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Mini Review

Can Allergic Disorders Decrease the Risk of Thromboembolic Events in Atherosclerosis? an Evidence-based Review

Ahmad Karkhah[1, 2*], Ebrahim Zabihi[1], Forough Ebrahimtabar[2], Tahereh Babajani Roshan[2]

1. Cellular and Molecular Biology Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran.

2. Student Research Committee, Babol University of Medical Sciences, Babol, Iran.

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Atherosclerosis is a complex inflammatory disorder of the medium and large-sized arteries. Recent experiments demonstrated that atherosclerosis is a Th1 dominant autoimmune condition, whereas Th2 cells are rarely detected within the atherosclerotic lesions. Several studies have indicated that Th2 type cytokines could be effective in the reduction and stabilization of atherosclerotic plaque. Therefore, modulation of the adaptive immune response by shifting immune responses toward Th2 cells could represent a promising approach to prevent from progression and thromboembolic events in coronary artery disease. Since Th2-mediated immune response is mostly implicated in asthma and most allergic disorders, this evidence-based review will discuss how asthma and other Th2-mediated allergic disorders can decrease the risk of thromboembolic events in atherosclerotic patients with focus on the suggested immune mechanisms.

Keywords: Atherosclerosis, allergic disorders, Th1/Th2 balance, atheroprotection

Atherosclerosis is an autoimmune disorder of arterial wall characterized by the formation of inflammatory lesions, which consist of many components of innate and adaptive immune systems including infiltrating T cells, macrophages, smooth muscles, cytokines, growth factors, and other pro-inflammatory mediators (1-2). According to the World Health Organization (WHO) reports, coronary atherosclerosis disease is the first cause of death in the world (3). Atherosclerosis has traditionally been assumed as a simple deposition of lipids within the walls of the medium and large-sized arteries. It is now considered as a complex endothelial dysfunction induced by various risk factors such as elevated and modified low-density lipoproteins (LDL), free radicals, infectious microorganisms, hypertension and smoking (4-5). These risk factors increase oxidative stress in vascular cells and intensify the upregulation of cellular adhesion molecules expression, which in

*Correspondence: Cellular and Molecular Biology Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran. E-mail: ahmadkarkhah@ymail.com

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turn facilitate the adherence and infiltration of leukocytes to the dysfunctional endothelium and subsequently into the arterial wall (6). In this review we considered the inflammatory aspect of atherosclerosis development.

Adaptive T cell immunity and atherosclerosis

Accumulated evidence have revealed a potential role for T helper (Th) cells in the progression of the atherosclerotic plaque (7). Th cells are usually classified functionally into Th1 and Th2 subtypes based on the different patterns in cytokine production. Although both Th1 and Th2 cellular immune responses are responsible for different types of protection in human body, dysregulation in homeostasis of Th1/Th2 activity leads to several immunopathological disorders such as atherosclerosis (8). In atherosclerosis as a Th1 dominant autoimmune disease, the Th1 cells produce various pro-inflammatory cytokines including IFN-γ, interleukin (IL) 2 and tumor necrosis factor (TNF) which play pivotal roles in the initiation and progression of atherosclerosis (9-10). Several studies demonstrated that pro-inflammatory Th1-related cytokines levels in serum are positively correlated to the severity of atherosclerosis disease. In particular, high circulating levels of IFN-γ and TNF-α are predictors of the incident coronary and cardiovascular events. Interestingly, Th2-mediated immune responses which are rarely detected within the atherosclerotic lesions could strongly neutralize pro-atherogenic and pro-inflammatory effects of Th1- mediated immune response and consequently improve atherosclerosis. Moreover, it is well-established that Th2 type cytokines such as IL-4, IL-5, IL-10 and IL-13 can inhibit the development of atherosclerosis (11-13). Taken together, the modulation of the adaptive immune response by maintaining an immunological balance between Th1 and Th2 immune responses or by shifting immune response properly toward Th2 cells could introduce new therapeutic approaches to prevent or decrease the risk of cardiovascular events in patients with coronary atherosclerotic disease (figure 1).

