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Atherosclerosis and Helminths Infection

Shi-Wei Shen, Yun Lu, Feng Li, Zhen-Hai Shen,
Ming Xu, Wei-Feng Yao, Hua-Jin Qi, Ling Zhou,
Yin-Bo Feng, Ling Wang, Jing-Ting Yun and
Da-Xin Tong

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Abstract

Atherosclerosis is a chronic disease that causes various cardiovascular complications. Plaque formation in atherosclerosis is considered similar to the pathogenesis of other autoimmune diseases; thus, immunomodulation and immunosuppression may present strategies for the treatment and prevention of these diseases. Interestingly helminth infection was found to inhibit T helper 1-mediated autoimmune diseases and T helper 2-mediated allergy and asthma, indicating significant potential for clinical application. Some study even found that therapeutic efficacy of the viable tapeworm was superior to dexamethasone treatment. Recently, some studies have shown an inverse association between helminth infections and inflammatory diseases, including diabetes mellitus, lipid abnormality, and atherosclerosis. Will the underlying mechanism bring us a new idea on the treatment for these diseases? We tried to find an answer by reviewing recent articles.

Keywords: previous helminth infection, cardiovascular diseases risk factors, negative regulation of immune response

1. Introduction

Atherosclerosis is a chronic disease that causes artery walls to thicken and become less elastic. The consequent restriction of blood flow can cause various problems such as heart attacks, stroke, renal failure, and other serious cardiovascular complications. In general, the susceptibility to atherosclerosis depends on diabetes, hypertension, high cholesterol, hyperhomocys-

teinemia, genetic factors, diet, smoking, and lack of exercise. In addition, some studies consider that inflammation and immunity are central to atherosclerosis onset [1, 2].

Interestingly, helminths infection is regarded not only as an infectious disease but also as an immunological disease. Helminth antigen has been shown to induce metabonomic changes and to mediate the host autoimmune response [3].

Helminth infection was also found to inhibit T helper 1 (Th1)-mediated autoimmune diseases and T helper 2 (Th2)-mediated allergy and asthma, indicating a significant potential for clinical application [4–10].

Some study even found that therapeutic efficacy of the viable tapeworm was superior to dexamethasone treatment [6].

Will the recent findings of the underlying mechanism on the inverse association between helminth infections and inflammatory diseases, including diabetes mellitus, lipid abnormality, and atherosclerosis, bring us a new idea on the treatment for these diseases? Now, let us go and review these interesting studies.

2. The relationship between helminth infections and diabetes mellitus

Diabetes is a chronic metabolic disease. It is characterized by elevated blood glucose levels caused by insufficient insulin production from β -islet cells of the pancreas, or impaired insulin sensitivity of insulin target organs. The number of people with diabetes mellitus is increasing worldwide. As reported by International Diabetes Federation, around 387 million people were living with diabetes in 2014. It is predicted that in 2035 up to 592 million will suffer from diabetes. At present, diabetes mellitus has been found in 8.3% of adults, and China is a major site of this rapidly emerging epidemic.

Inflammatory immune responses play a crucial role in the progression of β -islet cell destruction in both type 1 (T1D) and type 2 diabetes (T2D). As shown above, a strong predictor for the development of type 2 diabetes mellitus (T2D) is insulin resistance. Inflammation and altered innate immunity have also been implicated in the pathogenesis of diabetes through insulin resistance.

Conversely, helminth infections are well known to affect the metabolic profiles and risk of diabetes by inducing type 2 and anti-inflammatory immune responses that are able to modulate the activity of the innate immune response [11, 12].

Both experimental and epidemiological studies reported such a beneficial impact of helminth infections on T1D and more recently on T2D.

Schramm et al. [13] have shown that *Schistosoma mansoni* infections can adopt an immune evasion strategy by inducing regulatory T cells, which in turn may decrease systemic inflammation and the development of inflammatory diseases, including diabetes.

Paola et al. [14] found infection with *S. mansoni* or exposure to eggs from this helminth inhibits the development of type 1 diabetes in NOD mice. The host responses normally induced by

infection with *S. mansoni* or exposure to its antigens enable peripheral tolerance to β -cell antigens. Effects on the innate immune system may therefore deviate T-cell responses to the pancreatic beta cell towards a benign Th2 response but also influence the development of regulatory T cells.

