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REVIEW

Update on statin-mediated anti-inflammatory activities in atherosclerosis

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Abstract Anti-inflammatory activities of statins in atherosclerosis have been well documented by both basic research and clinical studies. Statins have been introduced in the 1980s as 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors to block cholesterol synthesis and lower cholesterol serum levels. In the last three decades, statins have been shown to possess several anti-inflammatory and antioxidant activities resulting in the beneficial reduction of atherosclerotic processes and cardiovascular risk in both humans and animal models. Inflammatory intracellular pathways involving kinase phosphorylation and protein prenylation are modulated by statins. The same intracellular mechanisms might also cause statin-induced myotoxicity. In the present review, we will update evidence on statin-mediated regulation of inflammatory pathways in atherogenesis.

Keywords Statin · Atherosclerosis · Inflammation · Kinases · Cholesterol

Introduction

Cardiovascular diseases are the leading cause of death and disability in the adult population of developed and developing countries [1–3]. In the majority of patients, clinical cardiovascular disease is the final step of the inflammatory state characterizing atheroprogression. Stable advanced atherosclerotic plaques mainly induce chronic arterial lumen stenosis and ischemia in peripheral tissues. This condition causes chronic organ remodeling and alters their functions. In the heart, chronic hypoxia can induce congestive heart failure (CHF). On the other hand, unstable plaques frequently progress to rupture with the consequent exposure to the blood lumen of intraplaque prothrombotic material. In that case, thrombus causes the sudden complete occlusion of the arterial lumen, and peripheral tissues are exposed to acute ischemia. If collateral arteries are not present and acute ischemia is prolonged, tissue necrosis can occur with dramatic consequences in the heart and brain. Several cardiovascular risk factors have been associated with CVD. More than 50 years ago, this concept was introduced by the Framingham Heart Study, with the identification of major coronary heart disease (CHD) risk factors, such as hypertension, hyperlipidemia, smoking, and diabetes [4]. However, although highly sensitive, these traditional factors showed a very low specificity [5–7]. Therefore, inflammatory soluble mediators, which have been shown to play a central role in all phases of atherosclerosis, have been investigated [8–10] with some preliminary encouraging results. In particular, the American Heart Association (AHA/CDC) has recently suggested that the high sensitivity dosage of the acute phase reactant C-reactive protein (CRP) might be useful when physicians are undecided about indications of a more intensive treatment for patients who are considered at intermediate cardiovascular risk [11, 12]. At present, the most promising therapeutic strategies to reduce cardiovascular diseases are represented by the selective blockade of both “classical” and new emerging

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factors promoting atherogenesis. Statins (3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors) should be considered as anti-atherosclerotic drugs capable of modulating different factors. Basic research and clinical studies have shown that statins lower LDL cholesterol levels and inhibit atherosclerotic inflammatory processes. Little is known on the possible statin-mediated molecular mechanisms to reduce cardiovascular risk. In the present review, we will focus on selective anti-inflammatory activities of members of statin family and the statin-mediated modulation of intracellular pathways in both immune and vascular cells, which play a crucial role in atherosclerosis.

Statins in cardiovascular diseases

The first identification of a fungal metabolite (compactin) blocking cholesterol synthesis has been performed in 1971 by Endo and coworkers [13]. In 1976, the "Compactin Development Project" composed by several experts started. Starting from 1978, a new statin (called lovastatin) has been discovered and developed. In 1980s, statins have been shown to lower LDL cholesterol levels in patients with hypercholesterolemia [14–18]. These first impressive results induced the US Food and Drug Administration to approve the commercial us of statins in 1986 [19]. After lovastatin, three generations of statins have been commercially introduced: pravastatin and fluvastatin (first generation), atorvastatin and simvastatin (second generation), and rosuvastatin and pitavastatin (third generation). Cerivastatin was also approved for the marketplace but was eventually discontinued for its myotoxic effects [13]. Statins have been tested in primary prevention for acute cardiovascular events in both high cardiovascular risk patients (diabetes, hypertension, and dyslipidemia) and subjects with low or no CVD risk [20–25]. For instance, aggressive treatment of diabetic subjects with statins has been shown to reduce coronary events and stroke [21–23]. This was also observed in diabetic patients with dyslipidemia [26]. The principal primary prevention study in hypertensive patients (Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA)) showed that atorvastatin reduces the relative risk of primary CHD [27]. On the other hand, The Intervention Trial Evaluating Rosuvastatin (JUPITER, a large multinational, long-term, double blind, and randomized clinical trial) showed that treatment with rosuvastatin significantly reduces the incidence of major cardiovascular events in healthy subjects without hyperlipemia but with elevated high-sensitivity CRP levels [28]. Statins have been also investigated in secondary prevention of cardiovascular diseases. Results have been reported in patients with stable coronary artery disease, acute coronary syndrome, stroke, or transient ischemic attack [29–36]. The Scandinavian Simvastatin Survival Study (4S), performed in patients with angina pectoris or previous myocardial infarction and high-serum cholesterol levels, demonstrated that long-term treatment with simvastatin improves survival and decreases cardiovascular events [37]. The Heart Protection Study (HPS; a primary and secondary prevention study) showed that simvastatin significantly reduced cardiovascular mortality and vascular acute events in 20,000 patients with coronary or peripheral vascular disease without hyperlipidemia [38]. The Greek Atorvastatin and Coronary Heart Disease Evaluation, Treating to New Targets (TNT), Aggressive Lipid-Lowering Initiation Abates New Cardiac Events, and Incremental Decrease in Endpoints Through Aggressive Lipid Lowering (IDEAL) studies confirmed a significant decrease of acute cardiovascular events in patients with stable CHD [39, 40]. The Pravastatin or Atorvastatin Evaluation and Infection Therapy, Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL), and IDEAL-Acute Coronary Syndromes studies demonstrated the benefits of high-dose-dosage atorvastatin therapy in patients with acute coronary syndromes [40]. In patients with heart failure, the efficacy of statins is still a matter of dispute [41, 42]. In the GISSI-HF trial, rosuvastatin did not reduce death or admission to hospital for cardiovascular reasons in patients with chronic heart failure [42]. The CORONA study partially confirmed these results showing only a reduction of the number of cardiovascular hospitalizations [43]. Statins also improved survival and cardiovascular events in patients after heart transplantation or percutaneous coronary interventions [41] promoting coronary collateral circulation, a modest antihypertensive effect and improving glucose metabolism and insulin sensitivity [44–46]. Although few controversies remain, these clinical studies indicate that: (1) statins should be considered as very promising anti-atherosclerotic drugs (also independently on lowering cholesterol) for secondary prevention in all patients and for primary prevention in high risk individuals (Fig. 1). (2) In persons without traditional cardiovascular risk factors, but with elevated hs-CRP levels, the use of statins might be indicated in the near future. (3) The marked cardiovascular risk reduction might be also related to the direct anti-inflammatory and pleiotropic properties of statins [47–59]. The National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III recommended the use of statins for the secondary prevention of cardiovascular diseases as the first-line choice drug for lowering LDL-cholesterol in the high-risk patients [60]. This group includes individuals with established coronary heart disease and diabetes mellitus or with a Framingham 10-year CHD risk greater

