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Do IgM antibodies protect against atherosclerosis in SLE?

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Abstract

Autoantibodies against end products of lipid peroxidation have unexpected effects on atherosclerosis in systemic lupus erythematosus (SLE).

The discovery of their effects could lead to new theories about the role of the adaptive immune system in SLE.

Systemic lupus erythematosus (SLE) is a disease characterized by the formation of pathogenic autoantibodies. Many of these autoantibodies, such as those specific for double-stranded DNA, SSA/Ro and cardiolipin, are believed to act as markers of disease activity and also contribute directly to disease pathogenesis. Current therapeutic options for SLE are mainly focused on reducing or eliminating pathogenic autoantibody formation, usually through dampening immune responses (glucocorticoids and hydroxychloroquine), nonspecific targeting of immune cells (mycophenolate mofetil), or directly targeting antibody-producing B cells (rituximab and belimumab). Patients with SLE are also known to have a greatly increased risk for cardiovascular disease; however, the exact role of autoantibodies in the pathogenesis of atherosclerosis in SLE is less clear. Rahman *et al.*¹ recently reported that autoantibodies against malondialdehyde (MDA) and phosphorylcholine (PC) are negatively associated with the prevalence of atherosclerotic plaques in patients with SLE.

Although the concept of autoantibody-driven diseases suggests that all auto-anti bodies are inherently pathogenic, accumulating evidence shows that some autoantibodies are, in fact, protective. Inducing autoantibody formation through oral tolerance to self-peptides is known to delay or prevent SLE-like disease in rodents². Translating these successes into treatments for human autoimmunity, however, has proven elusive.

‘Natural’ IgM autoantibodies that arise spontaneously without antigenic or microbial stimuli have also been described. These IgM autoantibodies are present in the circulation from birth,

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Competing interests statement

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recognize oxidized epitopes on lipoproteins and phospholipid-containing cell membranes exposed during the process of apoptosis, and have immunoregulatory functions in cardiovascular disease^{3,4}. Previous data suggest that the induction of these antibodies are not reliant on interactions between B cells and T cells^{5,6}.

Protective IgM autoantibodies, therefore, might be of particular interest in both atherosclerosis and SLE. Increased levels of IgM that recognize modified PC, a component of oxidized LDL, have been reported to correlate with lower disease activity and damage scores, reduced presence of carotid artery plaques, and reduced frequency of cardiovascular events in patients with SLE^{4,7}. The concept of 'protective autoimmunity,' which has been described in diseases of the central nervous system⁸, could also apply to autoimmune diseases. Thus, protective autoantibodies could represent a novel mechanism of 'checks and balances' in autoimmunity.

Indeed, data from the study by Rahman *et al.*¹ suggest that IgM antibodies against PC and the lipid-related epitope MDA seem to protect against atherosclerosis, but that serum anti-MDA antibody levels are negatively associated with SLE. Low levels of IgM anti-MDA were also associated with the presence of atherosclerosis; individuals with SLE in the lowest tertile for anti-MDA IgM levels had a nearly threefold higher adjusted odds ratio for the presence of carotid plaques. This finding complements previous work by the same group that suggested anti-PC antibodies are protective against plaque development in SLE⁷. Similarly, in their current study Rahman *et al.*¹ found that when levels of both anti-MDA and anti-PC antibodies were in the top tertile, patients with SLE were protected against the development of plaques. These findings mirror the group's previous observations that combinations of anti-MDA and anti-PC IgM are negatively associated with stroke risk in the general population and with progression of carotid artery intima-media thickness in patients with hypertension^{9,10}.

Unexpectedly, Rahman *et al.*¹ demonstrated that production of anti-PC and anti-MDA antibodies requires physical interactions between B cells and T cells in a manner dependent on CD40 and MHC class II. Although the kind of T cell help required is unclear, these data suggest the novel hypothesis that protective autoantibodies against potentially harmful endogenous epitopes, such as those created by protein oxidation, could be generated by the adaptive immune system.

IgM anti-MDA and anti-PC antibodies also seem to be involved in the clearance of apoptotic cells. Rahman *et al.*¹ found that anti-PC and anti-MDA antibodies increased macrophage phagocytosis of apoptotic Jurkat cells. This observation confirms previous *in vivo* and *in vitro* work⁶. Given that dysregulation of apoptosis in SLE promotes inflammation, the deficiency of these antibodies in SLE could provide insights into other pathogenic mechanisms. Furthermore, apoptotic cells are known to accumulate in atherosclerotic lesions, and they can further drive plaque formation and inflammation through endothelial cell activation and monocyte recruitment. The oxidized-PC-specific autoantibody E06 has been shown to inhibit this process⁶. Patients with SLE are at high risk of developing atherosclerosis, with the risk in young women with SLE being up to 50 times higher than in their age-matched healthy counterparts. Thus, identification of novel biomarkers for

atherosclerosis, such as low levels of autoantibodies against PC or MDA or other SLE-specific alterations, is essential to identify and treat at-risk patients.

The data presented by Rahman *et al.*¹ suggest new avenues for future research. The aetiology of the decreased levels of IgM anti-MDA and anti-PC antibodies in patients with SLE is unclear. One possibility is that a higher burden of apoptotic cells in patients with SLE leads to increased consumption of anti-PC and anti-MDA autoantibodies. Alternatively, patients with SLE might have an as-yet unidentified primary deficiency that leads to decreased production of these protective autoantibodies. The relationship of IgM anti-MDA and anti-PC antibodies to other potentially pathogenic autoantibodies, such as anti-cardiolipin antibodies, is also unclear. Moreover, the effect of SLE-targeted therapies on anti-PC and anti-MDA antibodies is unknown, particularly for frequently used treatments that specifically target B cells. Finally, the intriguing finding that autoantibodies against mediators of cardiovascular disease are generated by the adaptive immune system (through a mechanism involving T-cell help) suggests that a certain level of ‘protective autoimmunity’ is tolerated in healthy individuals but that this process becomes dysregulated in patients with SLE who have atherosclerosis. Further studies are required to determine the contributions of the adaptive and innate immune systems, the mechanisms of protective autoantibody generation and maintenance, and the effects of current and future therapies on the levels and functionality of protective autoantibodies in SLE.

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