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Review articles

Regulatory function of parasites in autoimmune disease – outcome from experimental model infection

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ABSTRACT. It is estimated that more than half of the nowadays known species are pathogenic parasites. Among macroparasites gastrointestinal nematodes are one of most common and having significant impact on life and health. Those organisms reveal strong, specific immune response in host, involving primary mechanisms associated with regulatory and Th2 cells. Referring to immunomodulatory abilities of helminths, parasite infections started to be considered as a possible therapy for many autoimmune diseases. Clinical trials on 2nd and 3rd stage are conducted in spite that treatment has not been recognized as safe for common use. Despite that the safety of treatment with parasites is still controversial and widely discussed. Our knowledge about mechanisms used by helminth to moderate immune response is still inadequate to predict possible effect of long lasting parasite infection on individual patients.

Key words: immunoparasitology, animal model, helminth, autoimmune disorders, parasite driven molecules

Autoimmune disorders

It is estimated that more than half of the nowadays known species are pathogenic parasites [1]. Although more than 70 chronic diseases are grouped as an autoimmune diseases, there is no one clear definition. They are characterized by pathogenic immune response against the patient's molecules. Systemic lupus erythematosus (SLE) and multiple sclerosis (MS) were the ones of the first described autoimmune diseases. Those autoimmune disorders are result of different hypersensivity types. The autoimmune disorders differ in the dominant mechanism involved in disease development – for example some may be due to T-cells reactivity [2], other depend on antibody mediation [3]. What is important to note; in most cases autoimmune disorders affect women more often and the difference between sexes is best seen in the Sjogren's syndrome, SLE, autoimmune thyroid disease and scleroderma [4]. The prevalence of autoimmune diseases is higher in developed countries and raised in the last century, change is noticed even in a 20 year long lasting period; Scotland prevalence of MS raised from 145 to 193 cases per 100 000 individuals [5]. Aetiology of autoimmune disorders remains unclear, but both genetic and environmental factors, such as smoking or Epstein-Barr virus infection, play considerable role in that process. Laboratory and epidemiological studies showed that hypersensitivity disorders were less prevalent in populations of pure hygienic conditions. For that reason hygienic hypothesis was proposed, which claims that the rise in allergic diseases is due to lower incidences of infection in early childhood. It might be interpreted, that higher hygiene level is also in accordance with more frequent civilization, neurodegenerative and autoimmune diseases.

Examples of autoimmune diseases in laboratory studies

Multiple sclerosis and its animal model – EAE

Multiple sclerosis (MS) is a chronic, inflammable, demyelinistation disease of central nervous system (CNS). It is considered to be autoimmune disease. MS is debilitating and often leads to permanent loss of nervous system function.

Typical symptoms of MS are: sensory disorders, muscle strength weakening, muscle crumps, difficulties in moving and motion coordination difficulties. Also speaking, swallowing and visual acuity disorders as well as chronic pain.

In Europe, the cases of MS distribution are irregular and prevalence of 35–200 per 100 000 individuals is observed [6]. Chronic lack of patients health has both economical and sociological consequences – most of all it affects young adults. It is not fully understood what is the reason of variation in worldwide disease's prevalence and incidence. The most common MS type is relapsing-remitting – almost 80% patients' cases. It is characterized by relapse of disease symptoms for several days, then it improves spontaneously or in a few weeks after symptomatic treatment.

Charcot [7] has characterized MS and its clinical and pathological symptoms over 100 years ago, but even these days disease aetiology remains unknown. MS appeared more frequently in economically developed countries. Immunological system of MS patients reacts against myelin proteins – antigens that have been unrecognized before. Leukocytes migrate through blood-brain barrier (BBB) and reach brain tissue. One of MS morphological exponent is self-creation of so called demyelinisation plaque, that is a brain area with an inflammatory infiltration causing damage of axon myelin sheath. It is characterized with infiltration of large amount of leukocytes, especially monocytes and T lymphocytes. B lymphocytes take part in diseases' pathogenesis since immunoglobulin presence is typical for demyelinisation plaques [8]. After prolonged time the demyelinisation plaque becomes non-active and further myelin damage on its territory is inhibited. Despite that fact lack of remyelinisation is observed, as results of considerable impair of oligodendrocytes [8].

