

Immunomodulatory Effects of Statins: Underlying Mechanisms and Experimental Evidence

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Clinical and experimental evidence suggest that apart from cholesterol lowering, statins offer additional benefits via modulation of immune response. The immunological effects mediated by statins are due to their ability to partially inhibit a common denominator of multiple regulatory pathways. The modification of signal transduction proteins by isoprenoid intermediates generated by the mevalonate pathway is responsible for these effects. The inhibition of MHC class II upregulation by statins provides a rationale basis for therapeutically exploiting the pleiotropic effects of statins. Consequently, statin therapy may be considered an attractive approach in the treatment of autoimmune diseases.

Key words: Experimental evidence, Immunomodulation, Isoprenoids, Mechanisms, Pleiotropic effects, Statins.

There are enormous evidence suggestive that statins modulate immune responses. The secretory activity of a number of immune cells, particularly monocytes/macrophages, intimal recruitment, differentiation and proliferation are some of the events attributable to the cholesterol-independent (pleiotropic) effects of statins¹⁻⁵. The implication of these pleiotropic effects suggest that the therapeutic benefits of statins may probably extend beyond cholesterol lowering, in reducing mortality and morbidity associated with cardiovascular disease. This paper reviews the mechanisms and experimental evidence underlying the role of statins on immunological function, emphasizing key biological targets.

Mechanisms of Immunomodulation by Statins

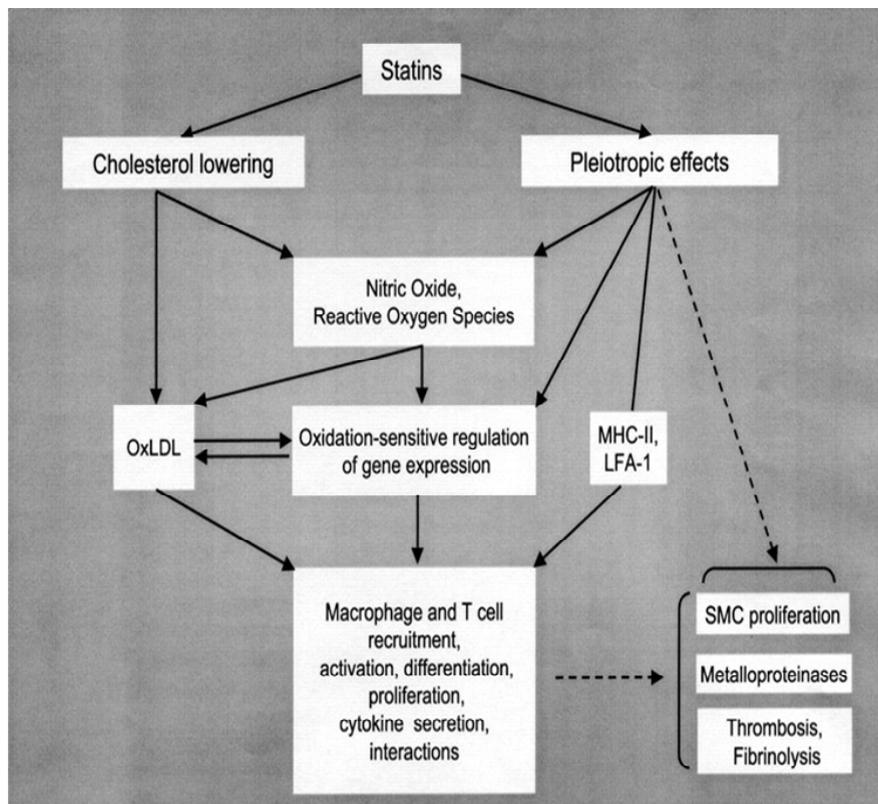
It has become increasingly evident that the beneficial effects of statins can no longer be

attributed solely to lipid lowering⁶⁻⁷. Statins inhibit the conversion of HMG-CoA to L-mevalonate through competitive inhibition of the rate-limiting enzyme HMG-CoA reductase, resulting to decrease in the biosynthesis of cholesterol and other intermediate metabolites, particularly the isoprenoids farnesyl pyrophosphate and geranyl geranyl pyrophosphate. Certain effects of statins are unrelated to cholesterol-lowering. Statins, for example, upregulate nitric oxide expression by interfering with the post-transcriptional regulation of endothelial nitric oxide synthetase (eNOS), thereby inhibiting induced ischemic cerebral stroke in normal, but not eNOS deficient mice⁸. It has been noted that the ability of statins to inhibit eNOS and induce smooth muscle cell (SMC) apoptosis is independent of cholesterol-lowering property⁹. The modification of signal transduction proteins by isoprenoid intermediates generated by the mevalonate pathway is responsible for these effects. These isoprenoid intermediates the 15-carbon farnesyl pyrophosphate (FPP) and the 20-carbon geranyl geranyl pyrophosphate

