J Am Soc Nephrol 13: 1673–1681, 2002

Immunomodulatory Effects of Statins: Mechanisms and Potential Impact on Arteriosclerosis

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Abstract. Clinical trials with statins have demonstrated a marked reduction of cardiovascular mortality. However, it remains controversial whether these clinical benefits stem from powerful cholesterol-lowering effects of statins or whether they are due in part to their cholesterol-independent effects on vascular function, plaque growth, plaque rupture, or thrombosis. The identification of several mechanisms through which statins decrease the recruitment of monocytes and T cells into the arterial wall and inhibit T cell activation and proliferation *in vitro* have prompted speculations that immunomodulatory effects of statins may be beneficial in recipients of organ transplants. Hypercholesterolemia is frequent in these patients, and delayed-type hypersensitivity reactions in the arterial walls of the graft may be compounded by chronic inflammation associated with conventional atherogenesis. To assess the potential clinical relevance of immunomodulatory effects of statins, the role of the immune system in atherogenesis and the effects of statins *in vitro* in experimental models and in clinical trials will be reviewed. It is concluded that despite solid *in vitro* evidence, clinical evidence for an independent immunosuppressive effect of statins in organ transplant patients is presently insufficient; however, further investigation of their *in vivo* occurrence and clinical relevance is warranted.

Hypercholesterolemia is a major contributor to atherosclerosis and its clinical sequelae, myocardial infarction, ischemic stroke, and peripheral vascular diseases. During the past two decades, cholesterol lowering by a variety of drugs has yielded a significant reduction of cardiovascular mortality, but none of these agents have been as efficacious as statins (1–4). Statins inhibit 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) reductase, the rate-limiting enzyme in the mevalonate pathway through which cells synthesize cholesterol. To compensate for decreased synthesis and to maintain cholesterol homeostasis, cells, particularly hepatocytes, increase the expression of LDL receptors, which increases the uptake of plasma LDL, the main carrier of extracellular cholesterol, resulting in lower plasma LDL concentrations. Decreased plasma LDL levels reduce the progression of atherosclerosis and may even lead to the regression of preexisting atherosclerotic lesions. However, the angiographic reduction in luminal diameter stenosis seen in clinical trials is fairly modest (5) and contrasts with the marked reduction of clinical events. Clinical benefits also appear after a relatively short treatment period that is inconsistent with the assumption of marked regression of lesions or the prevention of lesion progression from early to more advanced rupture-prone stages (1–4). In fact, recent studies observed at least some beneficial effects after 4 to 6 mo of treatment (6,7). Finally, the degree of cholesterol reduction in several studies was not consistent with the reduction of clinical endpoints, particularly with regard to the reduction of ischemic stroke (2,8). Although some trials explained virtually all clinical effects of statins by cholesterol-lowering alone (9), the above discrepancies have prompted speculations that the beneficial effects of statins stem in part from cholesterol-independent "pleiotropic" effects of these drugs (*vide infra*) (10–12).

Immunomodulatory Effects of Statins

There is substantial evidence that statins may modulate immune responses. These include effects on the intimal recruitment, differentiation, proliferation, and secretory activity of a number of immune cells, mainly monocyte/macrophages and T cells (13–22). Although many of these effects may be caused by—or be synergistic with—similar effects of lower cholesterol levels in plasma or atherosclerotic lesion, two previously unknown immune effects of statins of potential clinical relevance have been recently reported (23,24).

The first is that statins inhibit the expression of class II major histocompatibility antigens (MHC-II) on human macrophages, endothelial cells, and smooth muscle cells (SMC) stimulated by interferon γ (IFNγ) (reference 23, discussed in reference 25). This effect was exerted by both lipophilic and hydrophilic statins at nanomolar to micromolar concentrations, but it was limited to antigen-presenting cells requiring co-stimulation by IFNγ. Professional antigen-presenting cells constitutively expressing MHC-II, *e.g.*, B cells and dendritic cells, were not affected. Statins were shown to inhibit a promotor (promotor IV) of the MHC-II transactivator CIITA, which regulates transcription of MHC-II and thus synthesis of the MHC-II protein. The expression of MHC-II on the surface of antigen-presenting

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1046-6673/1306-1673
Journal of the American Society of Nephrology

