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Editorial

Therapeutic implications of statins beyond lipid lowering: In the perspective of their effects on the antigen presentation, T cells and NKT cells

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Statins are commonly used to lower the cholesterol level by inhibiting an important enzyme, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA), of the mevalonate pathway.[1] In addition, statins affect many cellular and biological processes, including cell proliferation and differentiation, apoptosis, antigen presentation, and immune responses by inhibiting the prenylation of important proteins, including Ras, Rho, and Rab GTPases that are critically important to alter the signaling of important molecules.[2] As a result of their cholesterol-dependent and -independent activities, statins exhibit pleiotropic effects that include anti-inflammatory, antioxidant, immunomodulatory, and anti-thrombotic actions.[1] Given the lipid-independent effect of statins in the inflammation and immunomodulation, it is not surprising that statins may alter T-cell activation through their prenylation inhibitory activity. In addition to monocyte/macrophages, T cells and natural killer T (NKT) cells also play critical roles in the disease progression of atherosclerosis. The plaques from the symptomatic patients have shown the presence of activated T cells.[3,4] By virtue of secreting pro-inflammatory cytokines, T cells perpetuate the inflammation and contribute to the further recruitment of the immune cells into the atherosclerotic plaques.[5] MHC class II and CD1d molecules traffic through the endocytic compartments in order to be loaded with proper ligands. It is critical for the antigen-specific activation of CD4+ T cells and NKT cells.[1] Activated CD4+ T cells and NKT cells secrete huge amounts of pro-inflammatory cytokines that aggravate the severity of atherosclerotic inflammation. Simvastatin has been shown to inhibit the T-cell proliferation and cytokine production by impairing MHC Class II-mediated antigen presentation.[6] This effect of statin on MHC Class II antigen presentation is dependent on its prenylation inhibitory activity. Earlier studies showed that the depletion of the isoprenoid pool using a specific inhibitor of HMG-CoA resulted in the regulation of T-cell migration.[7] By inhibiting T-cell activation, statins can alleviate the inflammation in atherosclerotic plaques through its lipid-independent effect. NKT cells comprise a set of T cells that are mainly activated by the lipid antigens presented by MHC Class I-like CD1d molecules. NKT cells play a very important role in host defense against tumors and infectious diseases.[8] On the other hand, NKT cells have also been implicated in the aggravation of atherosclerosis, asthma, and other inflammatory diseases. The pro-atherogenic role of NKT cells implies into their ability to secrete a huge amount of pro-inflammatory cytokines.[9] This assumption is supported by the report that the higher level of iNKT cells exacerbated the status of atherosclerosis in obese mice.[10] Furthermore, the presence of NKT cells and CD1d expressing antigen presenting cells have been detected in the atherosclerotic plaques.[11] Mitogen-activated protein kinase, protein kinase delta, and JAK/STAT cell signaling pathways regulate the CD1d-mediated antigen presentation by altering their intracellular trafficking through the endocytic compartments.[12] A small GTPase, Arl8b, has been known to influence the antigen presentation by CD1d by altering the lysosomal trafficking.[13] We earlier have reported that simvastatin inhibited the CD1d- and MHC Class II-mediated antigen presentation. Interestingly, it did not reduce the cholesterol level in the treated cells.[1] It suggested that the effect of statin on CD1d-mediated antigen presentation is dependent on prenylation inhibitory activity of the drug. Moreover, statin-induced inhibition of prenylation altered the trafficking and distribution of CD1d in the endocytic compartments of the treated antigen presenting cells. Overall, these findings clearly indicate that statin-mediated inhibition of prenylation modulates the activation of T-cell and NKT cell resulting in the alleviation of the inflammation in the atherosclerotic plaques. The prenylation inhibitory property of statin may further be exploited in the treatment of diseases where inflammation plays an important role in the pathogenesis of the diseases.

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