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Immunomodulation: a new role for statins?

Statins reduce the expression of the class II major histocompatibility complex (MHCII) by arterial cells, leading to a decreased T-cell response. This indicates that statins may be useful in treating graft atherosclerosis and other chronic inflammatory conditions. (pages 1399–1402)

WULF PALINSKI

Statins inhibit an enzyme crucial to cellular cholesterol synthesis, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. The resulting decrease in intracellular cholesterol leads to a compensatory increase in cholesterol uptake via low density lipoprotein (LDL) receptors and concomitant decrease in plasma cholesterol. A reduction in cholesterol levels can influence a number of pathogenic mechanisms that are thought to contribute to atherogenesis and its acute consequences, plaque rupture and thrombosis. Several large-scale intervention trials have demonstrated that statin treatment reduces the risk of coronary heart disease (CHD) (ref. 1). Mounting evidence also indicates that some beneficial effects of statins may result from their ability to modulate arterial cell gene expression by mechanisms independent of cholesterol reduction[2]. The fact that statins inhibit recruitment and activation of immune-competent cells, such as macrophages, raises the question whether they may also be beneficial in other chronic inflammatory conditions and immune diseases. In this issue, Kwak *et al.*[3] demonstrate that statins inhibit the interferon-γ (IFN-γ)–induced expression of class II major histocompatibility complexes (MHCII) on antigen-presenting cells (APC), and thus identify a new mechanism by which statins may modulate immune responses.

MHCII are required for antigen presentation and T-cell activation via the T-cell receptor (TCR) (Fig. 1). TCR activation may trigger both proliferation and differentiation of T cells and influence their effector functions, such as the release of cytokines. Cytokines released by activated T cells induce further T-cell proliferation and differentiation, APC activation and B-cell antibody production. $CD4^+$ helper T cells (TH cells) differentiate into two distinct effector cell populations. TH1 cells secrete proinflammatory cytokines such as IFN-γ and tumor necrosis factor. TH2 cells secrete anti-inflammatory cytokines (such as IL-4, IL-10, IL-13) and transforming growth-factor–β, but also factors that promote immediate-type hypersensitivity. A reduction of TH1 responses, a shift towards TH2-cell responses or both therefore seems desirable in diseases involving delayed-type hypersensitivity reactions, such as graft (transplant) atherosclerosis and other chronic inflammatory pathologies.

Progressive arterial occlusion occurs in a significant percentage of organ transplant recipients. In contrast to the lipid- and macrophage-rich lesions associated with other forms of atherosclerosis, the intimal thickening that occurs after organ transplantation is mainly due to smooth muscle cell (SMC) proliferation. Allogeneic organ transplants can induce chronic host T-cell activation and secretion of cytokines, despite therapy with cyclosporin and other immunosuppressive drugs. These cytokines are believed to induce macrophages to release SMC growth factors. Hypercholesterolemia does not appear to play a prominent role in transplant atherosclerosis, but statins are frequently given to heart transplant patients because of the prevalence of hypercholesterolemia in these patients. Two clinical trials with different statins reported reduced graft atherosclerosis and a significant prolongation of patient survival times, consistent with a potential role of statins in immunomodulation[4,5].

Kwak *et al.*[3] report a previously unknown inhibitory effect of statins on MHC expression and have elucidated the underlying mechanism. They show that nano- to micromolar concentrations of statins inhibit the expression of MHCII mRNA and cell-surface protein in primary cultures of human macrophages and endothelial cells stimulated with IFN-γ. Similar results were obtained with other cell types that express little or no MHCII in the absence of cytokine stimulation, including SMC. In contrast, no effect was seen in APC constitutively expressing MHCII, such as dendritic cells and B lymphocytes. The degree of inhibition varied among different statins and the greatest inhibitory effects were observed for atorvastatin, the least lipophilic compound tested. Expression of class I MHC, which activates cytolytic $CD8^+$ T cells, was not affected by statins.

Studies on people with MHCII deficiency led to the identification of MHC gene regulatory elements, including the non-DNA binding MHCII transactivator[6] (CIITA). Kwak *et al.*[3] observed that the reduction in MHCII mRNA expression seen after statin treatment was associated with a quantitatively similar reduction in CIITA mRNA expression. Expression of CIITA itself is regulated by several transcriptional regulatory proteins. One of these, promotor IV, is also inhibited by statins[3]. Mixed lymphocyte experiments confirmed that the inhibition of MHCII expression translated into reduced T-cell activation.

These results provide convincing evidence that statins can modulate T-cell activation. They also provide a rationale for studying the effect of statins on T-cell responses, and severity of disease in animal models of transplant atherosclerosis, hypercholesterolemia-induced atherosclerosis or autoimmune disease. However, in addition to establishing the *in vivo* relevance of this mechanism, several outstanding issues must be resolved before considering the use of statins as immunomodulators in humans.

One of these issues is whether the ability of statins to inhibit MHCII expression depends on their cholesterol-lowering activity. Several effects of statins that are unrelated to cholesterol regulation have recently been identified[2]. For example, statins upregulate nitric oxide expression by interfering with the post-transcriptional regulation of endothelial nitric oxide synthase (eNOS), and inhibit induced ischemic cerebral stroke in normal, but not in eNOS-deficient mice[7]. The ability of statins to inhibit eNOS, induce SMC apoptosis[8] and prevent integrin-dependent leukocyte adhesion9 is independent of their ability to reduce cholesterol levels. These effects result from the modification of signal transduction proteins by geranylgeranyl- or farnesyl-pyrophosphates generated by the mevalonate pathway (which statins inhibit).

