Statin therapy and autoimmune disease: from protein prenylation to immunomodulation

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Abstract | Statins have been prescribed extensively for their cholesterol-lowering properties and efficacy in cardiovascular disease. However, compelling evidence now exists that statins also have extensive immunomodulatory properties that operate independently of lipid lowering. Consequently, much attention has been directed towards their potential as therapeutic agents for the treatment of autoimmune disease. Modulation of post-translational protein prenylation seems to be a key mechanism by which statins alter immune function. In this Review, the effect of statin therapy on immune function, and how this relates to the pathogenesis of autoimmune disease, is reviewed alongside current opinion of what the key biological targets of statins are.

Hypercholesterolaemia
A clinical condition in which there is abnormally high circulating levels of blood cholesterol, which can be a significant contributing factor towards cardiovascular disease.

Low-density lipoprotein (LDL) cholesterol
Cholesterol is carried in the blood by proteins in the form of lipoproteins. There are five different lipoproteins, with cardiovascular risk associated with high circulating levels of LDL cholesterol.

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doi:10.1038/nri1839

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, generically referred to as statins, have emerged as the leading therapeutic regimen for treating hypercholesterolaemia and reducing cardiovascular morbidity and mortality. The clinical use of statins has become so prevalent that they are now prescribed to more than 25 million people worldwide, with the number expected to rise rapidly. These compounds mediate their biological effect by inhibiting HMG-CoA reductase, which is an upstream rate-limiting enzyme in the cholesterol synthesis pathway (FIG. 1). The consequent reduction in circulating low-density lipoprotein (LDL) cholesterol, which provided the original rationale for treating cardiovascular disease, was until recently believed to be the main therapeutic effect[1].

It has become increasingly apparent, however, that the beneficial effects of statins in cardiovascular medicine cannot be ascribed solely to their lipid-lowering properties[2,3]. So, just as it emerged that coronary disease has an important inflammatory component[4,5], it has become evident that statins modulate the immune response[6]. This revelation resulted in extensive clinical and laboratory studies that generated compelling evidence that statins have comprehensive immune-modulating properties that affect many facets of the inflammatory response. Because of the diverse effects of statins on the immune system, considerable interest has arisen in their therapeutic potential for treating autoimmune disease[7–10]. Statins are particularly attractive therapeutic agents as their safety profile is generally good and, because they are administered orally, they have an additional advantage over parenterally administered agents. As discussed below, the pleiotropic actions of statins and their ability to attenuate experimental inflammatory disease is impressive but the relative importance of each statin-modified pathway in bestowing this improved clinical outcome remains poorly understood.

Here we highlight, in the context of autoimmune disease, the different facets of the immune response that are modulated by statins and review current opinion regarding their mechanism of action, with particular reference to the inhibition of protein prenylation (also known as isoprenylation).

Statin pharmacology

The statin family of drugs comprises naturally occurring (lovastatin (Mevacor; Merck & Co. and Altoprev; Andrx Labs), mevastatin (Compactin), pravastatin (Pravachol; Bristol-Myers Squibb Company) and simvastatin (Zocor; Merck & Co.)) and synthetic members (fluvastatin (Lescol; Novartis), atorvastatin (Lipitor; Pfizer), cerivastatin (Baycol or Lipobay; Bayer A.G.) and rosuvastatin (Crestor; AstraZeneca)), which differ in their lipophilicity, half-life and potency. All statins, independent of their structural differences, bind to HMG-CoA reductase at nanomolar concentrations, leading to competitive displacement of the natural substrate HMG-CoA. This competitive inhibition results in a failure to catalyse the conversion of HMG-CoA to L-mevalonate, which in turn prevents the downstream biosynthesis of cholesterol (FIG. 1). Not only is cholesterol synthesis reduced, but

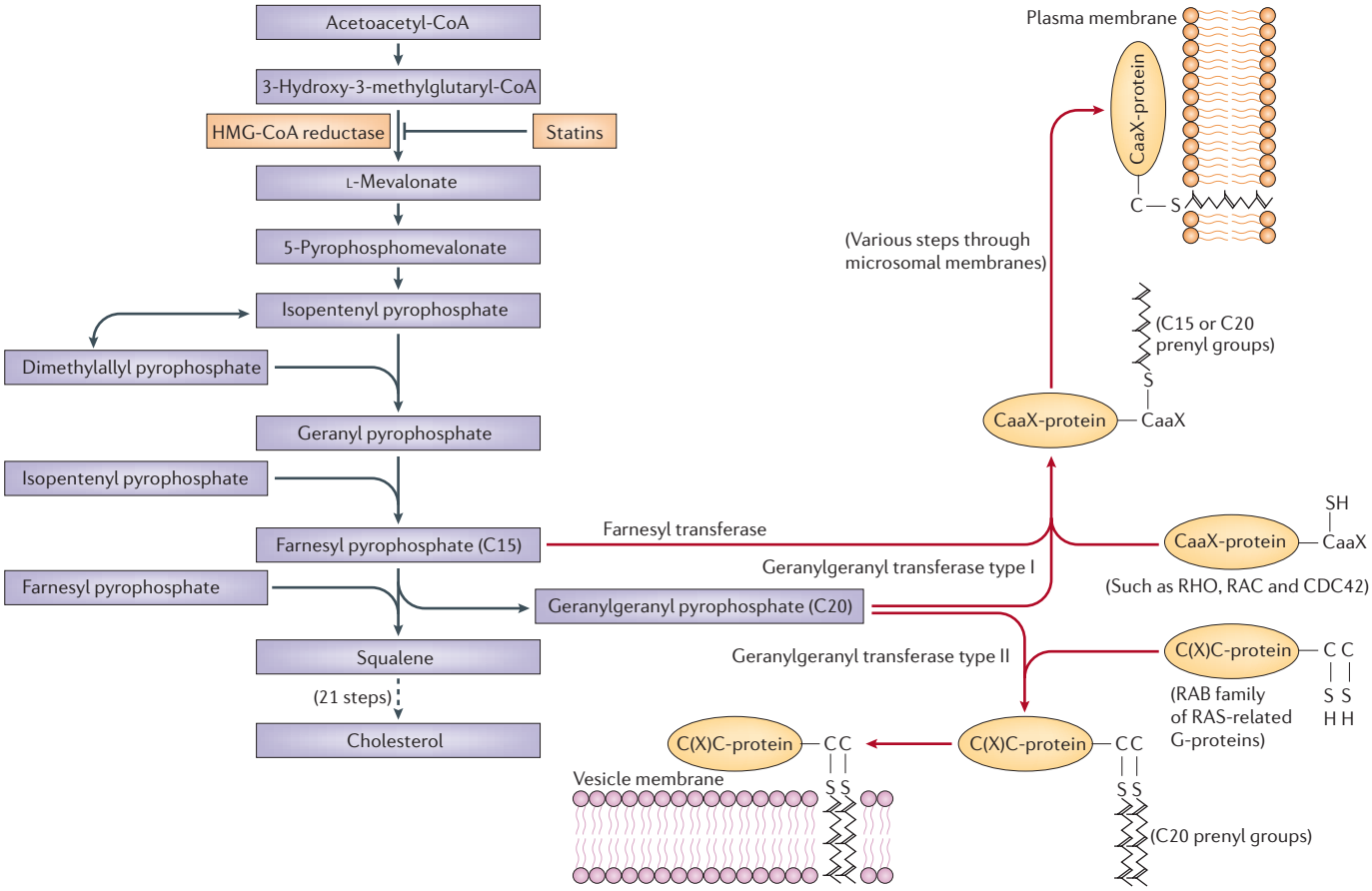

Figure 1 | **The cholesterol synthesis pathway and protein prenylation.** Statins inhibit the conversion of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) to L-mevalonate through competitive inhibition of the rate-limiting enzyme HMG-CoA reductase. This inhibition results in a decrease in the downstream biosynthesis of cholesterol and other intermediate metabolites, including the isoprenoids farnesyl pyrophosphate and geranylgeranyl pyrophosphate. These isoprenoid pyrophosphates serve as essential adjuncts in the post-translational modification of numerous key proteins that function as molecular switches, including the small GTPases RAS, RAC and RAS homologue (RHO). These proteins contain a carboxy-terminal CaaX motif (where C is cysteine, a is an aliphatic amino acid and X is any amino acid), or a CC or CXC sequence (denoted C(X)C) to which prenyl groups are added. This post-translational modification enables these signalling proteins to associate with membranes, which is a prerequisite for most of their biological function. CDC42, cell-division cycle 42.

also low intracellular-cholesterol concentrations activate sterol-responsive-element-binding proteins, leading to increased transcription of the gene encoding the LDL receptor and subsequent expression of the receptor at the cell surface. As LDL-receptor-mediated uptake of LDL cholesterol by the liver is a key factor in determining circulating levels, this further reduces blood LDL cholesterol. A reduction in circulating cholesterol is a primary clinical objective when treating hypercholesterolaemia, as it removes one of the main risk factors for atherosclerosis.