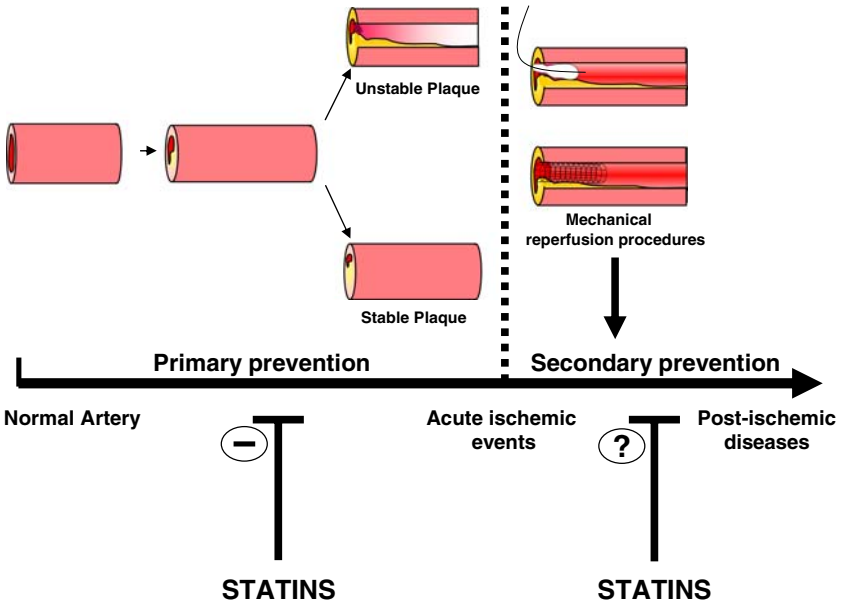

Fig. 1 Statin treatment reduces the risk of acute cardiovascular events. Several studies support that statins inhibit atherosclerotic plaque progression and the risk of rupture (primary prevention). These beneficial effects are mediated by statin-induced cholesterol reduction and statin-mediated "pleiotropic" activities. In secondary prevention, the use of statins has been suggested by promising results. However, the prompt restoration of antegrade flow in the infarct-related coronary artery, whether accomplished pharmacologically or mechanically, remain the mean therapy for improving both left ventricular systolic function and survival during the subsequent hours after the acute myocardial infarction. Further investigations are needed to investigate the possible use of statins to prevent post-ischemic diseases (such as CHF)

than 20%. For primary prevention, the NCEP ATP III recommended to treat individuals with metabolic syndrome and diabetic patients with moderate cardiovascular risk (Framingham 10-year CHD risk of 10–20%) [61]. Treatment with any of the statin family has been associated with transaminase elevations in comparison to placebo [62]. Despite the low frequency (1–2%) of raised asparatate or alanine aminotransferase, these adverse effects are completely reversible and almost never progress to hepatitis or liver failure [63]. A very low risk of neuropathy and gastrointestinal discomfort has been also reported. However, the main risk of statin treatment derives from myotoxicity which ranges from myalgias, creatine kinase elevation to the more serious rhabdomyolysis. This adverse effect has been reported in 1–7% of patients under statin therapy [64]. Itagaki and coworkers recently suggested that myotoxicity could be induced by the same mechanisms governing statin beneficial anti-inflammatory activities. In particular, RhoA dysfunction due to loss of lipid modification with the mevalonate product geranylgeranylpyrophosphate (GGPP) has been observed in statin-induced skeletal muscle toxicity [65]. Further investigations are needed to better clarify the role of intracellular signaling pathways in myotoxicity. Despite these few adverse effects, statins are generally well tolerated. Both second and third generations of statins have been shown to reduce LDL cholesterol more effectively than first generation without increasing toxicity [66]. In the following, we will discuss on the selective immunomodulatory properties of different statins (Table 1) [67].