Hussaarts [15] found that chronic helminth infection and helminth-derived molecules protect against metabolic disorders by promoting the Th2 response, eosinophilia, and WAT M2 polarization. Helminth parasites are the strongest natural inducers of type 2 immune responses, and short-lived infection with rodent nematodes was reported to improve glucose tolerance in obese mice. That is to say, chronic helminth infection and helminth-derived egg antigens promote adipose tissue M2 macrophages and improve insulin sensitivity in obese mice.

A cross-sectional study has been conducted on the basis of human being, in Jiading, a suburb of Shanghai [16]; it reported that previous helminth infection might reduce the prevalence of diabetes and metabolic syndrome.

Apparently, helminths infection can also reduce energy intake and thereby change the energy balance, which may be another beneficial in terms of insulin resistance [17].

At a molecular level, mTOR, a serine/threonine protein kinase, which is located downstream of insulin signaling, plays an essential role in immune cell energy metabolism and function [18]. Moreover, it has been shown that STAT6 signaling downstream of IL-4, as well as Th2 responses induced by helminths, has the capacity to improve glucose metabolism and insulin signaling [19].

In humans, immune intervention with IL-1 receptor antagonist (Anakinra) has also been shown to influence glucose metabolism [20].

A recent study by Locksley and colleagues [3] has demonstrated elegantly that helminth-induced adipose tissue eosinophilia enhanced glucose tolerance and improved insulin resistance in mice fed a high-fat diet. Moreover, although the parasite was cleared after 8 days, metabolic response was sustained.

Both epidemiological and experimental studies indicate that helminths may be able to ameliorate obesity-induced insulin resistance. The ongoing SUGARSPIN trial investigates the association of helminth infections with insulin sensitivity and the effect of anti-helminth treatment on insulin sensitivity in Indonesia, which will help to further decipher the impact of helminth infection on glucose homeostasis [21].

Type 2 and regulatory immune responses induced by helminths accompanied by increases in alternatively activated macrophages, anti-inflammatory cytokines and regulatory T cells present possible protective mechanisms to attenuate autoimmune responses in diet-induced insulin resistance in T2D and T1D. In addition to infections with living helminths, administrations of helminth-derived products have also played a role in protecting against both T1D and T2D in animal models. Hence, helminths and their products may provide new treatment strategies for diabetes [22].

3. The relationship between helminth infections and lipid abnormalities

Generally, dyslipidemia characterized by hypertriglyceridemia and low HDL-C is called “atherogenic dyslipidemia.” This disorder may increase the concentration of triglyceride-rich lipoprotein (TRL) and its remnants, accelerate the inflammatory reaction in the arterial wall, and aggravate the damage to endothelial cells [23]. Elevated TRL may result in an increase in small, dense LDL (sdLDL), which exerts a strong atherogenic action, and in a reduction in HDL-C, which is involved in reverse cholesterol transport [24]. Moreover, TRL remnants are deposited in the arterial wall, thereby promoting atherosclerosis [25]. Recently, this dyslipidemia was identified as a residual cardiovascular risk factor following the reduction in LDL-C by statin treatment [26]. Dyslipidemia has also been found in patients with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) [27].

Stanley [28] provide an evidence that the serum cholesterol-lowering effect is mediated by factors released from *S. mansoni* eggs and that high levels of lipids, particularly triacylglycerols and cholesteryl esters, present in the uninfected livers of both random-bred and apoE(-/-) mice fed a high-fat diet were not present in livers of the helminth-infected mice.

Our studies also indicate that the potential long-term effects of previous helminth infection may improve the blood lipid metabolism (reduction in TG and elevation of HDL-C) and reduce the atherogenic index of plasma [29–31]. Another study also found significantly lower plasma lipid levels in children (aged 7–13 years) infected with *Schistosoma haematobium* compared with controls ($p < 0.01$) (<http://www.pakmedinet.com>). Recent studies in rural Indonesia showed that intestinal helminth infections were negatively associated with lipid levels [4, 32–35].

Magen et al. [36] reported in an autopsy study that *Opisthorchis felineus* chronic helminthic infections was found to be associated with lower serum total cholesterol levels and a significant attenuation of atherosclerosis.