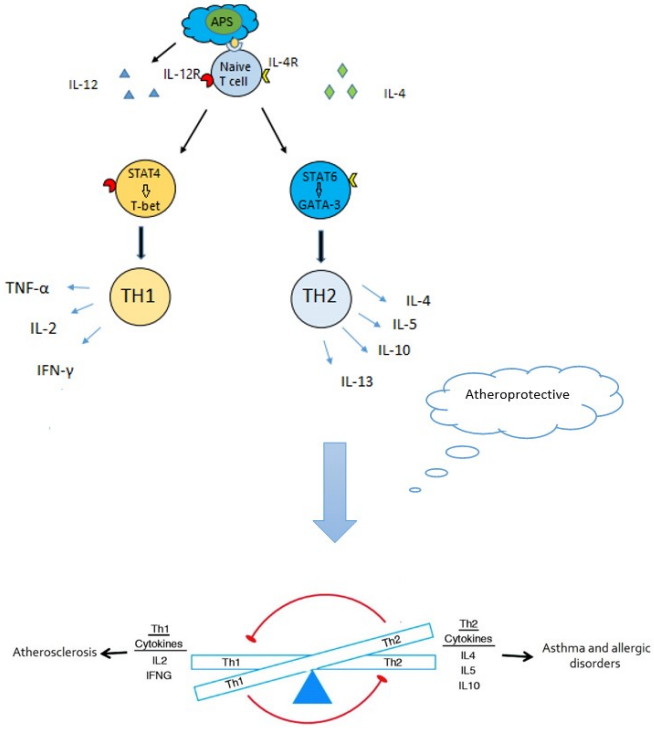

Figure 1. Atherogenic and atheroprotective immune responses.The inflammatory activity in atherosclerotic plaques is dependent on the balance between pro-inflammatory and anti-inflammatory immune responses.

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Allergic disorders as a protective factor in atherosclerosis: a novel immunol-ogical-based hypothesis

In this review, we suggest that asthma and other Th2-mediated allergic disorders can decrease the risk of thromboembolic events in atherosclerotic patients by balancing the Th1 and Th2 immune responses and also their related circulating cytokines (figure 2). Relatively, Th2-mediated immune response could potentiate the inhibition of the development of atherosclerosis and as asthmatic and allergic patients have elevated circulating levels of Th2- related cytokines as well as IL-33 in comparison with non-allergic subjects, this condition could be beneficial in the reduction and stabilization of atherosclerotic plaque. In addition, it is also suggested that the risk of thromboembolic events in healthy subjects without coronary atherosclerosis disease suffering from asthma and allergic disorders might be lower than other people.

Atheroprotective potential of allergic disorders in atherosclerosis: current immune mechanisms

During the last decade, it was suggested that reduced microbial exposure in early life as a result of improved hygiene leads to a Th1/Th2 dichotomy and immunological shift toward a Th2 instead of the Th1 immune response (14). Many investigations confirm that Th2 lymphocytes are presently considered as a central orchestrator in allergic disorders and asthma. Activated Th2 lymphocytes produce various cytokines including IL-4, IL-5, IL-9, IL-10 and IL-13 which are involved in IgE production by B cells, eosinophil activation /recruitment and mucus production (15-16). There are many studies indicating that Th2-related cytokines have both anti-atherogenic and atheroprotective roles and can also inhibit the development of atherosclerosis (10, 17-18). IL-4 is an important Th2-secreted cytokine which is involv-