Lovastatin

Together with pravastatin and fluvastatin, lovastatin is included in the first generation of statins. Lovastatin represents the drug with the lowest potency and is necessary to use high doses to observe a significant reduction of LDL cholesterol levels [68]. However, lovastatin (together with simvastatin and pravastatin) is less expensive, and it is available in generic formulation. Clinical studies have also confirmed the efficacy of lovastatin in both primary and secondary prevention of cardiovascular diseases. The AFCAPS/TexCAPS study showed that daily treatment with 20–40 mg lovastatin-reduced incidence of acute major cardiac events in comparison with placebo. The study was performed in a middle-aged or elderly population (n=6,605) without symptomatic cardiovascular disease [69]. The beneficial effects of lovastatin were confirmed by the ACAPS study that enrolled 919 subjects asymptomatic for clinical cardiovascular disease but with evidence of early carotid atherosclerosis [70]. On the other hand, secondary prevention studies showed that 2–2.5-year therapy with lovastatin-reduced progression of atherosclerosis in dyslipidemic patients with CHD [71–73]. Lovastatin has been also

Table 1 Pharmacokinetic and anti-atherosclerotic activities of statins

Statin	Dose (mg/day)	Lipophilic	Bioavailability (%)	T 1/2 (h)	Protein binding (%)	Cytochrome metabolism	Metobolites	Urinary excretion (%)	Fecal excretion (%)	Anti-atherosclerotic activities			
										Endothelial cells	Leukocytes	Smooth muscle cells	Bone marrow progenitor cells
Lovastatin	10–80	Yes	5	2.9	>95	CYP3A4	Active	10	83	++	++	Not known	+
Pravastatin	5–40	No	18	1.3–2.8	43–55	Sulfatation	Inactive	20	71	+++	++	++	+
Fluvastatin	20–80	Yes	19–29	0.5–2.3	>99	CYP2C9	Inactive	6	90	+++	+	Not known	Not known
Simvastatin	5–80	Yes	5	2–3	94–98	CYP3A4	Active	13	58	+++	+++	+	Not known
Atorvastatin	10–80	Yes	12	15–30	80–90	CYP3A4	Active	2	70	+++	+++	+	+
Rosuvastatin	5–80	No	20	20.8	88	CYP2C9	Active	10	90	++	+	Not known	+

shown to induce in vitro anti-inflammatory activities in different cell types at lower doses. Lovastatin is a potent immunomodulatory and neuroprotective drug. It strongly reduces the migration of monocytes and lymphocytes across in vitro-cultured human blood–brain barrier endothelial cells [74]. Lovastatin also reduces apoptosis and downregulates CD40 expression in TNF-alpha-treated cerebral vascular endothelial cells and in IFN-gamma-treated microglial cells [75, 76]. Lovastatin-induced reduction of transendothelial T cell migration is dependent on the inhibition of rho pathway [77]. Lovastatin directly modulates immune cell functions by both disrupting or upregulating chemokine and chemokine receptor expression [78, 79]. Furthermore, lovastatin inhibits maturation and functional changes of bone marrow-derived dendritic cells [80]. Lovastatin also increases macrophage apoptosis involving the Rac1/Cdc42/JNK pathways [81]. Taken together, these studies support lovastatin as an immunomodulatory therapeutic agent in atherosclerosis and its cerebral complications.

Pravastatin

Pravastatin is the most rigorous tested drug in the "first generation" of statins. Two important primary prevention studies (WOSCOPS and PROSPER) indicated that pravastatin treatement (40 mg/daily) reduced LDL-cholesterol levels, cardiac mortality, and coronary events in comparison with placebo [82, 83]. ALLHAT-LLT study (enrolling 10,355 patients) did not confirm pravastatin-induced reduction in coronary events or mortality [84]. These different results in primary prevention were probably due to the lower reduction of LDL cholesterol levels (−28%) in ALLHAT-LLT study. Furthermore, a strong limitation was represented by the populations, which was exclusively enrolled in developed west countries. To investigate the efficacy of pravastatin in primary cardiovascular prevention in another population, the MEGA study was planned in Japan. Treatment with a low dose (10–20 mg) of pravastatin reduced the risk of coronary heart disease in Japan similarly to that observed in Europe and the USA in the presence of higher doses [85]. Differently from fluvastatin or simvastatin (that are "lipophilic"), pravastatin is a "hydrophilic" compound as the new rosuvastatin and almost not metabolized by the cytochrome P450 complex [86]. Probably for this property, treatment with pravastatin induced different effects in vascular cells. Wiesbauer and coworkers showed that among six different statins, only pravastatin does not decrease PAI-I production in human endothelial cells and smooth muscle cells [87]. Furthermore, pravastatin increases E-selectin and vascular cell adhesion molecule (VCAM)-1-induced expression on vascular endothelial cells stimulated with TNF-alpha or LPS [88]. This study also showed that treatments with simvas-