DOI: 10.1097/01.ASN.0000018400.39687.8C

cells together with processed antigens and cellular cofactors results in activation of the T cell receptor. It can therefore be postulated that a reduction of MHC-II molecules on the vast majority of arterial cells leads to a reduction of T cell proliferation and differentiation. Mixed lymphocyte reactions showed that statin treatment of endothelial cells and SMC indeed reduced T cell proliferation and interleukin-2 (IL-2) release (23). Two main subgroups of T helper cells, Th1 and Th2 cells, are thought to modulate atherogenesis, but only one of them, Th1 cells, secrete cytokines that promote inflammation, such as IFNγ (25). In contrast, secretory products of Th2 cells seem to be atheroprotective and also inhibit Th1 proliferation by a negative feedback mechanism. Nevertheless, it is likely that the overall effect of reduced T cell activation and proliferation in the arterial wall would be beneficial. To date, however, it is not known whether this actually occurs *in vivo*, as a result of clinical doses of statins, whether reduced T cell activation by some antigen-presenting cells is compensated by increased activity of other cells, or whether immunosuppression is associated with detrimental effects in the form of weakened immune responses to exogenous pathogens or neoplasms. Large-scale clinical trials have not provided any indication for such effects, but they were not designed to detect minor adverse effects.

The second recently discovered immunosuppressive effect of statins is a selective blocking of the β2 integrin, leukocyte function antigen-1 (LFA-1) (24). LFA-1, also known as CD11a/CD18, is expressed on the surface of leukocytes and, when activated, binds to intercellular adhesion molecule 1 (ICAM-1). In addition to its role in leukocyte adhesion and extravasation, LFA-1 is a co-stimulator of T cells. At least one clinically used statin, lovastatin, as well as several modified statin compounds subsequently developed, bound selectively to a novel site of LFA-1 and prevented LFA-1–mediated adhesion and lymphocyte co-stimulation. This effect was unrelated to the statins' inhibition of HMG-CoA (24).

These reports suggested that immunomodulation by statins may be beneficial not only in conventional atherosclerosis, which involves chronic inflammatory processes, but also in graft atherosclerosis and autoimmune diseases, such as rheumatoid arthritis or multiple sclerosis. As already shown for the inhibition of LFA-1 (24), future statins may be optimized for specific immunosuppressive effects, in particular for indications not involving hypercholesterolemia. However, the combination of a powerful cholesterol-lowering effect with an immunosuppressant action would be particularly desirable in organ transplant recipients. Indeed, a high incidence of hypercholesterolemia has been described in many organ transplant recipients (26). The highest percentage of posttransplantation hypercholesterolemia (80%) is found, not surprisingly, in heart transplant recipients, many of whom had preexisting hypercholesterolemia and atherosclerosis, but increased posttransplantation levels of total and LDL cholesterol are also common after renal and hepatic transplantation (26). Two of the standard immunosuppressants administered to all transplant patients, cyclosporine and corticosteroids, have been linked with hypercholesterolemia independent of the transplantation. It is therefore tempting to assume that pathogenic events caused by delayed-type hypersensitivity reactions in these subjects are compounded by chronic inflammation associated with conventional, cholesterol-driven atherogenesis and that the postulated immunosuppressant effects of statins may be particularly beneficial (27).

Pleiotropic Effects of Statins

The term "pleiotropic effects" has been liberally used for effects of statins other than cholesterol lowering; upon closer inspection, only a small number have been proven to be independent of their hypocholesterolemic action. Pleiotropic effects potentially affecting atherogenesis include an improvement of endothelial function, attributed to the preservation of endothelial nitric oxide production, and an inhibition of smooth muscle cell (SMC) proliferation (13). Various effects on platelet activation, coagulation, and fibrinolysis have also been reported but have to be viewed with some skepticism because different members of the statin family exert opposite or no effects (10).

The rate-limiting step in cholesterol synthesis (Figure 1) is the formation of mevalonate from HMG-CoA (the step that is inhibited by statins). The mevalonate pathway then branches out before the synthesis of squalene and cholesterol. Other biologically important products are dolichols (involved in lipoprotein synthesis), ubiquinone, and the isoprenoids, farnesyl-pyrophosphate (PP) and geranylgeranyl-PP (28). Isoprenoids play an important role in the posttranslational modification of regulatory proteins, such as G proteins, Ras, Rho, and Rab. By covalently binding to these proteins, isoprenoids create lipid binding sites that influence the membrane binding and intracellular trafficking and thus the biologic activity of these proteins (29). Several of the pleiotropic effects of statins have been traced to prenylation of these proteins. For example, geranyl-geranylation of the GTP binding protein Rho decreases endothelial cell nitric oxide synthase (eNOS) expression and inhibits nitric oxide–induced vascular relaxation. By blocking synthesis of geranyl-geranyl-PP, statins decrease