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(GGPP) function as adjuncts in post translational prenylation of various important cell signaling proteins¹⁰. Statins have been shown to exhibit immunomodulatory properties that alter the functions of both antigen presenting cells (APCs) and T cells. Statins inhibit interferon- γ (IFN γ) inducible expression of major histocompatibility complex class II (MHC II) molecules by APCs and prevent antigen presentation to CD4⁺ T Cells¹¹. Indeed, previous studies have stressed that antibodies specific for MHC class II molecules may be useful in the treatment of autoimmune diseases¹²⁻¹⁴. MHC class II upregulation is inhibited by statins through selective inhibition of expression from the IFN- γ inducible CIITA-promoter pIV, although statins also inhibit IFN- γ inducible CIITA expression from pI, indicating that IFN- α inducible CIITA expression is generally

inhibited by statins¹⁵. Mevalonate and GGPP but not squalene, both reverse inhibition of MHC class II expression by simvastatin, implicating small GTPases involvement in the inhibitory process. The effect of statins in inhibiting induced MHC class II expression was not demonstrated in APCs constitutively expressing MHC II such as dendritic cells and B lymphocytes. These findings no doubt give credence to the rationale basis for the use of statins in treating T-cell mediated disease. The endocytosis of antigen, its internal processing and subsequent presentation by MHC class II molecules on the cell surface are pre-requisite for antigen presentation by APCs. Remodeling of the cytoskeleton influences this process and the input of small GTPases required. The inhibition of GTPase-mediated cell proliferation is consistent with the finding that statin inhibition of antigen induced



The pleiotropic effects of statins are linked to upregulation of endothelial cell nitric oxide synthase (eNOS) due to inhibition of geranyl-geranylation of GTP binding protein Rho. Statins also selectively inhibit the $\alpha 2$ integrin LFA1 (leukocyte function antigen-1) expressed on the surface of leukocytes.

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Fig. 1. Modulation of Immune Responses by Statins

T-cell proliferation is linked to negative regulation of cell-cycle progression. It has been suggested that decreased cholesterol level may affect the integrity of cell membrane lipid rafts since it is possible that MHC class II expression may also be affected by statins in a cholesterol-dependent manner. Statins disrupt cell-membrane lipid rafts, which are believed to be important microdomains for the assembly of signalling complexes resulting to a loss of association of MHC class II molecules. Statins have been shown by addition of L-mevalonate to reverse the downregulation of MHC II¹¹. The requirement of isoprenoid intermediates (FPP and GGPP) to reduce MHC II expression is significant, otherwise drugs that lower cholesterol by mechanisms other than HMG-CoA reductase inhibition should also affect MHC II expression.

Experimental Evidence of Statin Immunomodulation

The beneficial effect of statins *in vivo* on immune mechanisms has been demonstrated in a number of studies in experimental models. Ischemic myocardial reperfusion injury was prevented in normocholesterolemic rats treated with simvastatin¹⁶. Another study reported the attenuation of renal injury and upregulation of constitutive endothelial nitric oxide synthase in a rat ischemic-reperfusion model¹⁷. Evidence for beneficial role of the active modulation of specific immune response has been demonstrated. Humoral and cellular immune responses as well as marked reduction in atherogenesis was reported following immunization of rabbits and mice with atherogenic oxidized LDL¹⁸.

The beneficial effects of statins have been demonstrated in animal studies. Experimental rat model of severe nephropathy revealed that therapy with an Angiotensin Converting Enzyme (ACE) inhibitor and simvastatin or cerivastatin significantly attenuated renal function¹⁹. Renal function improvement following simvastatin treatment was associated with inhibition of inflammatory and oxidative processes as determined by immunohistochemical analysis reported in a porcine model of hypercholesterolemia²⁰. The protective role of statins has been demonstrated in experimental models of ischemia-reperfusion injury²¹⁻²². Statin treatment ameliorated the enhancement of collagen IV deposition in the peritubular interstitium that follows ischemia-reperfusion injury during

which a transient upregulation of IL-6 induced by cerivastatin was observed²³. There is need for caution in the extrapolation of cell culture experiments and studies in animal models to human subjects.

CONCLUSION

In conclusion, it is quite evident that the therapeutic benefits of statins clearly extend beyond its usefulness in treatment and prevention of hyperlipidemia and cardiovascular diseases. This could be attributed to their modulating influence on immune mechanisms mediated by inhibition of prenylated proteins. It is pertinent, however, to note that the down regulation of these prenylated proteins and other small GTPases, is fundamental in the efficacy of statins as complete inhibition may be fatal. Consequently, statin therapy may be considered as an attractive approach for modifying autoimmune disease conditions.

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