Despite an unambiguous association between lipid lowering and improved clinical outcome in patients with coronary atherosclerosis, not all the benefit can be attributed to cholesterol reduction. In particular, the inflammatory component of atherosclerosis seems to respond to statin-mediated effects that are independent of cholesterol reduction. In recent years, numerous reports have highlighted the important role played by intermediate metabolites of the cholesterol biosynthetic pathway in the pathogenesis of coronary disease[11] and consequently their potential as immunomodulators in other immune-mediated diseases. Foremost among the alternative downstream pathways that are affected by statins are those that depend on the supply of intermediate products of the cholesterol biosynthetic pathway (FIG. 1). In particular, the 15-carbon farnesyl pyrophosphate (FPP) and the 20-carbon geranylgeranyl pyrophosphate (GGPP). These isoprenoid pyrophosphates have attracted considerable attention, because they function as adjuncts in post-translational prenylation of various important cell-signalling proteins[12].

Prenylation occurs on proteins containing a carboxy-terminal CaaX (where C is cysteine, a is an aliphatic amino acid and X is any amino acid) motif, and it has been estimated that there are in excess of 100 known and hypothetical prenylated CaaX-containing proteins encoded in the human genome. Among these proteins are about 40 members of the small GTPase family of molecular switch proteins that include cell-division cycle 42 (CDC42), RAC and RAS homologue (RHO). These small proteins cycle

Prenylation
Prenylation (or isoprenylation) is the post-translational modification of a protein through the addition of an isoprenoid lipid; namely the 15-carbon farnesyl or 20-carbon geranylgeranyl lipid moiety derived from the cholesterol synthesis pathway.

Lipophilicity
The measure of a molecules ability to dissolve in lipid (oil) as opposed to water. Lipophilic or 'lipid-loving' molecules show a preference for dissolving in lipids.

between an inactive GDP-bound state and an active GTP-bound state, and they have crucial roles in controlling multiple signalling pathways, many of which are involved in reorganization of the cytoskeleton[13].

Prenylation, however, is not confined to proteins containing the CaaX sequence, but also occurs on members of the RAB family of RAS-related G-proteins — of which there are in excess of 60 proteins — most of which contain a CC or CXC C-terminal sequence in place of the CaaX motif. The RAB family of small GTP-binding proteins are essential signalling elements in the control of intracellular membrane trafficking[13]. For all prenylated proteins identified so far, and they constitute up to 2% of total cellular protein, the lipophilic prenyl group enables these proteins to anchor to cell membranes, which in most cases is an essential requirement for their biological function. In addition to promoting membrane interactions, prenylation also seems to have an important role in crucial protein–protein interactions. By inhibiting HMG-CoA reductase, statins reduce the availability of these intermediate metabolites and so the activity of key cell-signalling molecules. Given the central role these small GTP-binding proteins have in determining cell function, it is not surprising that the immune response will be modified independently of their lipid-lowering effect (TABLE 1).

Modulation of immune function by statins

Although it has been appreciated for the past 15 years that statins have antiproliferative effects on lymphocytes and other cell types[14,15], more recent studies indicate that statins also have immunomodulatory properties that alter the function of both T cells and antigen-presenting cells (APCs) (FIG. 2). In 1997, Pahan *et al.*[16] observed that *in vitro* treatment of macrophages and central nervous system (CNS)-resident APCs (such as microglial cells and astrocytes) with lovastatin prevented expression of tumour-necrosis factor (TNF) and interleukin-1β (IL-1β). Inhibition of these pro-inflammatory mediators raised the possibility that statins might provide benefit in neuroinflammatory disease and, by extrapolation, other autoimmune disorders. This concept was first tested by Singh and colleagues, who showed that lovastatin reduced mononuclear-cell infiltration into the brain and attenuated the clinical signs of experimental autoimmune encephalomyelitis (EAE), the animal model of multiple sclerosis[17,18]. Since then, further *in vitro* studies have shown that statins suppress several key functions of the immune system that influence the development of autoimmune disease. The testing of statin therapy in animal models of inflammatory disease and, more recently, in clinical trials has provided tantalizing evidence that this class of drug might be of benefit to patients with diseases such as multiple sclerosis, rheumatoid arthritis and systemic lupus erythematosus (SLE).

MHC class II expression. Of particular relevance to immune modulation in T-cell-mediated inflammatory disease was the observation that statins inhibit interferon-γ (IFNγ)-inducible expression of MHC class II molecules by APCs (human monocyte-macrophages and saphenous vein endothelial cells) and prevent antigen presentation to $CD4^+$ T cells[19] (FIG. 2). This finding was of special importance as earlier studies raised the possibility that autoimmune disease might be treatable with antibodies specific for MHC class II molecules[20–24]. Indeed, Feldmann had proposed that a crucial step in the pathophysiology of autoimmune disease was the aberrant expression of MHC class II molecules in tissues in which these molecules are not constitutively expressed[25]. Increased MHC class II expression has been shown to occur in several autoimmune diseases, including multiple sclerosis, rheumatoid arthritis, myocarditis and SLE.

Therapeutic targeting of MHC class II molecules is, therefore, an attractive strategy for modifying autoimmune disease, and the recent seminal finding by Kwak *et al.*[19] reinforces this view. Statins inhibit IFNγ-inducible expression of the MHC class II transactivator (CIITA), the master regulator for MHC class II expression[19], with atorvastatin being more potent than either lovastatin or pravastatin. Although these observations indicated that statins inhibit MHC class II upregulation through selective inhibition of expression from the IFNγ-inducible CIITA-promoter pIV, more recent data indicate that statins also inhibit IFNγ-inducible CIITA expression from pI, indicating that statins are not selective for pIV, but inhibit IFNγ-inducible CIITA expression in general[26]. Interestingly, inhibition of MHC class II expression by simvastatin can be reversed in human microvascular endothelial cells by both mevalonate and GGPP, but not squalene, indicating the involvement of small GTPases in the inhibitory process. Although statins clearly inhibit induced MHC class II expression, it seems that constitutive expression by mature professional APCs is largely unaffected. These data provided a compelling rationale for the use of statins in treating T-cell-mediated disease and have led to various studies that further reveal the pleiotropic effects of such drugs in an autoimmune setting.