In MS immunological response is probably directed against myelin oligodendrocyte glycoprotein (MOG), myelin basic protein (MBP) and proteolipid protein (PLP), which are the most immunogenic proteins. Owing use of above mentioned proteins to immunization of animals creating experimental model over MS – experimental autoimmune encephalomyelitis (EAE) – was possible. In EAE model clinical and immunopathological symptoms are very similar to be observed among MS patients. In EAE the main role play CD4+ lymphocyte – auto-reactive cells against myelin antigens. Both, MS and EAE are associated with Th-1 response and increased pro-inflammatory cytokines concentration, like IFN-γ, TNF-α, IL-12 and IL-17. Increased concentration of those cytokines in both peripheral blood and cerebrospinal fluid (CSF) among MS patients was proven [9]. During MS oligodendrocytes damage is caused by cytokines such as IFN-γ or TNF-α, and also higher expression and activation of Fas-FasL receptors. Besides oligodendrocytes damage cytokines also stimulates astrocytes and microglia to become antigen presenting cells, what promotes further development of CNS inflammatory conditions. Active lymphocytes induce macrophages for nitric oxide (NO) and free radicals production, which are toxic for CNS cells, including neurons [10]. During acute phase of MS pro-inflammatory cytokine level is growing, and regulatory, anti-inflammatory cytokines, production is reduced. A balance between pro- and anti-inflammatory cytokines is considered to play an important role in disease progression [9].

MS effective therapy doesn't exist at present. Treatment of the disease depends on elevating symptoms and also modification in the disorder development. IFN-γ, glucocorticosteroids and glatiramer acetate is being used. Many experimental therapies, which may appear to be very promising in future, exist. For example low dose naltrexone (LDN) therapy is effective, however not accepted due to the unknown mechanism of treatment.

Colitis

Colitis is a nonspecific large intestine inflammation. Usually it refers to inflammation of colon, caecum and rectum mucosa. Typical symptoms are the loss of weight, diarrhoea, strong stomach aches and blood in faeces. In disease aetiology genetic predispositions as well as environmental factors play a crucial role. The highest prevalence of ulcerative colitis is observed in Europe (24,3 per 100 in North America (19,2 per 100 000 person) and Asia an Middle West (6,3 per 100 000 person) [11]. *Colitis* is caused by long-term immune cells activity in intestine mucosa, resulting in inflammation and tissue damage. Among healthy individuals in colon permanent low inflammation is observed. It is regulated by balance between pro- (TNF-α, IFN-γ, IL-1, IL-6, IL-12) and anti-inflammatory (IL-4, IL-10, IL-14) cytokines [12]. Among *colitis* patients imbalance between Th1 and Th2 response is observed. The Th1 lymphocyte

response is crucial in Inflammatory Bowel Disease (IBD) development. Cells isolated from *colitis* patients' colon produce large amounts of IFN-γ and TNF-α, but very low IL-4 and IL-10 [13].

Animal models are widely used to researches over *colitis*. Disease is induced by chemicals administration (most often 2,4,6-trinitrobenzene-sulfonic acid or dextran sulfate sodium) or with use of transgenic animals with regulation factors production defect [14]. The inflammation occurrence is associated with tissue damage, resulting in proinflammatory mediators release [15]. During the Th1 response IL-12 and other cytokines level noticeably rises. Ongoing inflammation successfully inhibits production of regulatory cytokines, like TGF-β or IL-10, and also suppress Th2 response. In *colitis* model induced by DSS macrophages response leads to strong lymphocyte T activation. Classically activated macrophages produce chemokins, nitric oxide (NO) and other proinflammatory factors, intensifying Th1 response. Producing large amounts of TGF-β lymphocyte subpopulation T-reg is significant in *colitis* down-regulating, but to its differentiation IL-10 production is necessary, which is suppressed during inflammation. Synthesized during *colitis* IL-1 and TNF-α increase NO production by macrophages and fibroblasts. Expression of μ-opioid receptors on leukocytes and glucocorticoids synthesis are increased. Presently many researches are focused on creating new therapy against IBD. Gene therapy and those related to cytokines are under considerations [12]. Inhibition of lymphocyte T activation by cluster of differentiation 40L (CD40L) receptor blockade is another possible treatment, but still need a lot of studies [12]. Unfortunately, all of the above listed and used therapies have significant side effects.