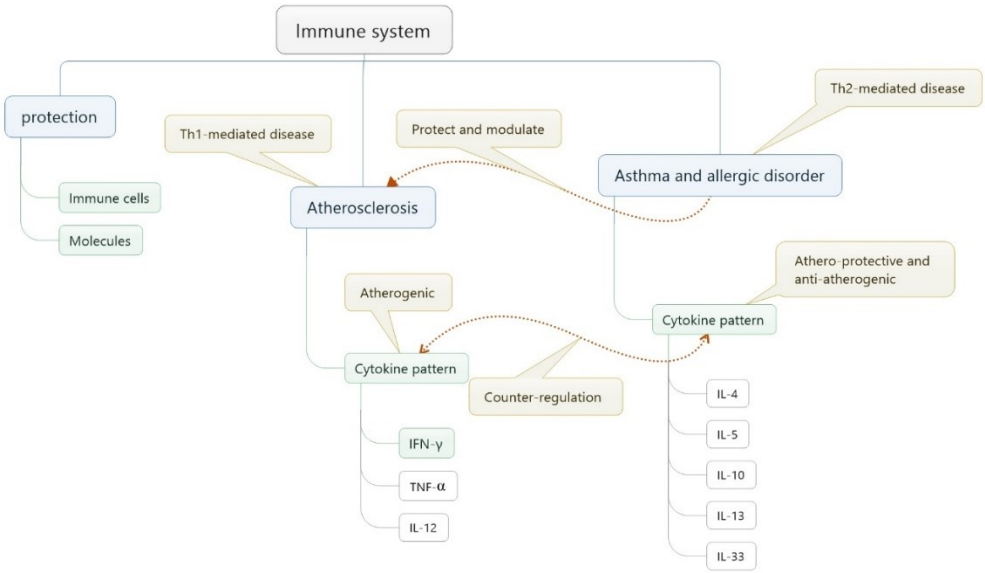

Figure 2. Schematic diagram of related immune mechanisms suggesting atheroprotective potential of asthma and allergic disorders in atherosclerosis.

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ed in Th2 cells differentiation. IL-4 also down regulates the expression of IFN-γ. Some studies have indicated that IFN-γ inhibits cell proliferation of the vascular smooth muscles, reduces collagen production and also upregulates the expression of matrix metalloproteinases (MMPs) leading to thinning and instability of the atherosclerotic plaque (13, 19). Therefore, down regulation of IFN-γ expression by IL-4 may reduce the risk of plaque rupture. In addition, IL-4 inhibits the production of most MMPs from macrophages which have crucial role in digesting the fibrous cap of coronary atherosclerotic plaque and in consequence plaque instability and finally plaque rupture (20-22). In conclusion, high circulating levels of IL-4 in atherosclerotic patients suffering from asthma and other Th2- mediated allergic disorders could down regulate IFN-γ expression and MMPs production which provides more stability in atherosclerotic plaque.

A large body of studies support a substantial anti-inflammatory role for IL-10 in both early and advanced human atherosclerotic plaques. IL-10, mainly secreted by Th2 lymphocytes, is an anti-inflammatory cytokine with potent deactivating properties on both macrophages and T cells (20). IL-10 was reported to downregulate the pro-inflammatory functions of macrophages and also most aspects of their activity including the secretion of matrix degrading enzymes such as MMPs. IL-10 also inhibits many cellular processes which play an important role in plaque progression, rupture and thrombosis including nuclear factor-kB (NF-kB) activation, metalloproteinase production, the synthesis of tissue factor (TF) and the production of thrombin (21, 23-25). Hence, based on mentioned evidence, high circulating levels of IL-10 in asthma and allergic patients could be considered as a preventive factor decreasing the risk of thromboembolic complications in these patients.