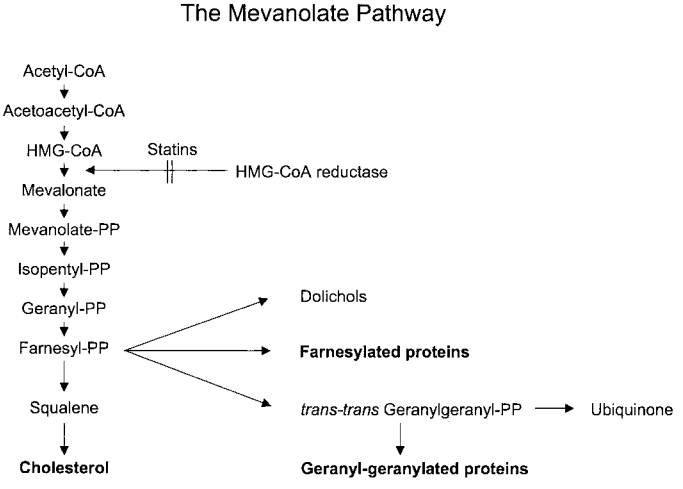

Figure 1. The Mevanolate pathway.

geranylation of Rho and upregulate eNOS (30–32,13). Nitric oxide generation in endothelial cells is also promoted by another mechanism. Statins activate the protein kinase Akt/PKB, which results in enhanced phosphorylation (activation) of its natural substrate, eNOS (33–35). Increased formation of NO promotes arterial vasodilatation and inhibits atherogenesis (36,37). NO is therefore emerging as a prime target for pharmacologic intervention (38). In addition to preventing the Rho-mediated downregulation of eNOS, other effects of statins have been linked to geranyl-geranylation, such as inhibition of proliferation and induction of apoptosis in SMC (13,39), inhibition of integrin-dependent leukocyte adhesion (40), and increased fibrinolytic activity (41). The observation of some of these effects, *e.g.*, improved vascular function (42,43), in the absence of hypercholesterolemia supports the notion that they are cholesterol-independent (44). Unequivocal evidence that many of the above effects are due to protein prenylation has been provided by the fact that they are reversible by addition of geranylgeranyl-PP (or farnesyl-PP), which does not restore cholesterol synthesis, but not by addition of squalene or cholesterol (31,39–41).

Statins and Oxidation-Sensitive Signaling Pathways

That many effects of statins are independent of cholesterol lowering *in vitro* does not mean that they are not affected by hypercholesterolemia *in vivo* or jointly achieved by the cholesterol-lowering effect of statins. Extensive evidence links hypercholesterolemia with increased lipid peroxidation and increased oxidative stress (45,46). It is also well established that multiple signaling pathways regulating the expression of atherogenic genes are oxidation-sensitive, either because oxidized LDL (OxLDL) activates them by binding to cell surface receptors or because increased extracellular lipid oxidation causes a shift in the intracellular redox balance (47,48). Among the many oxidation-sensitive pathways that affect cell growth, secretory activity, and death, three are particularly relevant in inflammation and atherogenesis. The first of these is nuclear factor–κB (NFκB), which regulates adhesion molecules and growth factors, including VCAM-1, ICAM-1, and MCP-1, important contributors to monocyte and T cell recruitment into the arterial intima (49,50). The second is the apoptotic signaling pathway that is activated through Fas/FasL and tumor necrosis factor (TNF) receptors and regulates the expression of caspases and other effectors of apoptosis (51–53). The third oxidation-sensitive pathway is the peroxisome proliferator–activated receptor γ (PPARγ) pathway. PPARγ is a nuclear receptor that regulates fat cell development and glucose homeostasis and is the molecular target of insulin-sensitizing agents used for the management of type 2 diabetes mellitus. It is also highly expressed in macrophage/foam cells of atherosclerotic lesions. Activation of PPARγ by OxLDL or synthetic ligands upregulates the expression of the ABC-A1 transporter involved in reverse cholesterol transport from peripheral cells, but it also downregulates a number of pro-inflammatory factors, including TNFα, IL-1β, IL-6, the inducible nitric oxide syntase (iNOS), and gelatinase B, one of the metalloproteinases thought to promote plaque rupture (54–57).