Co-stimulatory molecule expression. For an effective T-cell response to antigen presentation, not only do T cells require antigen presented in the context of MHC class II molecules, but they also require the recognition of other co-stimulatory molecules. In professional APCs, both simvastatin and atorvastatin prevent cytokine-induced maturation, resulting in a failure to express high levels of CC-chemokine receptor 7 (CCR7), CD40, CD83, CD86 and HLA-DR[28]. Unsurprisingly, the ability of these statin-treated dendritic cells (DCs) to induce T-cell proliferation was greatly reduced and, consistent with this being mediated by an effect on protein prenylation, could be reversed by either mevalonate or GGPP. In the CNS, where microglial cells are thought to function as tissue-resident APCs, expression of co-stimulatory molecules is also modulated by statins. *In vitro* treatment of microglial cells with atorvastatin results in inhibition of IFNγ-inducible expression of CD40, CD80 and CD86 (REF. 26). Moreover, in vascular endothelial cells, statins reduce cytokine-induced *CD40* mRNA and protein expression, which may[29] or may not[30] be reversed by mevalonate. Overall, these data indicate that statins inhibit cytokine-mediated activation of co-stimulatory gene expression (FIG. 2). Of particular

Table 1 | **Summary of the role of prenylated proteins in mediating immune function**

Prenylated protein	Function
Leukocyte motility	
CDC42, RAC1	Forward cell movement through formation of membrane protrusions (lamellipodia and filopodia)
CDC42, RAC1, RHOA	Formation of focal complexes and podosomes
CDC42	Directional leukocyte migration; macrophage and lymphocyte chemotaxis
RHOA	Leukocyte tail retraction during transmigration
RAP1	Increased leukocyte substrate motility and migration
RAC1	LFA1-induced T-cell motility
Antigen uptake, processing and presentation	
CDC42, RAC	Cytoskeleton remodelling for antigen endocytosis and immunological synapse formation
RAB proteins	Antigen processing and presentation
CDC42, RHO	Antigen presentation
RAC1, RAC2	Formation of mature DC dendrites; polarized short-range migration to T cells for T-cell priming
RAP1	Regulation of LFA1 avidity for ICAM1
Leukocyte activation, proliferation and function	
RAP1	TCR clustering and increased LFA1 avidity for ICAM1 after activation by TCR ligation; increased integrin-mediated adhesion after chemokine activation
RAS	Regulation of transcription factors that control cytokine transcription after ligation of TCRs and some cytokine receptors
RAC1	T-cell fate in the thymus; regulation of actin cytoskeletal dynamics for clustering of TCRs, adhesion molecules and signalling receptors, and immunological synapse formation; IL-2 secretion and T-cell proliferation after TCR ligation
RAC2	$CD4^+$ T-cell differentiation to T_H1 cells through activation of *IFN*γ gene expression
RHOA	Regulation of BCR signalling and B-cell proliferation
CDC42, RAC1, RAS, RHO	Cell-cycle progression and proliferation
RAC, RHO	PKCθ-dependent AP1 and NF-κB activation during proliferation; JNK activation in T_H-cell differentiation; cytoskeletal reorganization, receptor clustering and IL-2 secretion after CD3 stimulation; NF-κB activation in monocytes
CDC42, RAC, RHO	Inhibition of CTL- and CD95-induced apoptosis
RAB27A	Exocytosis of lytic granules in CTLs
Phagocytosis	
CDC42, RAC1	Formation of the phagocytic cup
RAC	Induction of NADPH oxidase production of superoxide-mediated phagosome function
RHO	Superoxide formation during phagocytosis
RAP1, RHO	Complement-mediated phagocytosis
Leukocyte transvascular migration	
RAP1	Chemokine-receptor-mediated integrin activation and lymphocyte transvascular migration through ICAM1 and VCAM1; PECAM1-mediated leukocyte signalling to increase integrin adhesion
RAS, RHO	Expression of monocyte matrix metalloproteinase 9 for leukocyte migration
RHOA	Induction of high-affinity state of LFA1
RAP1, RAP2	CXC-chemokine-ligand-12-induced B-cell migration
RAP2	LFA1- and VLA4-mediated B-cell adhesion
CDC42, RAC1	Chemokine-induced lymphocyte polarization and directional migration
RAC2	Neutrophil migration
Endothelial-cell immune function	
RHO	Formation and maintenance of the endothelial-cell docking structure; ICAM1-mediated endothelial-cell signalling for lymphocyte migration; endothelial-cell actin cytoskeletal reorganization for monocyte migration; endothelial-cell junction opening; inhibition of eNOS and NO production; adhesion-receptor clustering on endothelial cells for monocyte adhesion and spreading; LPS-induced ICAM1 expression and TNF-induced E-selectin expression by endothelial cells
RHO, RAC1	Induction of ICAM1, VCAM1 and E-selectin expression through activation of NF-κB-family members
RAC1	VCAM1-mediated endothelial-cell signalling for NADPH oxidase activation, ROS production, junction opening and monocyte transvascular migration
RAP1	Increased endothelial-cell junction assembly by reducing leukocyte transmigration

AP1, activator protein 1; APC, antigen-presenting cell; BCR, B-cell receptor; CCR, CC-chemokine receptor; CDC42, cell-division cycle 42; CTL, cytotoxic T lymphocyte; DC, dendritic cell; eNOS, endothelial-cell nitric-oxide synthase; E-selectin, endothelial-cell selectin; ICAM1, intercellular adhesion molecule 1; IFNγ, interferon-γ; IL-2, interleukin-2; JNK, JUN N-terminal kinase; LFA1, lymphocyte function-associated antigen 1; LPS, lipopolysaccharide; NF-κB, nuclear factor-κB; NO, nitric oxide; PECAM, platelet/endothelial cell-adhesion molecule; PKCθ, protein kinase C-θ; RHOA, RAS homologue gene-family member A; ROS, reactive oxygen species; TCR, T-cell receptor; T_H, T helper; TNF, tumour-necrosis factor; VCAM1, vascular cell-adhesion molecule 1; VLA4, very late antigen 4.