tatin or fluvastatin increase adhesion molecule expression in TNF-alpha-stimulated endothelial cells [88]. Therefore, statins might increase TNF-alpha-mediated proinflammatory activities in endothelial cells. Conversely, pravastatin has been shown to protect mouse cerebral endothelial cells against ceramide-mediated cytotoxicity through vascular endothelial growth factor upregulation and the activation of hypoxia-inducible factor-1 [89]. Furthermore, pravastatin inhibits the production of monocyte chemoattractant protein 1 (MCP-1), interleukin (IL)-6, and IL-8 in irradiated microvascular endothelial cells [90]. These beneficial effects were persistent up to 14 days after irradiation, suggesting that pravastatin could be considered a very promising agent against endothelial dysfunction in patients treated with radiation therapy. These controversial data suggest a still unclear immunomodulatory role of pravastatin on vascular cells. Recent evidence also showed a possible role of pravastatin in vascular endothelial cell protection from oxidative stress. In a rat model of myocardial infarction, Abe and coworkers showed that pravastatin prevented cardiac dysfunction. The suggested mechanism for pravastatin-induced beneficial effects was represented by the inhibition of H_2O_2-mediated caspase-3 activation and endothelial nitric oxide synthase (eNOS) reduction that was observed in cultured vascular endothelial cells [91]. More recently, Suzuki and coauthors showed that pravastatin also improves dysfunctional hibernating myocardium in a swine model of chronic left anterior descending artery (LAD stenosis) [92]. These investigations clearly indicate that improvement after pravastatin administration was exclusively related to mobilization of CD133(+)/cKit(+) bone marrow progenitor cells, without involving endothelial cell function. Controversial immunomodulatory properties of pravastatin have been also shown in immune cells [93]. Pravastatin increases inflammation by activating human peripheral blood mononuclear cells to produce IL-18, TNF-alpha, and IFN-gamma [94]. Furthermore, it increases the phagocytic index of mouse peritoneal macrophages [95]. Conversely, pravastatin induces important immunosuppressive effects by prolonging lung graft survival and inhibiting chronic rejection in renal allograft in rats [96, 97]. Pravastatin treatment also inhibits circulating dendritic cell activation in patients with coronary artery disease [98].

Fluvastatin

Fluvastatin is a lipophilic statin. Differently from other statins that are metabolized by the cytochrome P450 3A4 complex (CYP3A4), fluvastatin is metabolized by another P450 complex [99]. This aspect reduces the risk of pharmacological interactions between fluvastatin and other drugs. Furthermore, it suggests the possible use of fluvastatin in patients, which are intolerant to second and third generation of statins. The ALERT study investigated the possible reduction of cardiovascular risk in patients who received renal transplant. Fluvastatin treatment reduced cardiac deaths and nonfatal MI but not coronary intervention procedures or mortality in these patients [100]. In two other secondary prevention studies (BCAPS and HYRIM) respectively conducted in patients who had carotid plaque without symptoms of carotid artery disease [101] and hypertensive men [102], fluvastatin-reduced acute cardiovascular events. On the other hand, the Lescol Intervention Prevention Study showed that fluvastatin treatment significantly reduces the risk of adverse cardiac events in patients with average cholesterol levels undergoing their first successful percutaneous coronary intervention [103]. Fluvastatin has been shown to induce cardioprotective effects in both acute and chronic treatments. In a rat model of acute myocardial infarction and reperfusion, the administration of fluvastatin 20 min before the onset of ischemia significantly attenuated the decline of myocardial blood flow, thus, reducing myocardial infarction size [104]. These promising data are in contrast with in vitro studies showing that fluvastatin induces cardiac myocyte and vascular endothelial cell apoptosis [105, 106]. Furthermore, it increases the expression of adhesion molecules, MCP-1, and tissue factor in human umbilical vein endothelial cells stimulated by antiphospholipid antibodies [107]. It is possible that fluvastatin exerts its activities in endothelial cells through its uptake into these cells via nonspecific simple diffusion [108]. These apparent negative effects might be counterbalanced by other protective activities induced by fluvastatin in vascular cells. In fact, fluvastatin inhibits matrix metalloproteinase-1 expression and oxidative damage in vascular endothelial cells, thus, improving endothelial dysfunction [109–112]. Fluvastatin also increases prostacyclin production and reduces endothelin-1 secretion in human umbilical vein endothelial cells (HUVEC) contributing to vasodilation and, thus, preventing cardiovascular diseases [113]. At very high concentration (10 μM), fluvastatin also reduces CRP-induced TNF-alpha secretion in HUVEC [114]. Despite the important limitation represented by the high dose used, this study supports a direct activity of fluvastatin in the inhibition of CRP-mediated proinflammatory effects. Fluvastatin has been shown to reduce inflammatory cells activation and functions. Mononuclear leukocytes represent the most investigated cell population [115–117]. The anti-inflammatory properties of fluvastatin have been observed in patients with chronic heart failure or allergic asthma [118, 119]. These studies suggest the potential therapeutic use of fluvastatin not only in atherosclerosis but also in other inflammatory diseases.