One of the possible mechanisms of helminth anti-atherosclerotic action might be a disorder in the liver function after helminth infection, resulted in a decrease in the synthetic ability of the liver, which reduce its production of cholesterol.

Another mechanism of lipid lowering in the host might be a direct uptake of lipids by flat worms or as an alteration in the uptake of lipids by the host. Parasites are able to remodel host lipids for their growth [37]. They have developed unique metabolic pathways that allow them to survive and multiply by scavenging nutrients from the host [38].

Additionally, immune modulation causing Th2 polarization can change lipid metabolism; total plasma cholesterol levels were found to be increased in Th1 polarized, IL-4-deficient or STAT-6-deficient mice [39, 40].

4. The relationship between helminth infections and atherosclerosis

Plaque formation in atherosclerosis is considered similar to the pathogenesis of other autoimmune diseases; thus, immunomodulation and immunosuppression may present strategies for the treatment and prevention of these diseases [41].

Parasitic helminths have coexisted with human beings throughout time. Success in eradicating helminths has limited helminth-induced morbidity and mortality but is also correlated with increasing rates of “Western” diseases, including atherosclerosis [42].

The immune response induced by helminth infection is an important host defense mechanism against pathogens. Specific immune pathways, such as modified type-2 responses, induced by helminthes have been implicated in protective host responses to homeostatic perturbations, such as metabolic dysfunction and atherosclerosis [43].

A preventive injection of soluble egg antigen (SEA) of *S. japonicum* to ApoE/mice has also displayed anti-atherosclerosis activity by increasing the proportion of CD4+CD25+ regulatory T (Treg) cells and inhibiting inflammatory cytokine production in the early stage of the disease [44]. This alleviated the immunopathological injury to the host liver and directly inhibited the host immune response to infections, which help the antigen escape from host immunity [45]. Treg cells exert an immunosuppressive function which is very important in the maintenance of immune homeostases and immune tolerance [46].

Subramanian et al. [47] also reported that the immune system can develop resistance to atherosclerotic lesions and the anti-inflammatory T-cell effect produced by the immune system may help inhibit the progression of atherosclerosis. Helminth antigens have been found to induce metabonomic alterations and mediate the host immune response, which produce a strong anti-inflammatory response to help suppress the development of arteriosclerosis in mice.

A negative correlation between a helminth, *Schistosoma* infection, and the risk of cardiovascular disease has been reported both in the past and at present [31, 48]. Helminths are eukaryotic parasitic worms, which induce a Th2 response and alternatively activate macrophages that are crucial for host survival. After *S. mansoni* infection, a higher expression of alternative macrophage markers is observed [49]. The *S. mansoni*-derived soluble egg antigens (SEA) have been reported as new modulators of the macrophage phenotype in vivo [50]. Indeed, plaque size of LDLR^{-/-} mice reduced after SEA treatment, with the reduction in cholesterol content in lesion, decreased expression of inflammatory markers [51].

The dendritic cells (DCs) are able to prime strong Th2 responses that indicated these cells are also an attractive target for therapeutic manipulation of the immune system in the context of metabolic disorders. As DCs have the capacity of regulating a wide array of T-cell responses, they are widely studied as targets for development of vaccines and immunotherapies [52–54]. Therapeutic manipulation of DCs might also provide a new strategy for targeted treatment of atherosclerosis [55].

Further studies to investigate the exact mechanisms underlying immunomodulation and immunosuppression in previous helminth infection and the likelihood of schistosomiasis vaccines to inhibit atherosclerosis development seem justified.

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Author details

Shi-Wei Shen^{1,4}, Yun Lu^{2,4}, Feng Li^{2,4}, Zhen-Hai Shen^{2,4*}, Ming Xu³, Wei-Feng Yao¹, Hua-Jin Qi², Ling Zhou², Yin-Bo Feng², Ling Wang², Jing-Ting Yun² and Da-Xin Tong²

*Address all correspondence to: shentaihu@126.com

1 Wuxi No. 2 People's Hospital Affiliated to Nanjing Medical University, Wuxi, Jiangsu, China

2 Jiangsu Provincial Taihu Cadre's Sanatorium of Jiangsu Provincial People's Hospital Group, Wuxi, Jiangsu, China

3 Jiangsu Institute of Parasitic Diseases, Wuxi, Jiangsu, China

4 Co-first authors.

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