Helminths as inhibitors of inflammation

Helminth infection can alter the host immune system, what can change the disease progress surprisingly having an protective effect on the host. As many other parasites nematodes can also induce regulatory mechanisms, that down-modulates immune cells activity also during autoimmune disease [16]. In 2003 a new edition of hygiene hypothesis called "the old friends hypothesis" was presented [17]. During million years of evolution human beings were more frequently exposed to the environment rich in harmless organisms, like microbiota in food and water, which successfully had been colonizing human bodies. So, due to impact on immunomodulation 'the old friends' might have become a physiological necessity to the host. The lack of an early exposition to these organisms can lead to a failure of acute response termination, and in consequence to chronic inflammatory disorders [17]. It seems that during evolution of the host-parasites' relationship, a regulatory response replaced aggressive damaging response. It is observable for specified and long evolutionary host-parasite relationship that harmful immune response does not appear. In that process crucial role plays maturation of dendritic cells to drive Treg and Th2 effector cells response [17].

What is important to note, pathogens (including helminths) can induce diversity in MHC genes [18]. Parasites have also influence on diversity in interleukin genes polymorphism – the selective pressure is stronger than made by bacteria, fungi or viruses what was recognized by comparison of pathogen richness and interleukin gene polymorphism in 52 human population occurrence in specified world areas. It might be associated with higher autoimmune diseases prevalence, especially in case of IBD [19]. Research over the gastrointestinal helminth-mediated balancing selection on MHC genes is conducted and compared in many vertebrate species, also from evolutionary point of interest [20].

Epidemiological data clearly shows negative correlation between the occurrence of autoimmune diseases and parasitoses. It was also proven that helminth infection can have beneficial effect on patients with autoimmune disease, causing inflammation down-regulation and symptoms reduction [21]. In 2007, Correale and Farez [22] described a long-term study describing changes in MS development among patients infected with nematodes. During almost 5 years long observation, they compared disease progress and changes in immunological response in MS patients infected with several species of nematodes and MS patients without parasites. After helminth infection significant reduction in relapse, new lesions and disability accumulation in infected MS patients were noticed. The cytokine pattern in those patients was related to Th-2 response more than pro-inflammatory Th-1 response – the one characteristic for the disease. Protection driven by parasite was also associated with T regulatory lymphocytes and production of having suppressive function

regulatory cytokines (IL-10 and TGF-β). In the same study induction of B regulatory cells producing IL-10 in MS patients after parasite infection was demonstrated. Few years later, in 2011 Correale and Farez [23] described a great increase in MS activity after anti-helminth treatment of infected patients. What should be emphasized is very fast disease progress after nematode removal – new inflammatory brains' lesions were observed during 3 months post treatment. MS course in those patients after 6 months was very similar to non-helminth control patients'. That clearly shows how beneficial nematode infection can be for MS patients. Since than many scientist, started to consider helminth infection as alternative therapy for MS patients. In many nematode infections an inhibition of inflammation is observed. *Trichuris suis* or *Necator americanus* infections effectively reduce inflammation in autoimmune diseases like Inflammatory Bowel Disease (IBD) or MS [24].

The animal model research

To investigate helminth' immunomodulatory mechanisms animal models are used. Several helminth laboratory infections are used as a model for human disorders e.g. living in the digestive system (*Heligmosomoides polygyrus*) [25], in the tissue (*Trichinella spiralis*) or blood and lymph nodes (*Acanthocheilonema viteae*) [26].

