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Anti-atherosclerotic mechanisms of statin therapy

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HMG-CoA-Reductase inhibitors, also known as statins, are currently the most powerful cholesterol-lowering drugs available on the market. Clinical trials and experimental evidence suggest that statins have anti-atherosclerotic effects. These are in part consequence of lipid lowering but also result from pleiotropic actions of the drugs. In this article, the anti-atherosclerotic actions of statins will be reviewed.

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Introduction

Hypercholesterolemia is a main driver of atherosclerosis. Cholesterol-containing lipoproteins induce endothelial dysfunction and macrophage activation. Foam cell formation, which results from the uptake of cholesterol-containing lipoproteins by macrophages, is an essential step in the initiation and progression of atherosclerosis. Pro-atherogenic lipoproteins facilitate the continuous influx of lipids into the atherosclerotic plaque and contribute to its growth [1]. The process also increases plaque vulnerability and maintains the inflammatory activity of the atherosclerotic process [2•].

On such basis, lipid lowering drugs have been developed. Among these drugs, statins are by far the most clinically and financially successful ones. Although novel cholesterol lowering drugs will become available soon, statins will remain the fundament of pharmacological lipid-lowering therapy. All other compounds currently available in clinics are less effective. To be successful, all coming lipid lowering drugs will have to be more effective than statins or superior if given in combination with a statin to maximized statin therapy alone.

Statins block the rate limiting enzyme of the cholesterol de novo synthesis, the HMG-CoA reductase. They lower cholesterol in situations of low intake with the food. The cholesterol de novo synthesis, however, also yields isoprenoids. These are important lipid anchors for many proteins involved in metabolism and signal transduction. Thus, statins elicit many effects beyond cholesterol lowering [3•].

The pleiotropic actions of statins are numerous. They increase endothelial NO formation and suppress vascular inflammation. Statins are known to reduce circulating biomarkers of inflammation like hs-CRP. Whether this is consequence of the anti-inflammatory action of lipid lowering therapy or mediated by pleiotropic effects of statins is still debated. Clinical data on inhibitors of intestinal cholesterol absorption suggest that also these compounds elicit some anti-inflammatory activity. Although these effects are less pronounced than those of statins, they cannot be consequence of pleiotropic effects [4]. Irrespectively of the mechanistic cause, reduction of inflammation is considered the second approach (lipid lowering being the first one) in limiting progression of atherosclerosis. Therefore, anti-inflammatory compounds without lipid lowering activity are currently developed for treatment of atherosclerosis [2•].

Anti-atherosclerotic effects of lipid lowering

Although multicellular and exceedingly complex, the atherosclerotic plaque has two main components: the large necrotic lipid core and the surrounding tissue. The latter consists of smooth muscle cells, fibroblasts, small vessels, inflammatory cells but also of connective tissue. If the lipid core occupies >40% of the total volume, the plaque becomes prone to rupture [5]. Thus, not only reduction in plaque growth but also reduction in the size of the lipid-rich core is a main goal of lipid lowering therapy. Lowering LDL-cholesterol (LDL-C) will reduce plaque lipid influx and favor reverse cholesterol transport from macrophages back to the liver. Although it is still unclear whether this mechanism can be pharmacologically exploited, some data suggest that statins reduce plaque size [6].

In animal studies, statins promote plaque regression, in part by reducing plaque macrophage content [7,8]. In patients, intravascular ultrasound studies suggest that statin treatment reduces plaque volume, potentially by reducing the size of the necrotic lipid-rich core [9•] or by lowering the amount of interspersed lipids in the fibrofatty tissue. The effect, however, only occurred if statin administration was performed at sufficient dosage (i.e. >10 mg atorvastatin or equivalent) and if LDL-C was reduced below 100 mg/dl [10]. Even at lower dosages, statins reduce cardiovascular events in large clinical trials.