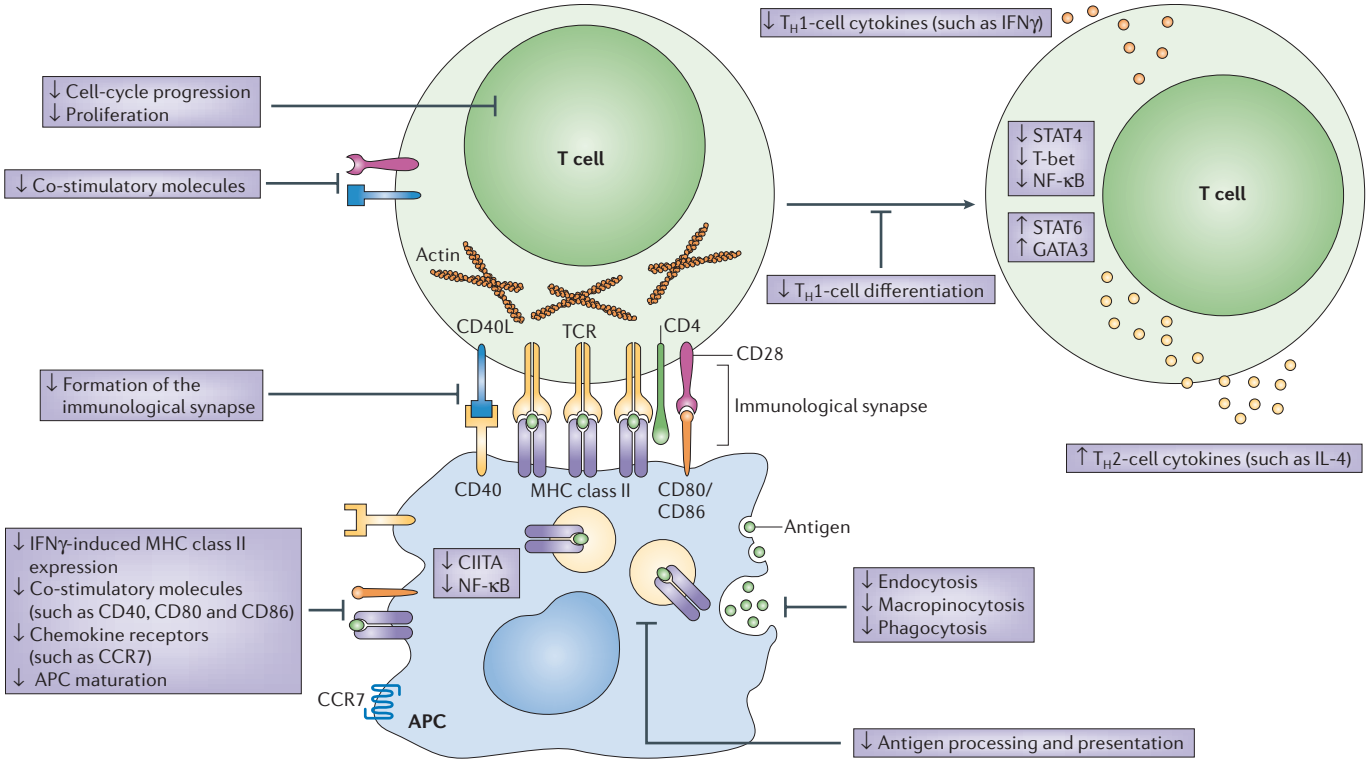

Figure 2 | **The effect of statins on T-cell and antigen-presenting cell function.** Statins inhibit cytokine-inducible expression of MHC class II molecules and co-stimulatory molecules by antigen-presenting cells (APCs) and prevent antigen presentation to $CD4^+$ T cells. T-cell proliferation is abrogated through modulation of GTPase-linked regulation of cell-cycle progression and proliferation. In addition, the effect of statins on cytoskeletal organization interferes with formation of the immunological synapse. Statins also alter the T-cell profile by inhibiting the secretion of pro-inflammatory cytokines through inhibition of signal transducer and activator of transcription 4 (STAT4) and the transcription factor T-bet, which are required for T helper 1 (T_H1)-cell differentiation. Conversely, statins might also increase the secretion of anti-inflammatory T_H2-type cytokines through the activation of both STAT6 and GATA-binding protein 3 (GATA3), which are involved in T_H2-cell differentiation. CCR7, CC-chemokine receptor 7; CD40L, CD40 ligand; CIITA, class II transactivator; IFNγ, interferon-γ; IL-4, interleukin-4; NF-κB, nuclear factor-κB; TCR, T-cell receptor.

relevance to SLE, which is a progressive autoimmune disease characterized by the production of high levels of autoantibodies, atorvastatin also reduces the expression of MHC class II molecules and of the co-stimulatory molecules CD80 and CD86 by B cells. Concomitant with this was impaired antigen presentation and T-cell responses[31] and a reduction of disease severity in an experimental animal model of SLE.

Antigen presentation and T-cell proliferation. A prerequisite for antigen presentation by APCs is endocytosis of antigen, its internal processing and subsequent presentation by MHC class II molecules on the cell surface. It is clear that this process is governed in part by remodelling of the cytoskeleton and, as such, requires the input of small GTPases. In DCs, the endocytic pathway requires activation of RAC and CDC42 (REF. 32), and accordingly the process might be subject to modification by statins. In agreement with this suggestion, constitutively active CDC42 and RHO enhance the ability of DCs to present antigen to T cells. Any reduction in small GTPase activity will also have a significant impact on other functions that require modification of the actin cytoskeleton. For example, both CDC42 and RAC are involved in the formation of the T-cell-receptor complex as it binds to the MHC class II complex on APCs to form the immunological synapse, whereas CDC42, RAS, RHO and RAC1 are all involved in cell-cycle progression and proliferation. The observation that statin inhibition of antigen-induced T-cell proliferation is linked to negative regulation of cell-cycle progression is consistent with inhibition of GTPase-mediated cell proliferation[33]. There are multiple stages at which statins might have an effect during T-cell activation and proliferation (FIG. 2), and it is, therefore, not surprising that one of the most common features of statin treatment in experimental autoimmune disease is reduction in T-cell proliferation (TABLE 2). Moreover, lovastatin, simvastatin and mevastatin have all been shown to inhibit, in a dose-dependent manner, the proliferation of peripheral-blood mononuclear cells (PBMCs) harvested from untreated or IFN-β1b-treated patients with multiple sclerosis[34].

It is possible that MHC class II expression might also be affected by statins in a cholesterol-dependent manner, as it has been postulated that reduced cholesterol might affect the integrity of cell-membrane lipid rafts. These structures, which are believed to be important microdomains for the assembly of signalling complexes, have been reported to be disrupted by simvastatin, leading

to a loss of association of MHC class II molecules[35]. By contrast, it has been shown that in Jurkat T cells lipid rafts were only disrupted when statins were applied in the absence of serum[36]. Furthermore, *in vivo* data indicate that treatment of mice with atorvastatin (10 mg kg^{-1}) has no effect on T-cell cholesterol content[37]. Therefore, the effect of statins on lipid-raft formation and subsequent signalling remains uncertain.

T-cell phenotype. In most cases reported so far, statin administration *in vivo* has been found to prevent the induction of experimental T helper 1 (T_H1)-cell-mediated autoimmune diseases (TABLE 2). More importantly, however, statins can modulate disease progression after the induction of disease. In a chronic-relapsing model of multiple sclerosis, EAE, statin treatment commenced after onset of the acute phase was found to reverse disease[26] and when initiated during disease remission, it prevented relapse[26,33,38]. An important effector mechanism that was responsible, at least in part, for this statin-mediated disease amelioration seemed to function through a change in T-cell phenotype (FIG. 2).

Following atorvastatin treatment of EAE, which resulted in a decrease in CNS inflammation and T-cell proliferation, Youssef *et al.*[26] showed that there was a concomitant shift in the pattern of T-cell cytokine secretion. More specifically, there was a significant induction in the secretion of anti-inflammatory T_H2-type cytokines (IL-4, IL-5 and IL-10) and phosphorylation (activation) of signal transducer and activator of transcription 6 (STAT6), which is involved in IL-4-dependent T_H2-cell differentiation. Conversely, phosphorylation of STAT4 — which is required for IL-12-dependent T_H1-cell differentiation — was inhibited and the secretion of IL-2, IL-12, IFNγ and TNF was reduced.

Additionally, using an adoptive transfer model, it was shown that these T_H2-differentiated cells could protect recipient mice from developing disease. This was corroborated by Stanislaus *et al.*[39], who showed that compared with untreated EAE rats, lovastatin-treated animals had decreased levels of IFNγ, whereas IL-10 levels were markedly increased. That this was a key effector mechanism in alleviation of T_H1-cell-mediated autoimmune disease was further elaborated by Nath *et al.*[40]. They reported that statin treatment might also promote T-cell expression of GATA-binding protein 3 (GATA3) — a transcription factor involved in T_H2-cell differentiation — and downregulate activation of nuclear factor-κB (NF-κB) and T-bet — a T-box transcription factor associated with T_H1-cell differentiation[41–43]. This group also showed that there was a concomitant increase in the levels of T_H2-type cytokine transcripts[44]. In addition, Aktas *et al.*[33] found that atorvastatin, when inhibiting the development of chronic EAE and reducing autoreactive T-cell proliferation, caused a strong attenuation of the T_H1-type immune response, with evidence for increased secretion of T_H2-type cytokines. The capacity for statins to cause a shift in T-cell phenotype, from T_H1 to T_H2 bias, is not restricted to EAE but has also been observed in a T_H1-driven model of experimental autoimmune myocarditis (EAM)[45].