It is therefore not surprising that increased oxygen radical formation accompanying hypercholesterolemia influences many of the same factors that are modulated by statins via inhibition of prenylation. For example, LDL oxidation interferes with NO-mediated vasodilation by promoting the conversion of NO into the less active peroxynitrate. Conversely, statins and other drugs that increase endothelial NO production (*e.g.*, angiotensin-converting enzyme inhibitors) also decrease the production of superoxide radicals and other reactive oxygen species (ROS) by decreasing the activity of NAD(P)H oxidase, and thus reduce both LDL oxidation and intracellular oxidative stress (58).

The interactions between cholesterol-dependent and independent mechanisms of statins make it difficult to assess whether effects on immune cells observed *in vivo* are due to either, and thus to predict to whether statins will exert clinically relevant immunomodulatory effects under normocholesterolemic conditions. Evaluation of the impact of immune effects of statins on their undisputed beneficial overall effect on conventional atherosclerosis is even more complex. Figure 2 summarizes the mechanisms through which hypercholesterolemia enhances atherogenesis and that, conversely, are inhibited by statins.

LDL entering the arterial wall is progressively oxidized by endothelial cells, smooth muscle cells, and macrophages (for a review of OxLDL, see reference 59). Hypercholesterolemia increases both the amount of LDL that penetrates into the artery wall and its oxidation. Extensively oxidized LDL is rapidly taken up by macrophages via scavenger receptors and induces foam cell formation, a key feature of atherosclerosis. As discussed above, even minimally modified LDL (mmLDL), *i.e.*, LDL that is not oxidized enough to be recognized by scavenger receptors, profoundly affects gene expression in vascular cells. This leads to decreased endothelial NO expression and increased vascular tonus and promotes the recruitment of monocytes and T cells through increased expression of adhesion molecules and chemotactic factors. Statins reduce both extracellular LDL oxidation (by reducing substrate availability) and intracellular oxidative stress (by cholesterol-independent effects on NO and, indirectly, by reducing OxLDL). It is therefore not surprising that statins inhibit the recruitment of T cells and macrophages and their activation *in vitro*. Because macrophages are immune-competent cells, this is considered an "immune-modulating" effect of statins. However, it clearly is not an effect on the immune system alone but many other atherogenic mechanisms, such as foam cell formations and macrophage-induced SMC proliferation. A direct link between one of the products of lipid peroxidation, lysophosphatidylcholine, and autoimmune diseases has also recently been reported (60).

When considering the role of macrophages in atherosclerosis, we primarily think of foam cell formation and secretion of cytokines, but macrophages are also antigen-presenting cells. One of the antigens prevalent in atherosclerotic lesions is none other than OxLDL. During the oxidation of the lipid core of the LDL particle, highly reactive lipid peroxidation products are