When the hygiene hypothesis was proposed, scientists assumed that the inhibition of auto-immune disease is associated with Th2-mediated immune response against parasite, what down-mediated inflammatory Th1-response. The change in Th1/Th2 balance was suspected to be a reason of more common autoimmune disease prevalence. It did not match studies over allergies, where symptoms were also inhibited during helminth infection [27]. More recently the crucial role of Treg cells and alternatively activated macrophages has expanded the paradigm – regulatory response not only suppress the disease but also is involved in tissue repair. That hypothesis was well documented [28], e.g. with use one of the best model for immunomodulation studies – *H. polygyrus*, the nematode which penetrate mucosal layer of the small intestine [29]. In many experiments of autoimmune diseases animal models, especially IBD, helminth infection causes recalling the disease symptoms. In mice affected with DSS-induced *colitis H. polygyrus* infection caused lowering of disease symptoms, also through an endogenous opioid system. Those changes were present 6 days post infection, and the mechanism related on the endogenous opioids, especially on local β-endorphin production by leukocytes [29]. The same nematode alters peripheral immune response by reducing inflammation in the nervous tissue from 3rd day post infection when larvae L4 dwelled in the muscular layer of the small intestine. Despite recent findings, data suggest that mechanism of reduced inflammation is much more complicated than suspected. In earlier studies higher IL-10 production in this process appeared, but *Trichuris muris* or *H. polygyrus* inhibited development of *colitis* even in IL-10 mice [30].

As a result of above intriguing observations and studies over other autoimmune disease many scientists got interest in the inhibition of central nervous system (CNS) inflammation during helminth infections. Interestingly, the treatment of mice with *Schistosoma mansoni* eggs was protective, and both dead and alive *S. mansoni* eggs inhibited MS and EAE in animal model [16,31]. S. *mansoni* in both CNS and spleen cells decreased Th1 response reducing pro-inflammatory IL-12, IFN-γ and TNF-α cytokine production, the same time promoting regulatory cytokine e.g. TGF-β, IL-10, IL-4 production associated with Th2 and Treg response. Even *S. mansoni* ova pretreatment reduces the EAE symptoms in animal model. In this process IL-10 production was risen and IL-12 production was lowered by mechanism associated with Toll-like receptors (TLR), TLR 2. Results of mentioned work were confirmed by *in vitro* research with dendritic cells (DC) stimulation with *S. mansoni* ova antigen [32]. Other parasites which reduce or prevent EAE are *Trypanosoma cruzi*, *T. spiralis* and *H. polygyrus* [33,34]. In *H. polygyrus* infection both larvae and adult worms inhibited ongoing inflammation during EAE however by different mechanisms [29].

In spite of prominent Th2 and Treg response during infection, the inhibition of chronic inflammation is not a common feature for all helminth species. Many parasite-driven mechanism involved in inflammation reduction still remains unclear. Cells of innate response and epithelia may play a crucial role in immune modulation. The example is based on the studies with tapeworms when infection with the parasite ended in strong inflammatory response in the host and exacerbate inflammation. During *Hymenolepis diminuta*

infection *colitis* severity was reduced only after dinitrobenzene sulfonic acid (DNBS)-induction but not in *colitis* other animal model – induced by oxazolone with mechanism involving IL-5 and eosinophils [35].

Clinical studies

Nowadays the 3rd phase, the most advanced, studies over IBD therapy with *T. suis* use were conducted in Australia and Europe. First clinical trials of parasite infection as a therapy were accomplished for IBD (for example Crohn's disease) treatment. In one of them the patients knew they received nematodes, they were given 2500 *T. suis* embryonated ova. Carried out observations proved beneficial role of helminth infection and symptoms weakening [36]. In another trial greater number of patients received *T. suis* ova every 3 weeks during 24 weeks period. Almost in 80% of cases symptoms reduction was observed. In 3rd trial with placebo- receiving group of patients, during 12 weeks period IBD patients were given or 2500 *T. suis* ova or placebo every 2nd week, it was proven that the parasite significantly reduced symptoms [37].

During last 5 years few publications appeared, describing 1 phase study about probiotic helminth administration in MS patients. Most often *T. suis* ova antigen was used. What important to note, patients' well tolerated TSO. In 3 out of 4 patients TSO administration altered MS course, down-regulating inflammation and alleviating MS symptoms. Immunomodulatory effect correlation with Th1 response decrees was suggested. Also, differences in CD4+ and CD8+ count were observed in MS patients after TSO administration. Although the results were really promising, that alternative therapy immune regulation mechanism is not clear [24,38]. Although the described treatments were quite safe, they seemed beneficial only in a few cases [39,40]. Placebo-controlled trial in asthma was conducted by Feary et al. [41] with use of *N. americanus* infection. Despite promising results in earlier study, they observed insignificant beneficial impact of hookworm infection on patients' bronchial hyperresponsiveness. Even during larvae migration through skin and lungs asthma symptoms exacerbation does not appear.

