of the effectiveness of the preventive application of helminths or their eggs has been obtained [25–27]. The most frequently observed biological effects contributing to the prevention of the disease development included: increased production of interleukin (IL)-4, IL-10, and IL-13 as well as decreased secretion of interferon γ (INF-γ) and INF-α. Differences in the immunomodulation by particular species of parasites have been observed, for instance with the additional activation of regulatory T cells and the reduction in IL-12 levels [17]. The application of helminths in the mouse model of multiple sclerosis – experimental autoimmune encephalomyelitis (EAE) – has generated similar outcomes. In several conducted studies an identical protocol has been followed: the course of EAE in mice previously infected with helminths has been compared with a non-infected group. All studies have reported an evident decrease in the incidence and severity of EAE in mice with an active infection. This has occurred with the suppression of Th1 and Th17 cells, enhanced production of IL-4 and TGF-β, as well as a decreased INF-γ activity. Interestingly, the effects of infection have been less significant in the cerebral tissue and limited to increased IL-4 levels [28–31]. The outcomes of a study conducted in Serbia in 2010 are particularly interesting. The authors confirmed their previous results revealing helminth-generated modification of the EAE course in rats. Additionally, they alleviated the disease progression by transferring T cells obtained from the spleen of animals infected with *Trichinella spiralis* to non-infected rats with EAE. This can serve as a starting point for research into possible vaccination against multiple sclerosis [32]. The effectiveness of helminthic therapy has also been assessed in type 1 diabetes. The proven autoimmune vehicle of this disease involves the destruction of insulin-producing pancreatic cells by autoreactive T cells. Studies are conducted on non-obese diabetic (NOD) mice that spontaneously develop autoimmune diabetes in about the fifth week of their lives [33]. In a few studies conducted thus far, helminth infection of NOD mice has proven effective only as a preventive measure, delaying the occurrence of the symptoms and only on condition that the infection occurred very early – prior to the development of inflammatory

lesions in the pancreas. The mechanism of helminth infection on the immune system has been analogous to the one already described and involved the increased production of IL-4, IL-5, and IL-10 [34–36]. Thus far only a small number of studies involving helminthic therapy in animal models of rheumatoid arthritis and systemic lupus erythematosus have been conducted. In the animal model of rheumatoid arthritis, inflammatory processes in joints are induced via immunisation with autologous or heterologous type 2 collagen, or alternatively studies are conducted on MRL/Lpr mice that spontaneously develop an autoimmune process affecting multiple sites, including joints. The MRL/Lpr strain is also used as a model for systemic lupus erythematosus [37, 38]. Both in the spontaneous and induced models of rheumatoid arthritis helminth infection has reduced the incidence and alleviated the course of disease if it developed. Inhibition of inflammation has been due to the increase in IL-4, IL-10, and IgG1 levels as well as INF-γ reduced activity [39, 40].

Potential therapy with excretory-secretory (ES) products of helminths (including synthetically produced substances or those produced by modified bacteria strains) would be safer than infection with living parasites, as well as being perceived better by patients. In some experimental studies the effectiveness of ES products obtained from helminth colonies in sterile conditions have been confirmed. Having employed supernatant from an aseptic colony of *Taenia crassiceps* in EAE mice, Peón *et al*. have radically alleviated the disease symptoms, the results being better than those obtained with dexamethasone [41]. The authors have thus confirmed earlier reports by researchers who used excretory-secretory products of other parasites – *Trichinella spiralis* and *Schistosoma japonicum* – in EAE [42, 43]. Both the superinfection with living helminths and the use of ES substances produced by them leads to a global and non-specific decrease in the host's immunity. This is associated with the risk of being prone to infections and disturbances as regards the effects of vaccinations [44]. Consequently, single molecules that are most strongly and most specifically involved in the modification of immune response are sought. Very few attempts to administer purified proteins yield interesting outcomes. In one study, the results of which were published in Nature in 2016, the FhHDM-1 peptide obtained from *Fasciola hepatica* was employed in the mouse model of type 1 diabetes and multiple sclerosis. The protein was administered before the expected development of diabetes in NOD mice strain and before the EAE induction. A reduction of almost 50% in diabetes incidence was obtained, in the EAE group a significant reduction in the disease relapses was observed, and in 20% of mice complete and permanent remission of the symptoms after the first disease attack. It has been shown that FhHDM-1 reduces the secretion of proinflammatory cytokines – TNF and IL-6 – by macrophages [45]; whereas glycoprotein omega-1 obtained from Soluble Egg Antigen (SAE) produced by *Schistosoma mansoni* induces Foxp3 expression and IL-4 in NOD mouse, a proven protective factor against the development of type 1 diabetes [46]. The best-known substance produced by helminths is glycoprotein ES-62 obtained from *Acanthocheilonema viteae*. It induces the promotion of Th2 cells and inhibition of Th1 cells as well as polarisation of Th17 cells. It also inhibits mastocytes activity and induces the production of IL-10 by B cells and macrophages [47]. Its effectiveness has been confirmed on a mouse model of asthma. The administration of the helminth product ES-62 to animals has resulted in a significant reduction of inflammatory lesions in bronchial walls [48]. A study conducted by McInnes *et al*. revealed interesting data concerning the effectiveness of ES-62 in arthritis. In the mouse model of arthritis ES-62 reduced the severity of symptoms, whereas its further administration had a noticeable effect on the milder course of the disease. An evident influence on the disease progression was also observed in mice administered with ES-62 once the disease had already developed. In lymph nodes of the studied mice the production of TNF-α, TNF-γ, and IL-6 was reduced, whereas the production of IL-10 increased. Importantly, this study also assessed the impact of ES-62 on human cells *in vitro*. As in mice, a significant decrease in the production of proinflammatory cytokines by T cells was revealed [49]. The following years devoted to the study of ES-62 led to the creation of a synthetic analogue of ES-62. Its creators have documented a similar effectiveness and mechanism of both molecules in the animal model of rheumatoid arthritis and systemic lupus erythematosus. This can be treated as one of the last stages before the production of the drug [50, 51].

Helminths have accompanied humans for thousands of years, and during that period they have learnt how to remain in an immune balance with the host's organism. Treated as parasites until recently, with an evident increased incidence of autoimmune diseases, they have come to be perceived as a specific symbiont. It has been revealed that the human organism benefits from infection in the form of desired modulation of its own immune system. Diminishing the biological variety of microbiota and the resulting absence of 'immune training' may lead to proneness to autoimmune diseases. The appreciation of the role of helminths, along with the accumulation of scientific evidence, has stimulated research into medical applications of the worms. As the

reports and data discussed here indicate, studies concerning the application of helminths in medicine have gone through many stages, beginning with epidemiological studies, through research on animal models and clinical trials, to an artificial synthesis of biologically active substances. This mirrors progress that has been observed in medicine and experimental sciences over the years. Industrial synthesis of substances produced by helminths, or their production by modified, safe bacterial strains, should improve their safety when administered to people and increase access to therapies. Importantly, the selection of a particular molecule for therapeutic purposes will no longer be conditioned by potential harmfulness of the worm producing it but will depend on the effectiveness of its activity.

Conflict of interest

The authors declare no conflict of interest.

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