Simvastatin

Together with atorvastatin, simvastatin has been actively investigated [120], and it has been shown to induce several in vitro and in vivo beneficial effects to reduce atherosclerotic inflammatory process. Clinical trials in primary and secondary prevention of cardiovascular risk demonstrated the beneficial effects of simvastatin. In primary prevention, the HPS provided direct evidence that cholesterol-lowering therapy-reduced cardiac mortality and coronary events mainly in diabetic subjects without a manifest coronary disease [121]. In secondary prevention, the 4S showed that treatment with simvastatin strongly reduced cardiac mortality and coronary events in comparison to placebo [37]. Simvastatin reduces endothelium dysfunction through a direct benefit on endothelial cells and their precursors [122]. High concentrations of simvastatin (25 μM) reduced TNF-alpha-mediated apoptosis of endothelial progenitor cells (EPC) [123]. Furthermore, the treatment with 80 mg/day simvastatin for 5 days increases in vivo EPC mobilization [124]. Then, simvastatin also promotes endothelial differentiation of bone marrow stromal cells through the Notch signaling pathway [125]. On the other hand, simvastatin might prevent endothelial dysfunction through a direct protective activity on endothelial cells. Simvastatin inhibits CRP-induced CD32, VCAM-1 expression as well as monocyte adhesion to human umbilical vein endothelial cells [126]. Simvastatin treatment also inhibits TNF-alpha-induced adhesion molecule (selectins) expression on HUVEC [127]. Furthermore, simvastatin protected the vascular endothelium against damages induced by LDL or ox-LDL in rats or a cultured cell line (ECV304 cells) [128]. On the other hand, emerging evidence shows that simvastatin also increases endothelial cell apoptosis suggesting that the clinical benefit of simvastatin in endothelial dysfunction could be due to an unbalance between positive (endothelial cell and endothelial progenitor protection) and negative (endothelial cell apoptosis) activities [129–131]. Simvastatin has been also shown to modulate eNOS in humans and animal models, thus, contributing to reduce endothelial dysfunction [132, 133]. The inflammatory functions of other vascular and immune cell types involved in atherosclerotic processes have been modulated by simvastatin. Simvastatin induces the cytoprotective molecule heme oxygenase-1 in mouse smooth muscle cells in vivo and in vitro [134]. Treatment with 1 μM simvastatin significantly downregulates chemokine and chemokine receptor expression in human macrophages [135]. These morphological changes result in a reduced locomotory response towards CCL2, as shown in vivo by Han and coworkers [136]. More recently, we showed that simvastatin at 1 μM reduces CRP-induced chemokine secretion, ICAM-1 upregulation, and chemotaxis in human primary monocytes cultured in adherence to polystyrene [137]. In CD14+ monocytes, simvastatin reduces toll-like receptor 4 expression suggesting that this drug might directly modulate innate immunity [138]. Neutrophil migration, adherence, and membrane integrity have been also modulated by treatment with simvastatin [139, 140]. Simvastatin also interferes with inflammatory activities mediated by humoral and cell-mediated immunity in vivo and in vitro [141]. Simvastatin inhibits both human B- and Th1-lymphocyte activation [142–144]. On the other hand, simvastatin promotes Th2-type responses through the direct modulation of dendritic cell function [145]. Accordingly with these data, simvastatin treatment in vivo inhibits lymphocyte and NK cell functions and downregulated angiotensin II type 1 receptor on circulating T lymphocytes and monocytes [146, 147].

Atorvastatin

Atorvastatin is the first statin approved to reduce the risk of hospitalization in heart failure patients [148]. Large clinical trials have been performed to assess primary and secondary prevention of cardiovascular diseases. In primary prevention, the ASCOT-LLA and the Collaborative Atorvastatin Diabetes Study showed a significant reduction in cardiovascular events with 10 mg/day atorvastatin in comparison to placebo [27, 149]. In secondary prevention, the majority of clinical studies performed investigated high dose treatments versus low dose. In the TNT and in the IDEAL studies, intensive atorvastatin treatment (80 mg/day) reduced any coronary events in comparison to lower statin doses (respectively 10 mg/day atrovastatin and 20 mg/day simvastatin) in patients with stable coronary artery disease or a history of acute myocardial infarction. In 2001, the MIRACL study further confirmed the need of high-dose atorvastatin therapy to prevent recurrent coronary events in patients with recent acute coronary syndrome. However, in all these studies, no reduction in mortality was observed [30–32, 141–149]. The Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 is the only study showing a reduction in mortality in the presence of intensive atorvastatin treatment in secondary prevention of acute cardiovascular events [150]. Chronic treatments with atorvastatin have been shown to induce direct beneficial effects in cardiomyocytes by protecting from hypertrophic cardiomyopathy, cardiac fibrosis, and remodeling, catecholamine deleterious effects in several animal models [151–154]. Several studies investigating the possible effect of atorvastatin in inflammatory diseases have been performed with some controversial results [155–157]. For instance, atorvastatin treatment failed to reduce inflammatory processes in a mouse model systemic lupus erythematosus [157]. Ator-