Kwak *et al.*[3] were able to reverse the downregulation of MHCII by adding L-mevalonate (the product of uninhibited HMG-CoA reductase) to cells. They did not, however, establish the mechanisms by which promotor IV function is inhib-

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ited. Whether geranylgeranylation or farnesylation of proteins is required to reduce MHC II expression is important, because if this is not the case, drugs that lower cholesterol by other mechanisms than HMG CoA reductase inhibition should also affect MHCII expression. The immunological consequences of MHCII inhibition must also be considered. The widespread clinical use of statins has not revealed an increased susceptibility to infections, but adverse effects on the ability to mount an immune response against foreign antigens cannot be ruled out.

The effects of statin treatment on TH1 and TH2 cell differentiation and arterial- wall thickening must be determined *in vivo*. Knockout experiments have demonstrated the atherogenic role of INF-γ, and the anti-inflammatory effect of interleukins produced by TH2 cells is well established. The ability to decrease production of pro-inflammatory TH1 cells or induce differentiation toward a TH2 cell type would therefore be useful for treating autoimmune diseases and preventing graft rejection. A simple downregulation of TH1 responses, however, may not be the only consequence of inhibiting MHCII expression. As recently discussed in *Nature Medicine*[10], immunomodulation by altered peptide ligands of MHCII—which in theory should compete with natural antigenic peptides and thereby also prevent activation of the TCR—may yield different results. By analogy, a partial and cell-specific inhibition of MHCII expression in different pathological environments may have multiple effects on immune cell differentiation pathways.

The potential for pharmacological immunomodulation of conventional atherosclerosis is an even more complex issue. Hypercholesterolemia promotes inflammation by many different mechanisms, in particular through modulation of oxidation-sensitive signaling pathways, such as altering activation of the transcription factor NF-κB. Hypercholesterolemia also increases the modification of proteins by oxidized lipids and phospholipids[11]. Such modified proteins may already be formed during fetal development[12] and are commonly found in atherosclerotic lesions. They are avidly taken up by macrophages via scavenger receptors and trigger extensive humoral and cellular immune responses.

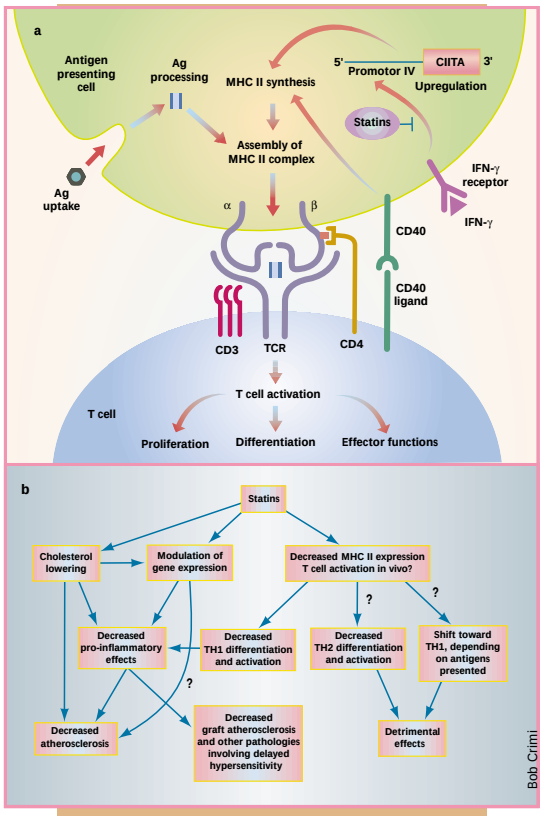

Fig. 1 Statin modulation of the immune response. ***a***, Extracellular antigens taken up by APC are processed into peptides fitting into the peptide-binding cleft formed by the α- and β-chains of MHCII, assembled with MHC into a heterotrimeric complex, and transported to the cell surface. IFN-γ, the major macrophage-activating cytokine, induces MHC expression by macrophages and other APCs. It does this by activating the class II transactivator (CIITA) through a transcriptional regulatory element known as promoter IV. Kwak *et al*.[3] demonstrate that statins inhibit this pathway and lead to reduced CIITA and subsequently reduced MHC expression. However, MHCII expression on macrophages can also be induced by direct cell to cell contact, such as through CD40–CD40 ligand interactions. APC that constitutively express MHCII are not affected by statin treatment. T-cell activation results from the joint interaction of the T-cell receptor (TCR) with MHCII and the antigenic peptide. Interaction of the T-cell co-receptor CD4 with MHCII is also required for T-cell activation. CD3 and other proteins contribute to transduction of the TCR signal. ***b***, Statins reduce atherosclerosis by lowering plasma cholesterol and decreasing inflammatory processes. The ability of statins to downregulate expression of MHCII may lead to decreased TH1 differentiation and activation *in vivo* and thus inhibit the release of pro-inflammatory cytokines. This suggests that statins may be beneficial in reducing graft atherosclerosis and treating other chronic inflammatory conditions. The immunomodulatory effects of statins could also be detrimental, however, because a reduced MHCII expression may inhibit anti-inflammatory effects resulting from TH2 activation, or lead to a shift towards a TH1-type immune response, depending on the antigens presented.

Selective modulation of the immune response may affect the progression of atherosclerosis[11]. However, the multiple cellular effects of statins, the presence of many different antigens in atherosclerosis (such as oxidative neoepitopes, pathogenic bacteria and heat shock proteins), and the presence of conventional atherosclerosis in transplant patients will present many challenges to researchers attempting to determine the *in vivo* relevance of the transcriptional regulation of MHCII by statins.

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