Notwithstanding these intriguing findings, not all studies have observed a statin-induced bias towards a T_H2-type cytokine profile. In experimental autoimmune uveitis , lovastatin[46], but not atorvastatin[47], was found to attenuate disease and inhibit T-cell IFNγ production with little effect on T_H2-type cytokine production. Similarly, high-dose simvastatin treatment of mice with collagen-induced arthritis resulted in a significant suppression of collagen-specific T_H1-type humoral and cellular immune responses[48] without any evidence of a corresponding upregulation of T_H2-type cytokines. In an identical arthritis model, however, atorvastatin and rosuvastatin had no effect, whereas the same regimen of simvastatin resulted in attenuation of disease but was associated with serious side-effects[49]. In a seperate study, low doses of atorvastatin were efficacious in a rat model of adjuvant-induced arthritis[50], although cytokine profiles were not reported. Additionally, fluvastatin treatment of EAM was found to decrease the production of T_H1-type cytokines[51], but this also coincided with a significant reduction in the production of the T_H2-type cytokines IL-4 and IL-10. Conversely, *in vitro* studies with human PBMCs from patients with multiple sclerosis revealed that simvastatin, lovastatin and mevastatin all failed to induce either a T_H1 or a T_H2 bias, but they did increase both IFNγ and IL-12 production[34]. Furthermore, when cytokine profiles were determined in CD3-specific-antibody-activated T cells from simvastatin-treated multiple sclerosis patients who showed clinical improvement, no cytokine alteration was observed[52]. Despite such variations, throughout the animal studies the most consistent and robust finding is a beneficial suppression of the T_H1-cell response. Any reported deviations can probably be explained by differences in the model system and statin used. In light of this, it is interesting to note that in Brown Norway rats, which are less susceptible to EAE owing to an inherent T_H2 bias[53], atorvastatin fails to alleviate disease[54]. How the effect of statins on the T_H1/T_H2 balance is mediated remains to be fully elucidated. What is clear is that atorvastatin-mediated T_H2-cell differentiation can be reversed by mevalonate, indicating that either mevalonate or its metabolites might promote T_H1-cell differentiation[26]. In addition, recent studies have shown that specific isoprenoid intermediates modulate this effect through differential farnesylation and prenylation of RAS and RHO[37]. The role of GTPase in statin-mediated alleviation of disease is further endorsed by the finding that prenyl transferase inhibitors also attenuate EAE in a similar manner to statins[55]. It is of interest to note that in mevalonate kinase deficiency — which is characterized by periodic fever, neuralgic pain in the joints and hyperproduction of IgD — abnormal production of isoprenoids mediates many of the autoimmune abnormalities[56,57].

Leukocyte adhesion molecules. Leukocyte adhesion to the vascular wall and subsequent migration into the tissue is central to the pathogenesis of autoimmune disease (FIG. 3). This multistep process is comprised of adhesive and signalling events that begin with transient leukocyte tethering to the endothelial-cell surface, and culminate in leukocyte infiltration into the subendothelial space and beyond. Both leukocytes and endothelial cells participate

Table 2 | **Outcome of statin treatment in animal models of autoimmune disease**

Statin	Dose and treatment protocol	Animal model	Effect	Refs
Experimental autoimmune encephalomyelitis				
Atorvastatin	1 and 10 mg per kg, given orally each day	SJL/J mice (antigen: PLP) C57BL/6 mice (antigen: MOG) B10. PL mice (antigen: MBP)	Attenuation of disease; decrease in leukocyte infiltration; shift from T_H1- to T_H2-type cytokine profile; inhibition of T-cell proliferation; inhibition of co-stimulatory molecule expression	26
Atorvastatin	10 mg per kg, given orally or subcutaneously each day	SJL/J mice (antigen: PLP)	Attenuation of disease; decrease in leukocyte infiltration; blockade of T_H1-cell responses with increase in T_H2-type cytokines; inhibition of T-cell proliferation	33
Atorvastatin	10 mg per kg, given orally each day	C57BL/6 mice (antigen: MOG)	Attenuation of disease; decrease in leukocyte infiltration; blockade of T_H1-cell responses	46
Lovastatin	10 mg per kg, given intraperitoneally each day	Biozzi ABH mice (spinal-cord homogenate)	Attenuation of disease; inhibition of leukocyte migration across the blood–brain barrier	38
Lovastatin	2 and 5 mg per kg, given intraperitoneally each day	SJL/J mice (antigen: PLP)	Attenuation of disease; inhibition of pro-inflammatory cytokine biosynthesis; shift towards T_H2-biased T-cell responses	40
Lovastatin	2 mg per kg, given intraperitoneally each day	Lewis rats (antigen: MBP)	Attenuation of disease; inhibition of iNOS expression and pro-inflammatory cytokine production	17
Lovastatin	2 mg per kg, given intraperitoneally each day	Lewis rats (antigen: MBP)	Attenuation of disease; shift from T_H1- to T_H2-type cytokine profile	39
Lovastatin	2 mg per kg, given intraperitoneally each day	Lewis rats (antigen: MBP)	Attenuation of disease; reduction in mononuclear-cell infiltration; reduction in inflammatory cytokine production and LFA1 expression	18
Lovastatin	2 mg per kg, given intraperitoneally each day	Lewis rats (antigen: MBP)	Attenuation of disease; decrease in leukocyte infiltration; increase in T_H2-type cytokine transcription	44
Simvastatin	20 mg per kg, given orally each day	Brown Norway rats (antigen: MOG)	No effect on disease	54
Experimental arthritis				
Simvastatin	10–40 mg per kg, given intraperitoneally each day	DBA/1 mice (antigen: collagen)	Attenuation of disease; decrease in T_H1-cell responses	48
Atorvastatin	1 or 100 mg per kg, given orally each day	DBA/1 mice (antigen: collagen)	No effect on disease	49
Rosuvastatin	0.2 or 2 mg per kg, given subcutaneously each day	DBA/1 mice (antigen: collagen)	No effect on disease	49
Simvastatin	40 mg per kg, given intraperitoneally or orally each day	DBA/1 mice (antigen: collagen)	Attenuation of disease, with side effects	49
Atorvastatin	1–10 mg per kg, given orally each day	Holtzman rats (adjuvant)	Attenuation of disease	50
Experimental autoimmune uveoretinitis				
Lovastatin	20 mg per kg, given intraperitoneally each day	B10RIII mice (antigen: IRBP)	Attenuation of disease; decrease in leukocyte infiltration; modulation of T_H1-cell responses	46
Atorvastatin	10 mg per kg, given orally each day	B10RIII mice (antigen: IRBP)	Mild attenuation of disease	46
Atorvastatin	1 or10 mg per kg, given orally each day	B10RIII mice (antigen: IRBP)	No effect on disease	47
Experimental autoimmune myocarditis				
Atorvastatin	1 or 10 mg per kg, given orally each day	Lewis rats (antigen: porcine cardiac myosin)	Decrease in cardiac inflammation and improvement in cardiac function; shift from T_H1- to T_H2-type cytokine profile	45
Fluvastatin	3.75 or 7.5 mg per kg, given orally each day	Lewis rats (antigen: porcine cardiac myosin)	Improvement in cardiac function; decrease in $CD4^+$ T-cell infiltration; decrease in T_H1-type cytokines and inhibition of NF-κB	51
Experimental systemic lupus erythematosus				
Atorvastatin	30 mg per kg, given intraperitoneally each day	Female NZB/W F1 mice (spontaneous)	Improvement in clinical outcome with reduced glomerular injury; decrease in MHC class II and co-stimulatory molecule expression; decrease in T-cell proliferation	31

Atorvastatin, Lipitor (Pfizer); fluvastatin, Lescol (Novartis); lovastatin, Altoprev (Andrx Labs) and Mevacor (Merck & Co.); rosuvastatin, Crestor (AstraZeneca); simvastatin, Zocor (Merck & Co.). iNOS, inducible nitric-oxide synthase; IRBP, interphotoreceptor retinoid-binding protein; LFA1, lymphocyte function-associated antigen 1; MBP, myelin basic protein; MOG, myelin oligodendrocyte glycoprotein; NF-κB, nuclear factor-κB; PLP, proteolipid protein; T_H, T helper.