vastatin has been also shown to directly induce neuroprotection. It reduced neurological deficit by increasing synaptogenesis, angiogenesis, and neuronal survival in rats subjected to traumatic brain injury [158]. In the same rat model, atorvastatin also reduced intravascular thrombosis and increased cerebral microvascular integrity [159]. Furthermore, atorvastatin inhibited perihematomal cell death in adult rats after experimental intracerebral hemorrhage [160]. As other statins, atorvastatin directly antagonized inflammatory processes in human brain endothelial cells [161]. The direct neuro and endothelial protective activities of atorvastatin have been shown to reduce stroke consequences in stroke-prone spontaneously hypertensive rats and in a rat model of embolic stroke [162, 163]. These studies strongly suggest that atorvastatin could be a very promising drug with potent anti-inflammatory activities in different diseases. The possible use of atorvastatin to inhibit atherosclerosis represents the best investigated field. Atorvastatin reduced in vitro and in vivo endothelial dysfunction and inflammatory processes in atherogenesis. As previously indicated for simvastatin, atorvastatin protects endothelium through the increase of endothelial cell progenitor proliferation and mobilization and the induction of vessel wall stabilizing mediators and growth factors in endothelial cells [111, 164–166]. Atorvastatin has been shown to inhibit cytokine-inducible nitric oxide synthase, CD40, CD40L, chemokine, and thrombospondin-1 expression in endothelial cells [167–172]. Atorvastatin also regulates immune cell functions and the release of inflammatory mediators such as CRP. We have recently shown that atorvastatin inhibit CRP production on IL6-treated human hepatocytes [173]. Furthermore, this drug reduces CRP or granulocyte macrophage–colony stimulating factor-mediated proinflammatory activities in human monocytes [137, 174]. Atorvastatin also interferes with T lymphocyte, B lymphocyte, or dendritic cell activation and differentiation [175–179]. Atorvastatin-mediated anti-inflammatory effects have been observed also in clinical studies, investigating inflammatory cardiovascular risk markers in acute coronary syndromes, and coronary artery disease [180, 181]. Further investigations are needed to better assess the role of atorvastatin treatment in the reduction of inflammatory cardiovascular risk factors. Taken together, clinical and basic research studies suggest that high-dose atorvastatin treatments rather than low-dose could be considered as a promising approach to reduce cardiovascular disease.

Rosuvastatin

Rosuvastatin is a synthetic HMG-CoA reductase inhibitor noncompetitive with the cosubstrate nicotinamide-adnine dinucleotide phosphate [182]. Compared to other statins, rosuvastatin is the most effective to reduce total and LDL-cholesterol levels for mg/dose equivalent. As atorvastatin, rosuvastatin has been shown to additionally bind the enzyme complex not only at the HMG-CoA reductase site [183]. As pravastatin, it is significantly less lipophilic than other statins. Differently from other statins, rosuvastatin is metabolized mainly through CYP2C9 [183]. These pharmacologic and pharmacokinetic aspects support this drug as a very promising candidate to reduce myotoxicity and interaction with other drugs, and improve anti-inflammatory properties. Several clinical studies included in the global GALAXY program have been performed to assess rosuvastatin's clinical efficacy in atherogenic lipid profile, changes in atheroma volume, and cardiovascular morbidity and mortality in different subpopulations [184]. As described above, the recent JUPITER study is the first primary prevention study demostrating a benefit of statin therapy in individuals with elevated high-sensitivity C-reactive protein levels, but without hyperlipidemia [28]. In secondary prevention, rosuvastatin did not reduce mortality in patients with systolic heart failure and CAD but only the number of cardiovascular hospitalizations. Conversely, the ASTEROID trial demonstrated decrease of percent diameter stenosis and amelioration of minimum lumen diameter in coronary disease patients [185]. Although atherosclerotic lesion regression is not directly related to the reduction of future cardiovascular outcomes, the ASTEROID study strongly supports the possible use of rosuvastatin in secondary prevention. High concentrations of rosuvastatin (100 μM) suppressed monocytic cell adhesion and ICAM-1, MCP-1 IL-8, IL-6, and COX-2 expression on TNF-alpha-stimulated HUVEC [186]. Furthermore, although mechanisms have not been identified yet, rosuvastatin treatment protected mice from ischemic stroke [187] and rats from myocardial reperfusion injury [188]. Rosuvastatin also exerts favorable anti-atherosclerotic effects in several animal models [189–192]. These studies suggest that rosuvastatin-mediated benefits are dependent of its antioxidant and anti-inflammatory activity on endothelial cells. A recent study (performed in a small number of patients (n=48)) further confirmed the endothelial protective properties of rosuvastatin showing that short-term treatment increases endothelial cell progenitor mobilization [193].