Despite all studies over using helminth infections as a therapy, there are still a lot of doubts related to safety and ethic – parasites can induce also a pathological response causing great damage in the hosts' tissue.

Parasite driven molecules

In earlier studies, Harnett et al. [42], focused on finding a molecule responsible for the helminth ability of immunomodulation. They managed to do it in 1990s with a protein secreted by *Acanthochei - lonema vitae* called ES 62. The excretory-secretory protein of 63 kDa is a tetrameric glycoprotein with a phosphorylocholine (PC) moieties. The protein is beneficial in some allergies and autoimmune diseases like rheumatoid arthritis. Influence of ES 62 on disease inhibition is associated with PC moiety – it was confirmed in experiments with use of ES 62 without PC, which did not caused any changes in disease development. PC is expressed by a wide range of organisms like bacteria, fungi and of course nematodes; it is recognized by an immune system as a pathogen associated molecule pattern (PAMP). ES 62 alters proliferation of B cells, lowering IL-17 and IFN-γ production and immune response polarization towards anti-inflammatory and proregulatory phenotype by antigen presenting cells both dendritic cells and macrophages. Modulatory effects of ES 62 are highly dependent on TLR, especially TLR4. Damping of Th1 response by ES 62 was not associated with induction of corresponding Th2-associated response or induction of Treg. That is the reason why it is not beneficial in every autoimmune disease. The beneficial effect seems to be related to down-regulation of signalling enzyme – protein kinase C (PCK) – α. It is down-regulated in mast cells (causing internalization and non-proteosomal degranulation) and in B cells (altering their proliferation) [43]. ES 62 has an important potential but it is also quite big molecule causing immunogenic reaction and it should not be used as a drug. Inspired by ES 62, Al-Riyami et al. [44], presented their study over small molecule analogues (SMA) with PC moiety. In their *in vitro* study one of SMA exhibited immunomodulatory functions similar to those caused by ES 62, but with higher specificity and not immunogenic. A lot of work and studies still remains to be done, but it proves a further perspectives of helminth-driven molecules in medicine. Is seems probable that the beneficial impact on inhibited inflammation is associated with the cumulative effect of molecules revealed by parasite during infection [45,46].

ES-62 was the first discovered parasite driven

molecule effective as autoimmune disease treatment. Nowadays research over parasite driven molecules are more advanced, and new proteins were postulated as possible immunomodulators. For example, trematode antigens – *Schistosoma mansoni* soluble worm antigen (SWA) and *S.* soluble egg antigen (SEA) – prevent type 1 diabetes [47]. Both *Trichinella spiralis* soluble antigen and *Trichuris suis* soluble antigen pretreatement change EAE clinical course to less sevear [48]. The topic is very interesting and in the future research over the parasite driven molecules can contribute to proper autoimmune diseases' treatment.

Conclusions

All previously quoted studies and many epidemiological observations suggest that low-grade parasitism can be beneficial for autoimmune diseases, and may be in future used as a therapy. There is still a danger of harmful influence of parasite to the host's organism and Th2 polarization is thought to be beneficial in all inflammatory diseases but in some circumstances can cause pathology. Parasite infection is toxic because of radical species overproduction and pathological condition for host organism – that is why in many cases side effects can be observed: like anaemia, stomach aches or protein deficiency. There are also publications investigating changes in leukocytes proliferation and apoptosis as a result of helminth infection [49]. Because of those changes in hosts' cell function and physiology, can increase possibility of oncogenic transformation. Excretory-secretory products of many helminths were proven to promote tumour activity [50].

There is no doubt in necessity of further investigations, carefully designed studies over safety and mechanism of parasite influence should be conducted. There is a great need to conduct research on animal models of the diseases to look for parasite-driven molecules. It allows to prevent dangerous side effects of autoimmune disease treatment with parasite infection, without risking patients' health.

Animal models are not perfect as a representation of human autoimmune diseases, but they allow to examine potential therapies' mechanisms deeper than it would be possible on patients. Use of many invasive techniques, needed to examine changes in nervous tissue during EAE, are nescessary before any kind of treatment can be considered as safe and effective. Also research conducted on animal inbred strains allows scientists receive more reliable conclusions, reducing the risk for human health.

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