

# Are Helminths to be Trusted as Allies in the War against Autoimmunity and Chronic Inflammation?

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Experimental data obtained through new high-throughput techniques and big data analysis have provided a better understanding of the mechanisms leading to the onset of autoimmune disease, as well as the perpetuation of chronic inflammation. While infections and autoimmunity have been linked for decades, the role of microorganisms and parasites has not been definitively established since infections may act as triggers of autoimmune diseases in predisposed subjects [1-4] or, as proposed by the hygiene hypothesis, as protective agents towards the development of autoimmunity [5,6]. In recent decades the prevalence of autoimmunity has increased dramatically in Western countries, likely secondary to the growing awareness among physicians and an easier access to diagnosis (as in the case of disease-specific serum autoantibodies [7]), but the decrease in infection rates could be responsible for the rapidly increasing burden of chronic inflammatory conditions [8].

Beyond geoepidemiology, the evidence in support of the infection-autoimmunity link is seen in subjects living in a region of Northern Europe shared between Russia and Finland, where people living in the Finnish part of the region manifested a higher rate of autoimmune disease, while the Russian population was more likely to have infections [9,10]. In general terms, the link has been considered a one-way street, with infectious agents triggering or perpetuating inflammation, until this dogma was shattered by the enormous amount of data in support of the modulatory effect of the microbiota [11-13]. Indeed, bacteria and parasites could act as immunomodulatory organisms and shift the immune response towards regulatory pathways [9]. Based on these findings, manipulation of the microorganisms and parasites that live in conjunction with cells on our skin and mucosa represents an area of growing interest for many autoimmune diseases [14]. Helminths represent a fascinating area of research since, different from the majority

of infectious agents, their purpose is to coexist and thrive with rather than kill the host. Therefore, they try to induce a tolerable scenario [15]. Several mechanisms are involved in this immune response, such as switching the immune reaction from Th1 to Th2, changing the secreted cytokines toward interleukin (IL)-10, increasing the amount of T regulatory cells, and more recently identifying the suppression of Th17 and release of biologically active excretory-secretory antigens that directly modulate host immune function [6,9,15]. Thus, helminthic supplementation is gaining much interest as a therapeutic tool, and researchers are enthusiastic to explore its role in autoimmunity, as suggested by the increasing number of studies [16].

The road of helminthic therapies began in the 1990s, when these organisms were used as therapeutic agents in experimental models and clinical studies of several immune-mediated conditions, including inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, type 1 diabetes, celiac disease, Graves' disease and psoriasis [15]. Various species of helminths and different approaches were evaluated, including colonization by helminth larvae, oral administration of helminth ova, and the use of helminth-derived antigens. So far, in small clinical trials the ova treatments appear to be successful and safe for patients with inflammatory bowel disease and multiple sclerosis [17-19].

However, the benefit was not shown to be specific to single helminth species, and special interest has grown around the immunomodulatory molecules released by the parasites into the host environment [20], mainly phosphorylcholine-moiety glycoproteins [21]. Phosphorylcholine can be found in a wide range of bacterial infections, like *Streptococcus pneumoniae* and *Haemophilus influenzae*, and it is secreted by filarial nematodes. Phosphorylcholine mediates the regulation of adherence to cells, encountering the host's innate immune system and adaptive immune system, and in the regulation of cell growth.

Currently, as new methods are emerging and technology has improved, synthetic small molecules are available. Researchers developed the synthetic molecule tuftsin-phosphorylcholine (TPC) consisting of phosphorylcholine and tuftsin, considered to be a "natural adjuvant," already used in vaccines, that stimulates phagocytic activity, increases migration and activation of macrophages, and enhances chemotaxis of monocytes [22,23].

This small molecule has been shown in a mouse model of colitis to reduce its severity in all observed manifestations, including weight loss, intestinal bleeding, colonic length, and histological damage, resulting in improved survival [24]. Moreover, in genetically lupus-prone mice it ameliorated various manifestations of the disease, especially kidney disease, with a reduction in glomerular immune-complex deposition, less severe inflammatory response and reduced kidney damage, followed by delayed onset of proteinuria and improved survival. Interestingly, serum anti-dsDNA antibody titers did not vary with treatment [25]. Finally, TPC has been evaluated also in a collagen-induced arthritis mouse model, showing promising results in both subcutaneous and orally treated groups: TPC-treated mice had a significantly lower arthritis score, reduced histological modifications, decreased titers of circulating collagen II antibodies, reduced pro-inflammatory cytokines and increased anti-inflammatory cytokine expression, as well as expansion of Treg and Breg cells [26]. Interestingly, tuftsin or phosphorylcholine by themselves had a moderate effect on disease progression. It has been hypothesized that the clinical efficacy of TPC may be attributed to its potential to reduce pro-inflammatory cytokine production, such as interferon-gamma and IL-17, and to significantly increase the anti-inflammatory cytokine profile, such as transforming growth factor-beta and IL-10 [26]. Advantages of TPC and other small molecules include the possibility of both subcutaneous and oral administration. It could serve as treatment and prophylaxis for diverse autoimmune conditions, especially at early stages with minimal adverse effects.

In conclusion, there is an urgent need for new therapies for autoimmune diseases that can modify disease progression with an optimal safety profile, especially in patients who have high unmet medical needs, like tumor necrosis factor-alpha inhibitor refractory rheumatoid arthritis or psoriasis, multiple sclerosis or severe inflammatory bowel disease, or orphan diseases for which no therapies exist. Helminth-derived immunomodulatory therapies could serve as potential treatment for these patients, and we await the human data that are needed to ensure a good safety profile of such approaches.

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**"We make a living by what we get, but we make a life by what we give"**

Winston Churchill