The effects of statins on inflammatory intracellular signaling pathways

Statins have been introduced as HMG-CoA reductase inhibitors to lower LDL-cholesterol synthesis and serum levels (Fig. 2). However, emerging evidence has shown that the "classical" cholesterol pathway could also modulate intracellular signaling pathways involving protein kinases in

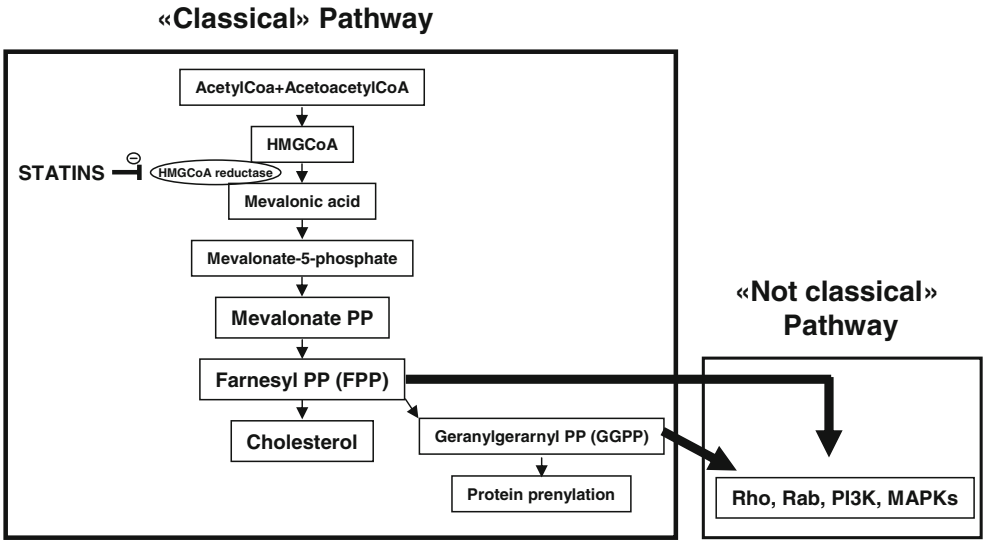

Fig. 2 Anti-inflammatory activities of stains depend on both "classical" and "not classical" HMGCoA-Mevalonate pathways. Simplified "classical" and "not classical" HMGCoA-Mevalonate pathways. Statin anti-inflammatory activities depend on the inhibition of both "classical" (HMGCoA–Mevalonate–FPP–cholesterol) and "not classical" (HMGCoA–Mevalonate–FPP–kinase) pathways. Other studies have shown that GGPP may be also involved in the intracellular signaling proteins regulating kinase activation

different cell types. Thus, statins could directly influence vascular and immune cells, hepatocyte, and adipocyte inflammatory functions through the activation of certain intracellular mediators or the inhibition of protein kinase phosphorylation of intracellular second messenger cascades (Fig. 3).

Statin-mediated activation of intracellular pathways

Recently, statins have been shown to directly activate anti-inflammatory intracellular pathways. AMP-activated protein kinase (AMPK) is a serine/threonine protein kinase involved in the regulation of cellular energy

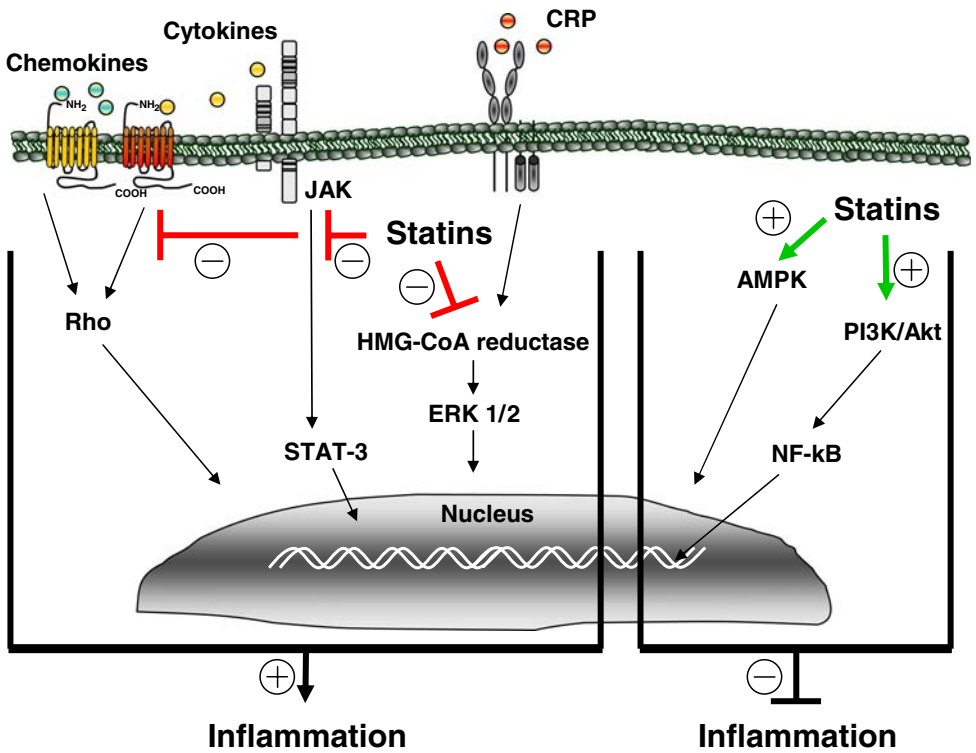

Fig. 3 "Activatory" and "inhibitory" intracellular signaling pathways regulate statin-induced pleiotropic activities. Statins diminish proinflammatory effects and promote anti-inflammatory activities through the direct inhibition/activation of chemokine-, cytokine-, and acute phase reactant-induced intracellular signaling pathways in several cell types (such as leukocytes, vascular cells, adipocytes, and hepatocytes). In particular, the inhibition of ERK 1/2, rho, JAK/STAT3, or mevalonate pathways is crucial to reduce inflammation. On the other hand, statins directly activates AMPK and PI3K/Akt/NFkB pathways, thus, increasing cell survival, endothelial, and neuronal protection