Recently, excessive and inappropriate production of IL-33 has been considered to be involved in the development of various disorders such as allergic and asthma diseases. The levels of circulating IL-33 increase in the serum and lung of asthmatic patients in comparison with healthy subjects. Interestingly, Miller et al. have shown that systemic administration of IL-33 reduces the development of atherosclerosis in apolipoprotein E-deficient (ApoE -/-) mice by inducing a Th1 to Th2 shift. They also found that IL-33 significantly increased IL-4, IL-5 and IL-13 levels while interestingly it decreased the level of IFN-γ in serum and lymph node cells of ApoE (-/-) mice (26). Taken together, the high levels of circulating IL-33 in the serum of atherosclerotic patients or healthy subjects having asthma and allergic disorders induce a Th1 to Th2 shift and decrease the level of IFN-γ which both of them have protective and beneficial roles in biology of atherosclerosis.

Discussion

The immunological balance between Th1- and Th2-type immune responses significantly affects the initiation and progression of numerous inflammatory diseases such as atherosclerosis (27). Recent investigations on human and animal models have demonstrated a critical involvement of Th1 immune response in pathogenesis of atherosclerosis (28). Th1 cytokines localize in atherosclerotic plaques of both humans and mice and promote the development of the atherosclerosis (29), whereas, Th2 cytokines are rarely detected within the atherosclerotic lesions (10). Various studies support that Th2-mediated immune response could strongly neutralize pro-atherogenic and pro-inflammatory effects of Th1-mediated immune response and consequently suppress and ameliorate the atherosclerosis-related inflammation. Moreover, it is well-established that Th2-type cytokines could inhibit the development of

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atherosclerosis (11). Therefore, it seems that modulation of the adaptive immune response with a new method which increases Th2-related response or shifts immune response towards Th2 cells could be regarded as a promising approach in prevention and treatment of coronary atherosclerosis disease. In this review, we propose that asthma and other Th2-mediated allergic disorders may be able to protect against atherosclerosis by shifting immune response toward Th2 and also maintaining an immunological balance between Th1 and Th2 immune responses (30). Immune response shifting toward Th2 as a therapeutic option has attracted attentions previously for the treatment of some autoimmune diseases. Similar to asthma and allergic disorders, chronic worm infection is a Th2-mediated disease which in some reports is indicated to have been associated with significant attenuation of atherosclerosis through both lowering lipid levels and directing immune balance toward Th2 cells (31). Mice infected with *Schistosoma mansoni* exhibit reduced atherogenesis through decreased expression of IFN-γ in vessel walls in ApoE -/- mice (32). In addition, chronic helminthic infections or in other words Th2-skewing infections, regulate activation and chemotaxis of monocytes to the site of inflammation and atherosclerotic plaques (33). Several lines of evidence have shown that chronic worm infection downregulates the expression of major histocompatibility complexes (MHC) and adhesion molecules through overexpression of IL-10 (34). IL-10 reduces inflammation at the site of vascular damage and inhibits the development of atherosclerotic plaques. Remarkably, chronic worm infection is associated with more stabilized atherosclerotic plaques which can be attributed to overexpression of IL-10 (33). Therefore, high circulating levels of allergic related cytokines such as IL-4, IL-5, IL-10, IL-13 and also IL-33 in patients with atherosclerotic lesions or healthy subjects suffering from asthma and allergic disorders might be considered as protective factors that decrease the risk of thromboembolic complications.

Finally, if confirmed by experimental data, new therapeutic approaches for immunomodulation and prevention of atherosclerosis may be introduced. For example, if asthma and allergic diseases downregulate the inflammatory condition of atherosclerotic plaques, it may be beneficial to avoid treating mild stages of allergic disorders in children. Because atherosclerotic lesions are formed in early childhood, routine immunosuppressive therapy in mild cases of asthmatic/allergic children would decrease the fine immune modulation towards Th2-mediated responses, leading finally to the development of early atherosclerotic plaques. The use of pills containing genetically modified allergens which can be released in human body and shift immune responses towards Th2 cells could also be considered in the future. Also, allergen therapy by safe allergens for the prevention of atherosclerosis may be considered as a future innovation that may become applicable once atheroprotective effects of asthma and allergic disorders have been proved.

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Conflict of interest

The authors declared no conflict of interest.

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