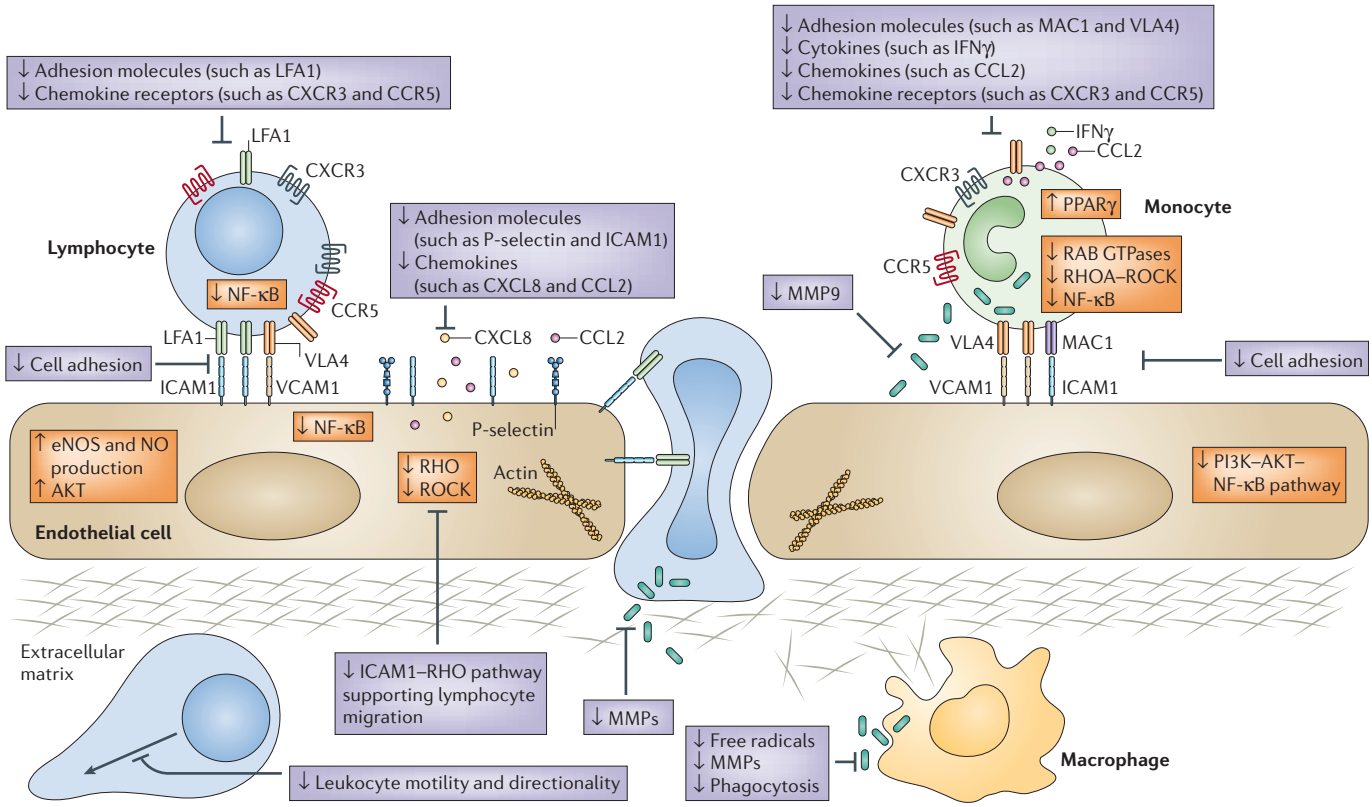

Figure 3 | **The effect of statins on leukocyte adhesion and migration and endothelial-cell immune function.** Cell-adhesion-molecule expression by leukocytes and endothelial cells are attenuated by statins, resulting in reduced adhesion and transvascular migration. In addition, statins inhibit chemokine and matrix metalloproteinase (MMP) secretion, which further interferes with leukocyte migration. In the endothelium, adhesion-molecule signalling that is required for leukocyte migration is blocked through the modulation of RAS homologue (RHO) and other small GTPases. This might also result in stabilization of the endothelial cell–cell junction. The effect of statins on the cytoskeleton alters leukocyte motility and directional migration in response to chemotactic gradients. CCL, CC-chemokine ligand; CCR, CC-chemokine receptor; CXCL, CXC-chemokine ligand; CXCR, CXC-chemokine receptor; eNOS, endothelial-cell nitric-oxide synthase; ICAM1, intercellular adhesion molecule 1; IFNγ, interferon-γ; LFA1, lymphocyte function-associated antigen 1; MAC1, macrophage receptor 1; MMP, matrix metalloproteinase; NF-κB, nuclear factor-κB; NO, nitric oxide; PI3K, phosphatidylinositol 3-kinase; PPARγ, peroxisome-proliferator-activated receptor-γ; P-selectin, platelet selectin; RHOA, RHO gene-family member A; ROCK, RHO-associated coiled-coil-containing protein kinase; VCAM1, vascular cell-adhesion molecule 1; VLA4, very late antigen 4.

pro-actively in this complex event, and each requires specific activation signals before successful leukocyte extravasation can occur. Of paramount importance to this process is the expression of cell-adhesion molecules in the correct configuration and state of activation, as these have a central and cooperative role in dictating the pattern and extent of leukocyte recruitment.

The integrin lymphocyte function-associated antigen 1 (LFA1; CD11a–CD18) on lymphocytes, which binds to the immunoglobulin-superfamily molecule intercellular adhesion molecule 1 (ICAM1), is one of the key adhesion molecules involved in both adhesion/migration and co-stimulation. Surprisingly, certain statins can alter the binding capacity of LFA1 to ICAM1, independently of either cholesterol lowering or inhibition of mevalonate and its metabolites. This is achieved through direct binding to the so-called lovastatin-binding site (L-site) on the extracellular domain of LFA1, which blocks binding to the cognate binding partner of LFA1 and inhibits both lymphocyte adhesion and co-stimulation[58]. However, the significance of the L-site is controversial, as several studies indicate that statin-mediated inhibition of APC-induced pro-inflammatory cytokines and inhibition of the upregulation of co-stimulatory molecules, as well as T_H2-cell differentiation can be reversed by mevalonate[26,33]. This indicates that, although statins might interact directly with LFA1 and possibly other proteins involved in T-cell regulation, many crucial components in immune regulation are influenced by the mevalonate pathway.

A reduction in leukocyte infiltration of the target organ is one of the most consistent outcomes of statin therapy in autoimmune disease (TABLE 2). This might be mediated, at least in part, by a direct effect on adhesion-molecule expression, resulting in an impaired ability of leukocytes to adhere to and migrate across the vascular barrier. In support of this, several reports have now showed that statins can modulate the expression of both leukocyte and endothelial-cell adhesion molecules. In monocytes, the integrin macrophage receptor 1 (MAC1;

CD11b–CD18) is involved in adhesion to endothelial cells through its interaction with ICAM1. Treatment of monocytes with lovastatin *in vitro* has been shown to reduce the cell-surface expression of CD11b and consequently monocyte adhesion. This was not due to steric hindrance, as co-incubation with mevalonate reversed the effects[59]. In a similar study, treatment of monocytic U937 cells with cerivastatin significantly decreased their ability to adhere to activated human umbilical vein endothelial cells (HUVECs) under conditions of flow without affecting rolling. This decrease in adhesive properties corresponded with the downregulation of cell-surface expression of the integrin chains CD11a and CD49d (a subunit of very late antigen 4, VLA4) by monocytic U937 cells and an apparent alteration of RHO gene-family member A (RHOA) function[60]. Moreover, simvastatin, atorvastatin and cerivastatin were found to downregulate PBMC expression of CD18 and CD11a at both the mRNA and protein level, and to decrease PBMC binding to TNF-stimulated HUVECs[61].