metabolism. Emerging evidence showed that AMPK might be crucial in vascular protection [194]. Statins directly activates AMPK in different cell types [194, 195]. In particular, statins have been shown to rapidly activate this protein kinase in vitro (cultured HUVEC) and in vivo (mouse aorta and myocardium). Such phosphorylation resulted in eNOS activation that could explain the direct beneficial effects of statins in cardiovascular diseases [196]. Interestingly, statin-mediated AMPK activation was dependent on the upstream activation of PKC-zeta as shown in endothelial cells and in vivo in mice [197]. AMPK-induced eNOS activation also increased endothelial cell progenitor differentiation in endothelial cells indicating a possible protective mechanism on endothelium mediated by statins [198].

On the other hand, the activation of phosphoinositide 3 kinase (PI3K)/Akt (protein kinase B) represents a critical step in inflammatory cell survival, locomotion in atherosclerosis, and cardiovascular disease [199]. Although, few studies (performed with lovastatin) suggested a possible inhibition of PI3K-Akt in endothelial cells [200], there is a general consensus that statins induce cardiovascular protection through the activation of PI3K/Akt pathway. Statin-mediated neuroprotection in animal models of traumatic brain injury and embolic stroke is dependent on PI3K/Akt pathway activation [163, 201, 202]. This pathway involves also the activation of NF-kB that suppresses caspase-3 and apoptosis cell death [203]. Neuronal nitric oxide synthase upregulation might represent the final effector of this protective pathway [204]. Statin-mediated myocardial protection has been also shown as dependent on PI3K/Akt activation pathway in both in vitro and in vivo models [205–207]. Atherogenesis is also regulated by PI3K/Akt pathway. Statins induce their activation on vascular and immune cells, thus, reducing atherosclerotic lesions in ApoE knockout mice [208] and endothelial dysfunction in type 2 diabetic mice [209]. Controversial results on statin-mediated MAPK phosphorylation have been showed. Statins induce anti-inflammatory activities through both activation and inhibition of these kinases. The statin-induced activation of extracellular signal-regulated kinase (ERK) 1/2 has been observed mainly in immune cells [210, 211]. On the other hand, statins increase macrophage apoptosis through JNK activation [81].

Statin-mediated inhibition of intracellular pathways

As largely discussed, statins have been approved as HMG-CoA reductase inhibitors. The HMG-CoA/mevalonate pathway is essential for cellular metabolism and the formation of precursors of bile acids, lipoproteins and hormones, and nonsterol isoprenoids. These molecules regulate cell growth and differentiation, gene expression, protein glycosylation, and cytoskeletal assembly [212]. Thus, by influencing cholesterol synthesis, statins not only reduce circulating LDL-cholesterol levels but also induce important cellular modifications which could interfere with immune and thrombotic response. Furthermore, statin reduce mevalonate-derived molecules, such as farnesyl-pyrophosphate (FPP) and GGPP which are essential players in cell signaling, endocytotic/exocytotic transport, and cytoskeleton dynamics [213]. Immune cell functions (including chemotaxis, chemokine secretion, and oxidative metabolism) are regulated by the "classical" mevalonate pathway. Endothelial and smooth muscle cells require this pathway for their proinflammatory functions [213]. Therefore, anti-inflammatory properties of stains might be due to their "classical" pharmacologic properties. Small GTP-binding proteins, which include in the Ras, Rho, Rab, and Ran superfamily, are directly modulated by the mevalonate pathway. These proteins act as molecular "on–off" switches regulating actin cytoskeleton changes in cell adhesion, migration and contraction [214]. They regulate several downstream intracellular messengers, such as protein kinase N, p21-activated protein kinase, and the rho-associated kinases, which control not only cellular locomotion but also cell growth and apoptosis in both immune and vascular cells [215]. Recently, it has been shown that the effects of statins on atherosclerotic processes in the vessel wall and in the brain are partially due to the inhibition of the Rho pathway [216, 217].

Conclusion

Due to their beneficial properties in cardiovascular diseases, statins are among the most widely prescribed medications in the world. Despite some differences between members of the statin family, all these drugs have been shown to reduce cardiovascular events in both primary and secondary prevention. The recent results of the JUPITER Study seem to indicate that statin treatment in CRP-elevated primary prevention markedly reduced cardiovascular events and total mortality. The safety of statins has been largely documented. Beside their well-known lipid lowering effects, statins also affect some immunomodulatory activities. These so called "pleiotropic" effects induce a decrease in pro-inflammatory and an increase in anti-inflammatory molecular pathways. Statin-mediated modulation of molecular intracellular mechanisms in both vascular and immune cells should be considered as a very promising approach to further clarify the statin-induced cardiovascular protection. Beside cardiovascular area, statin therapy is under investigation in other inflammatory diseases, such as rheumatoid arthritis and multiple sclerosis. Many hypotheses have been

already proposed to explain statin anti-inflammatory activities. A strong work is waiting for researchers in the next years.

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