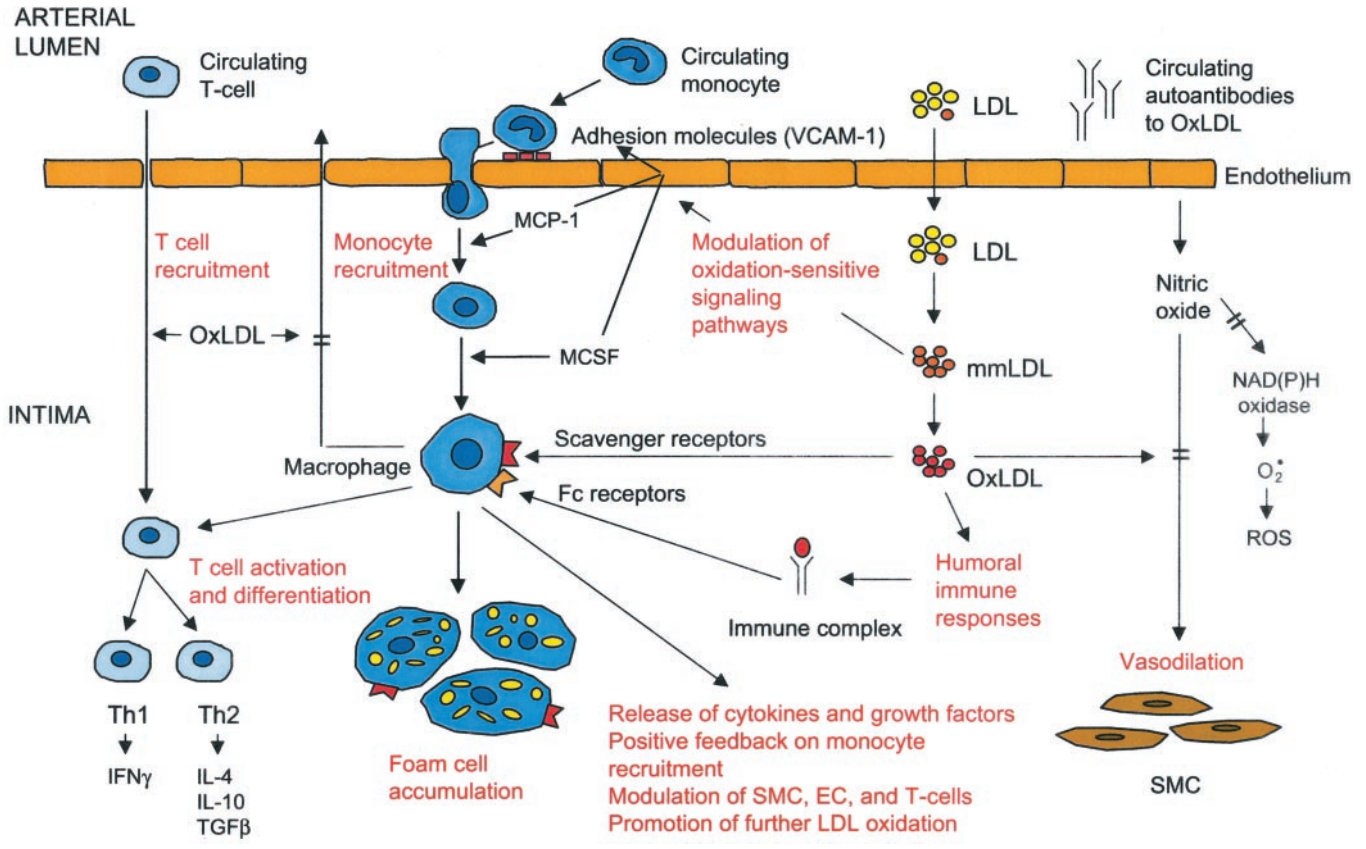

Figure 2. Atherogenic mechanisms of hypercholesterolemia potentially affected by statins (see text for detailed description).

formed, such as malondialdehyde, which react with free amino groups on the 360 lysine residues of apolipoprotein B. Modification of these lysines not only leads to the recognition of OxLDL by scavenger receptors, but it also renders OxLDL highly immunogenic (see reference 61 for a review of the immune responses triggered by OxLDL). Indeed, circulating autoantibodies to various epitopes of OxLDL are prevalent in humans (62). These enter the lesions and form immune complexes with OxLDL that are taken up by macrophages via Fc receptors, scavenger receptors, or phagocytosis. The processed antigens are then presented together with MHC-II antigens to T cells and activate them, aided by co-stimulators. In fact, about 10% of T cells isolated from human lesions proliferate in response to OxLDL (63). A number of other antigens may also be present in lesions, *e.g.*, heat shock proteins generated by stressed endothelial cells, or bacterial antigens, such as chlamydiae. Differentiation of $CD4^+$ T cells gives rise to distinct subpopulations, which may either promote or inhibit further atherogenesis. For example, IFNγ secreted by Th1 cells is clearly proinflammatory and atherogenic, whereas Th2 cytokines, IL-4, IL-10, and transforming growth factor–β (TGF-β), decrease Th1 mediated inflammation and lesion formation. It is therefore assumed that shifts between T cell subpopulations are important in modulating lesion progression. T cell–mediated delayed-type hypersensitivity reactions play an even greater role in transplant arteriosclerosis (64,65).

Role of the Immune System in Atherosclerosis

Atherosclerosis has many features of a chronic inflammatory process. Lesions contain large numbers of macrophages and T cells, and many of these are activated, *i.e.*, express MHC-II and IL-2 receptors, as well as interleukins involved in T cell proliferation and differentiation. Lesions are also rich in immunoglobulins and contain activated complement complexes. An involvement of the immune system in atherogenesis has therefore been long assumed (66). However, it is now well established that the immune system is not a single atherogenic entity but that different components of the humoral and cellular immune system may both promote and inhibit lesion progression.