Endothelial-cell adhesion molecules. Statins can also modulate endothelial-cell adhesion molecule expression, with most evidence tending towards the effect being inhibitory. This is particularly true for both platelet (P)- and endothelial (E)-selectin, where downregulation of E-selectin is reported to be mediated by inhibition of RHO and subsequent RHO-mediated gene expression[62]. Numerous studies have also shown that statins reduce both constitutive and induced expression of ICAM1, which is directly involved in sustaining both leukocyte adhesion and diapedesis. Contrary to this, Sadeghi *et al.*[63] reported that simvastatin augmented cytokine-induced ICAM1 expression and that this could be reversed by co-administration of GGPP or mevalonate. In the case of vascular cell-adhesion molecule 1 (VCAM1) expression, it has recently been reported that lovastatin inhibition of VCAM1 expression by brain endothelial cells — mediated through inhibition of the phosphatidylinositol 3-kinase (PI3K)–AKT–NF-κB pathway — results in a significant reduction in transendothelial-cell migration by monocytes[64]. This report of the ability of statins to inhibit NF-κB activation is in agreement with other studies, but at odds with reports in which AKT was activated (discussed later). Nevertheless, inhibition of NF-κB seems to be a robust outcome and raises the prospect of modulating other pro-inflammatory endothelial-cell-derived molecules that are also regulated by this transcription factor. This suggestion is supported by the finding that in human endothelial cells statins decrease the production of CXC-chemokine ligand 8 (CXCL8; also known as IL-8) and CCL2 (also known as MCP1)[65–67] — two chemokines that contribute to the process of leukocyte recruitment.

Leukocyte motility and migration. The RHO family of GTPases, of which CDC42, RAC and RHO are the best characterized, regulate actin and microtubule dynamics, and are consequently central to virtually all processes that involve motility (TABLE 1). It is hardly surprising that statins, which affect RHO GTPase function, also influence leukocyte motility and migration. Stabilization of directional movement by cells (chemotaxis) requires external cues such as chemokines[68], and this process is controlled by CDC42. Therefore, during chemotaxis of macrophages along a chemotactic gradient, inhibition of CDC42 results in random movement and loss of directionality (chemokinesis), whereas inhibition of RAC blocks all cell movement[69]. Also affecting this process is the observation that statins downregulate expression of chemokine receptors by B cells, T cells and macrophages[34,67], which results in a loss of outside–in signalling. Consistent with small GTPases being involved in cytokine-induced chemokine-receptor expression, Veillard *et al.*[67] showed that similar effects could be achieved using geranylgeranyl transferase inhibitors. Lymphocytes also use the small GTPase RAP1, which is activated within seconds following treatment with the chemokines CXCL12 (also known as SDF1) and CCL21 (also known as SLC). This results in enhanced integrin-mediated adhesion to endothelial-cell ICAM1 and VCAM1, as well as increased leukocyte motility and transendothelial-cell migration[70].

Leukocyte migration, especially once the leukocyte breaches the vascular barrier, is also reliant on matrix metalloproteinase (MMP) expression, to ease the passage through the basal lamina and the extracellular matrix beyond. As with many other pro-inflammatory molecules, statins also impair MMP secretion by leukocytes. This is especially true for immune cells of the monocyte/macrophage lineage, in which MMP9 secretion is inhibited in a dose-dependent manner, an effect that can be reversed by the simultaneous addition of exogenous mevalonate[71]. It was postulated that as RAB GTPases are essential for regulating membrane traffic and protein secretion, statin modulation of prenylation might underlie the mechanism through which inhibition is achieved. By contrast, secretion of MMP9 from human saphenous vein smooth-muscle cells can be inhibited by blocking the RHOA–ROCK (RHO-associated coiled-coil-containing protein kinase) pathway[72]. Also, secretion of MMP9 from the monocytic cell line THP1 can be induced using a geranylgeranyl transferase type I inhibitor and C3 exoenzyme, implicating RHO in this inhibitory process[73]. In addition, cerivastatin-mediated inhibition of monocyte MMP9 secretion was found to be accompanied by attenuation of NF-κB translocation into the nucleus and could be reversed by FPP, thereby implicating RAS[74]. Together, these data show that multiple small-GTPase-signalling pathways are involved in MMP9 production and as such might represent the mechanism by which statins mediate their effect. An alternative mechanism, however, has also been proposed whereby atorvastatin-mediated inhibition of MMP9 (as well as CCL2 and TNF) production by monocytes might be mediated through activation of the nuclear receptor transcription factor peroxisome-proliferator-activated receptor-γ (PPARγ)[75]. Interestingly, PPARγ expression is decreased by pro-inflammatory cytokines but is induced by the T_H2-type cytokine IL-4. In contrast to the inhibitory effect on secretion, exposure of MMPs to statins might actually increase their proteolytic capacity, especially that of MMP2 (REF. 76).

Outside–in signalling
The initiation of an intracellular signalling pathway through extracellular ligand engagement of a cell-surface receptor.

Endothelial-cell adhesion molecule receptor signalling. Endothelial-cell adhesion molecules serve not only as docking structures, but they also initiate signalling cascades that are necessary for successful leukocyte penetration through the vascular barrier. In this regard, ICAM1 fulfils an important role in controlling transvascular migration through the induction of signalling cascades that mediate endothelial-cell reorganization of the actin cytoskeleton. Therefore, on engagement of ICAM1 to its cognate binding partners (LFA1 on lymphocytes and MAC1 on monocytes), there is propagation of divergent signalling pathways, the functional consequences of which are subject to increasing investigation. So far, it has been shown that ICAM1-mediated signalling results in tyrosine phosphorylation of cytoskeletal-associated proteins, activation of MAP kinases (such as p38, extracellular-signal-regulated kinase (ERK) and JUN N-terminal kinase (JNK)) and of the transcription factors NF-κB and FOS, upregulation of *ICAM1* and *VCAM1* gene expression and reorganization of the actin cytoskeleton to facilitate lymphocyte migration[77,78]. In brain endothelium, RHO GTPases seem to be central upstream signalling components in the ICAM1-mediated pathway that is responsible for sustaining lymphocyte migration[79–81], and as such they represent an intriguing target for statins. Indeed, statins have been shown to inhibit RHO prenylation in endothelial cells, which results in inhibition of the ICAM1-mediated pathway and transvascular lymphocyte migration[38]. That this effect could be reversed by endothelial cells expressing RHO with a myristoylation site, which renders the cell insensitive to loss of isoprenylation[38], lends considerable weight to the assertion that endothelial-cell ICAM1-mediated signalling through RHO is of fundamental importance to lymphocyte extravasation in the CNS.

VCAM1 also transduces signals to the endothelial cell and initiates signalling cascades that are essential to leukocyte, especially monocyte, migration. Again, the activation of small GTPases is a key factor and therefore VCAM1-mediated processes are susceptible to statin inhibition. Engagement of VCAM1 results in calcium-mediated RAC1 activation[82], an increase in NADPH oxidase activity, which in turn results in reactive oxygen species (ROS) production, actin reorganization and loss of vascular endothelial cadherin (VE-cadherin) cell–cell contact[83]. Moreover, inhibition of either RAC1 or RHO inhibited VCAM1-mediated signalling pathways, which in turn blocked monocyte transendothelial-cell migration[83,84]. This endothelial-cell pathway can be blocked by statins, which inhibit the prenylation of RAC1 and, in so doing, diminish the production of ROS[85] — powerful activators of the NF-κB (also known as REL) family of transcription factors. As the NF-κB family of transcription factors are pivotal in controlling inflammatory and immune responses, including the expression of endothelial-cell adhesion molecules[86], downregulation of this pathway will affect disease progression.

The VCAM1–RAC1-mediated disruption of the endothelial-cell junction provides an important insight into the potential role of small GTPases in controlling vascular permeability and potentially leukocyte migration. Statins might have an important effect on cell-junction integrity through their indirect inhibitory effect on small GTP-binding proteins. It is now well established that both RHO and RAC modulate the actin cytoskeleton, which in endothelial cells has an important scaffold function at the cortical region stabilizing cell–cell junctions. Induction of RHO-mediated actomyosin contraction can result in cell-junction separation, which might be an essential element in transendothelial-cell migration by leukocytes. RAC activation in endothelial cells, in contrast to epithelial cells, leads to the promotion of junctional disassembly[87] and, as described above, loss of VE-cadherin-mediated cell–cell contact. Therefore, a reduction in RHO and RAC prenylation might make the endothelial cell unable to regulate the cell junction and facilitate leukocyte diapedesis. Interestingly, expression of the chemokine receptor CCR2 (a receptor for CCL2) by brain endothelial cells initiates junctional opening in a RHO-dependent manner[88]. This raises the possibility that statins, which reduce CCL2 expression, will also inhibit this RHO–RHO-kinase-mediated barrier opening.

Endothelial-cell nitric-oxide synthase and nitric oxide. Many studies have attributed the beneficial effect of statins in atherosclerosis to their role in upregulating the expression of endothelial-cell nitric-oxide synthase (eNOS), which is decreased in dysfunctional endothelium. Additionally, statins also reduce levels of oxidized LDL, which has been shown to inhibit eNOS transcription and protein synthesis. In autoimmune disease, however, the role of eNOS and its product nitric oxide (NO) in either the pathogenesis or resolution of disease is less obvious. Nevertheless, there is evidence that maintenance of vascular NO production is beneficial, as it prevents leukocyte chemotaxis[89] and downregulates leukocyte adhesion and migration at the vascular wall[90–92]. These effects of NO might be mediated by inhibition of NF-κB activity, thereby downregulating cytokine-induced adhesion molecule expression[93].

Statins can increase eNOS expression and both basal and induced NO production[94], either by inhibiting the RHO–RHO-kinase pathway that negatively regulates eNOS expression or by stimulating the eNOS-activating AKT- and AMP-activated protein kinase[95,96]. It has been proposed that inhibition of RHO prenylation by statins is a key factor in upregulating eNOS expression and stability[97–99], as the effects can be reversed by GGPP. Interestingly, inhibition of protein prenylation using a geranylgeranyl transferase type I inhibitor results in an increase in eNOS activity and NO production, with a concomitant decrease in NADPH oxidase activity and ROS production[100]. It is important to note, however, that the production of NO is not always beneficial. In the brain, pro-inflammatory cytokines induce inducible NOS (iNOS) expression by astrocytes, which, it is believed, contributes to oligodendrocyte degeneration in multiple sclerosis. Unlike the situation in endothelial cells, in which statins enhance the expression of eNOS,

lovastatin has been shown to inhibit cytokine-mediated expression of iNOS and NO production by astrocytes *in vitro* — in a manner that was reversible by mevalonate and FPP[16] — as well as EAE in rats[17].

Efficacy of statins in human autoimmune disease

It is too early to predict with any confidence whether the promising data, derived from statin therapy in experimental animal models of autoimmune disease, can be translated successfully to the clinic. Most experimental data lead us to believe that alone, or probably in combination with other therapeutic approaches, statins will improve clinical outcome. The relative safety of these agents and their ease of delivery also provides a compelling case for their evaluation in the clinical setting. In multiple sclerosis, the benefit of statin treatment in patients is only just beginning to be properly evaluated, although the outcomes from two small, open-label clinical trials have already been reported. In a purely observational study of seven patients with relapsing–remitting multiple sclerosis, Sena *et al.*[101] reported that lovastatin treatment over a 12-month period resulted in a reduction in the mean number of gadolinium-enhancing lesions but with no accompanying decrease in the expanded disability status scale (EDSS) score. In a separate open-label study involving 28 patients over a 6-month period, treatment with simvastatin significantly reduced the number and volume of gadolinium-enhancing lesions by 44% and 41%, respectively[52]. A concern when interpreting the results from this clinical trial, however, is that the observed reduction in gadolinium-enhancing lesions might reflect a statistical regression to the mean.

It is generally agreed that placebo-controlled clinical trials are necessary to establish whether statins will be efficacious in multiple sclerosis. In this regard, a larger Phase II placebo-controlled clinical trial (funded by the Immune Tolerance Network of the National Institutes of Health) is testing whether atorvastatin can reduce the risk of developing multiple sclerosis activity in patients who have experienced their first clinical CNS demyelinating event, a 'clinically isolated syndrome'. Other human autoimmune diseases are also receiving attention. McCarey *et al.*[102] carried out a 6-month, randomized, double-blind placebo-controlled clinical trial with atorvastatin in patients with rheumatoid arthritis. Although the outcome was modest, atorvastatin had a significant effect on disease activity. The authors quite correctly state that further studies are needed to establish what benefit can be derived from long-term treatment. Finally, in a very preliminary study, short-term simvastatin treatment of three patients with SLE resulted in a significant reduction in proteinuria, providing a tentative indication that statins might offer some clinical benefit[103].

Together, these clinical trials provide some encouragement, although it remains to be seen whether any such benefit is mediated by the same mechanisms that have been proposed in animal studies. In particular, the effect of statins on patient T-cell phenotype and cytokine production remains unclear and is awaited with anticipation. Whatever the mechanism, several issues relating to clinical application remain outstanding and need to be addressed. First, there are differences between statins with respect to their pharmacokinetics and potency[104], and it is still unclear which statin will provide the best outcome with respect to immune modulation in autoimmune disease. Second, the doses applied experimentally to elicit a beneficial effect are considerably greater than those that are currently recommended for the treatment of cardiovascular disease. Some comfort can be gained from the observation that circulating levels of active statin in mice were found to be much lower than could be predicted from the dose[46]. Nonetheless, the circulating concentration still exceeded that which would be acceptable in patients over an extended period and could lead to serious side-effects, such as rhabdomyolysis. The case for combining statins in a reduced dosage with other disease-modifying agents, so that efficacy can be retained while toxicity diminished, is therefore compelling. In fact, data from the EAE model indicate that atorvastatin can enhance the efficacy of glatiramer acetate (Copaxone; Aventis)[105]. Finally, many of the therapeutic effects of statin therapy seem to be mediated through modulation of isoprenoid biosynthesis and consequently small GTPase activity, but not all of these effects are necessarily beneficial. Therefore, GTPases might also act as negative regulators of inflammation and inhibition of these pathways by statins will result in promotion of a pro-inflammatory state. This might explain those reports in which a pro-inflammatory response to statins is observed. It is likely that the cell type, the statin used, the dose and duration will all determine which outcome predominates.

Concluding remarks

Most data now indicate that the greatest therapeutic attribute of statins is their ability to modulate a broad range of pro-inflammatory immune mechanisms through inhibition of small GTPases and other prenylated proteins. Given the enormous repertoire of cell functions that are mediated by prenylated proteins, it is not surprising that modulation by statins will have a diverse effect on immune function. However, the ability to induce downregulation without provoking complete inhibition of these crucial signalling proteins is fundamental to their efficacy — a complete blockade of these molecular switches would, in most cases, be lethal. What statins can accomplish is partial inhibition of an upstream common denominator of multiple regulatory signalling networks that control the immune system. Through subsequent attenuation of protein prenylation, many pro-inflammatory pathways are modulated without adversely affecting other crucial pathways that are necessary for cell survival. The pleiotropic nature of statins is impressive and the weight of data demonstrating efficacy in animal models of autoimmune disease provides us with a compelling rationale to translate such work to the clinical setting. Although caution must be applied, the high degree of patient tolerance to statins and their simplicity of delivery make them a highly attractive addition to currently available immunosuppressive drugs.

Gadolinium-enhancing lesions
Damaged areas (lesions) detected by magnetic resonance imaging (MRI) that have been enhanced by the intravenous administration of a contrast agent (gadolinium) to increase the sensitivity of MRI scans.

Expanded disability status scale (EDSS) score
A widely used neurological and functional scoring system for judging the clinical status of people with multiple sclerosis.

Rhabdomyolysis
Severe muscle toxicity resulting in the breakdown of muscle fibres. A potential side-effect of statins, either in monotherapy or in combination therapy.

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Acknowledgements
J.G. acknowledges support from The Wellcome Trust and Multiple Sclerosis Society (UK). L.S. acknowledges the support of the National Institutes of Heath, the National Multiple Sclerosis Society and the Phil N. Allen Trust. S.S.Z. is funded by the National Institutes of Heath, the National Multiple Sclerosis Society, The Dana Foundation and the Maisin Foundation.

Competing interests statement
The authors declare no competing financial interests.

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