Evidence for a detrimental role of the immune system in atherogenesis includes the following: (*1*) mice lacking IFNγ or IFNγ receptors (67,68), IL-8 (69), or TNF receptors (70) had less atherosclerosis; (*2*) inhibition of CD40 signaling reduced atherosclerosis in mice (71) (interaction of CD40 on the surface of an antigen-presenting cell and the CD40 ligand on T cells is an important element in MHC-II expression and T cell activation); (*3*) crosses between apoE-deficient mice and Rag-1 mice (which lack both B and T cells and therefore have severe combined immune deficiency) had less atherosclerosis when fed regular chow than immune-competent controls (72); (*4*) immunization of normocholesterolemic New Zealand White rabbits with mycobacterial heat shock protein 65 induced a

transitory form of inflammatory lesions and enhanced atherosclerosis in hypercholesterolemic rabbits (73,74). It is presumed that antibodies induced by immunization with the mycobacterial antigen crossreact with endogenous heat shock proteins produced by stressed endothelial cells and thereby further damage them.

On the other hand, substantial evidence also indicates that some elements of the immune response or active modulation of specific immune responses may be beneficial. For example, immunization of rabbits and mice with atherogenic OxLDL caused both humoral and cellular immune responses and markedly reduced atherogenesis (75). Evidence for a beneficial role of the immune system is also provided by the observation of increased atherosclerosis in some immune-compromised animal models, *e.g.*, MHC-I deficient mice (76), or rats after elimination of T cells with monoclonal antibodies (77). Of particular interest in the context of organ transplantation is that increased atherosclerosis was also seen in cholesterol-fed rabbits after suppression of cell-mediated immunity by cyclosporin (78).

Evidence for Immunomodulatory Effects of Statins in Experimental Models

In view of the fact that immune competent cells and their cytokines may exert both atherogenic and atheroprotective effects and that statins may inhibit several of these immune mechanisms by reducing cholesterol as well as by cholesterol-independent effects, great caution must be used in translating *in vitro* mechanisms of statins into biologic effects *in vivo*. For example, inhibition of eNOS by statins resulted in increased neovascularization in one study (33) but an antiangiogenic effect in another (79). A number of studies in experimental models nevertheless suggest—or at least are consistent with—a beneficial effect of statins on immune mechanisms *in vivo*. For example, reduced chronic rejection and decreased graft atherosclerosis was seen in rat recipients of heterotopic heart and liver transplants treated with statins (80–82). Simvastatin protected normocholesterolemic rats against ischemic myocardial reperfusion injury (83), and pravastatin upregulated constitutive endothelial nitric oxide synthase and attenuated renal injury in a rat ischemia-reperfusion model (84). Antiinflammatory effects of statins have also been reported in the central nervous system (85,86), and statin treatment resulted in marked reduction of ischemic stroke mortality (42,44). Similarly, neointimal inflammation was inhibited in a rabbit model of atherosclerosis (87). Both acute antiinflammatory and long-term antiatherogenic effects independent of cholesterol-lowering were also reported in apolipoprotein E–deficient mice (88), a model of spontaneous hypercholesterolemia and extensive aortic atherogenesis (89). Finally, an inhibition of SMC proliferation consistent with *in vitro* observations was seen in hyperlipidemic rabbits (90) but did not translate to clinical benefit in patients undergoing balloon angioplasty (91–93). Animal experiments have thus documented antiinflammatory effects, but many of these studies have not excluded an influence of cholesterol lowering. This is unfortunate, because in some models, the cholesterol levels in treatment and control groups could easily be matched by dietary modulations. Hypolipidemic effects of statins or hypercholesterolemia induced by standard immunosuppressants could therefore be compensated for, making it easier to establish cholesterol-independent effects on atherosclerosis.

Evidence for Immunomodulatory Effects of Statins in Humans

A major limitation of cell culture experiments and studies in animal models is the uncertainty about the dose of statins that would allow extrapolation of results to humans. Oral doses of statins administered to rodent models often substantially exceed clinical regimens when expressed per kg body weight, but this does not necessarily translate into higher plasma concentrations, because of the rapid metabolism in these models. Furthermore, there is a paucity of data on plasma—much less tissue—concentrations of statins in humans, which makes it difficult to determine optimal conditions for *in vitro* experiments. Therefore, results of *in vitro* and animal experiments may only provide proof in principle for certain effects but need verification in human subjects.

Much of the optimism regarding the postulated immunosuppressant effect of statins stems from several clinical trials in heart transplant recipients. Kobashigawa *et al.* (94) reported a significant increase of 1-yr survival and a reduction of acute rejection reactions in pravastatin-treated subjects compared with controls receiving only prednisone, azathioprine, and cyclosporine. Similarly, Wenke *et al.* (95) found a significant increase of 4-yr survival and reductions of coronary vasculopathy and intimal thickness in simvastatin-treated patients. These results are consistent with the observation in other studies that statin treatment reduced plasma levels of C-reactive protein, a marker of inflammation (96,97). Protective effects of simvastatin on coronary vasomotor function and the transcardiac gradient (*i.e.*, coronary release) of IL-6 and TNFα were also noted in cardiac transplant recipients without angiographically detectable disease, suggesting that endothelial functions are improved and inflammatory cytokine release is reduced (98). However, because improved endothelial function and reduced inflammation may also be due to lipid-lowering effects of statins, the reduction of mortality and arterial pathology in heart transplant recipients cannot be attributed to cholesterol-independent effects of statins alone, much less to specific immunosuppressant effects. In fact, another clinical study did not observe a significant impact of statins on lymphocyte numbers, nonspecific mitogenic responses, or IL-2 secretion (99).

In renal transplant recipients, some evidence for similar beneficial effects of statins on endothelial functions has been noted, including an improvement of brachial flow-mediated vasodilation, but not on arterial distensibility (100,101). A first study on 48 kidney transplant patients also reported that pravastatin significantly decreased acute rejection reactions (102). In contrast, a subsequent larger, randomized double blind study found no difference in the acute rejection rate or the severity of rejection in kidney transplant recipients, despite a significant improvement of lipid profiles (103). Two additional random-

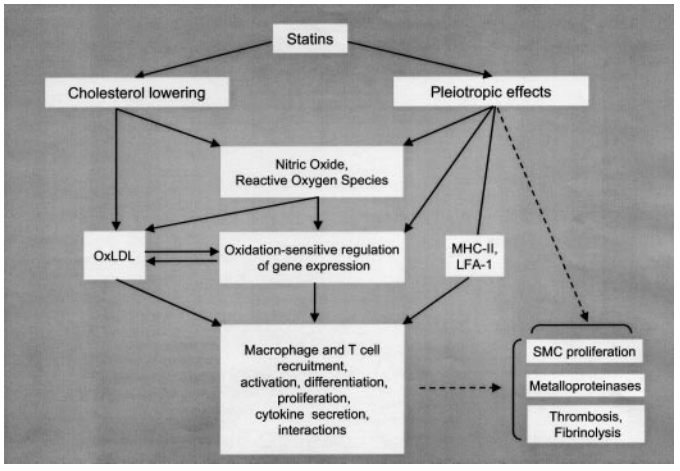

Figure 3. Immunomodulatory mechanisms of statins.

ized placebo-controlled trials also found no effect of simvastatin and lovastatin on acute renal allograft rejection (104,105). The results of the much larger ALERT (Assessment of Lescol in Renal Transplantation) trial are expected soon and may provide a more definitive answer (106).

Conclusions

A number of cholesterol-independent immunomodulatory mechanisms of statins have recently been identified, giving rise to expectations that statins may be beneficial in disorders involving delayed-type hypersensitivity reactions, *e.g.*, graft atherosclerosis. It is, however, difficult to differentiate between cholesterol-dependent and independent effects *in vivo*. As summarized in Figure 3, the recruitment or activation of immune cells is affected by both the cholesterol-lowering and cholesterol-independent pleiotropic effects of statins. Central mechanisms governing the recruitment, differentiation, proliferation, and cytokine secretion of monocyte/macrophages and T cells are affected by statins through both cholesterol-lowering and independent effects. The evaluation of the postulated immunomodulation by statins is further complicated by the fact that immune cells and their secretory products play a complex role in atherogenesis and can exert both atherogenic and protective effects. Reductions of mortality and vascular pathology in human heart transplant recipients appear promising, but they cannot be attributed to specific effects on immune mechanisms. Because other clinical trials have failed to demonstrate clinical benefits in transplant patients, the burden of proof for an indication of statins in purely immune-related pathologies has not yet been fulfilled. Clearly, extensive additional *in vivo* studies are needed to document the occurrence of immune effects of statins and an attenuation of arterial pathologies before the indication of statins can be expanded to chronic inflammatory conditions and autoimmune diseases.

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