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However, at low dosage, statins are not superior to other cholesterol lowering approaches regarding event rate reduction. This not only illustrates the pivotal role of hypercholesterolemia in driving the atherosclerotic process, but also emphasizes that the pleiotropic actions of statins are not the main mechanism of action of these drugs. Rather, pleiotropic effects are a highly appreciated, potent 'add on' feature of the drugs. Importantly, with increasing dosage of the drugs these beneficial effects become progressively more relevant. As the pleiotropic effects also mediate the unwanted actions of statin therapy, side effects like muscle pain also increase.

Anti-atherosclerotic effects of pleiotropic mechanisms

Isoprenoids are intermediates of the cholesterol de novo synthesis pathway, which derive from isopentenylpyrophosphate. Isoprenoids are important membrane anchors and their synthesis is suppressed by statin therapy. Small GTPases of the Rho-family, like Rac1 or RhoA are tethered to the plasma membrane by a geranylgeranyl-anchor (an isoprenoid). This association with the membrane is prevented by statins already at clinical relevant concentrations [11]. Moreover, also ubiquinone (also called co-enyzme Q10), which is central to mitochondrial energy transfer is attached to the mitochondrial membrane by this mechanism [12]. Thus, statin intoxication through mitochondrial dysfunction leads to myolysis. In lower concentration, however, statins preferentially limit GTPase signaling.

Small GTPases are central to a broad range of signaling events. They are required for cytoskeletal re-arrangement and via this mechanism also affect stability of mRNA and proteins. Small GTPases also mediate growth factor and cytokine signaling. Thus a general anti-inflammatory, anti-proliferative and anti-angiogenic effect can be inferred from inhibition of isoprenoid formation. Indeed, statins, if used at a sufficiently high concentration elicit all these effects. A few mechanisms, however, gained particular attention: HMG-CoA reductase inhibitors increase the expression of the endothelial NO synthase (eNOS) [13] and reduce that of arginase [14•]. This effect is mediated by a rhoA/cytoskeleton-dependent action affecting mRNA and/or protein stability of these enzymes. Thus, statins increase NO availability, improve endothelium-dependent relaxation and reduce endothelial dysfunction. Statins also limit Rac1 membrane binding. As Rac1 is required for NADPH oxidase activation, statins reduce oxidative stress. This anti-oxidant mechanism limits lipid peroxidation, eNOS uncoupling and peroxynitrite-mediated stress and inflammatory activation. Indirectly, the antioxidant action also promotes NO availability and improves endothelial function [3•].

Comparison of high dose simvastatin to low dose simvastatin given in combination with an intestinal cholesterol uptake inhibitor indicated that the anti-inflammatory effects of lipid lowering in hyperlipidemic patients already occurs at low statin concentrations. The inhibition of rhoA, as measured by Rho-kinase activity and improvement of endothelium-dependent relaxation however requires high statin concentrations [15••]. Similar observations with respect to endothelial function were made in heart failure patients [16] and patients with coronary artery disease [17].

More recently, it was reported that simvastatin, at least in cultured endothelial cells and mice, increases the scavenger receptor class B type I which through the uptake of HDL enhanced eNOS activity. Similar as for eNOS expression, this was mediated by mRNA stabilization through changes in the cytoskeleton [17].

The endothelial effects of statins occur rapidly within a few hours after intake. They mediate the organoprotective actions of the drugs after ischemia, the improvement of angiogenic response of endothelial cells and in part the anti-inflammatory action [3•]. Statins also increase the numbers of circulating monocytic cells with angiogenic potential. This is probably mediated by affecting cytokine and matrix metalloproteinase signaling in the bone marrow. By such a mechanism, the compounds promote vascular healing, which will also reduce the proliferative response after vascular injury. On the whole organ level, collateral growth is stimulated by this mechanism and renders the tissue less vulnerable to ischemic incidences [3•].

A more recent observation was that statin mimic shear stress signaling in endothelial cells by inducing the protective transcription factor Krüppel-like Factor 2 (KLF-2) [18,19]. Although the mechanisms underlying this effect are still unclear, this pathway appears to be of major importance for the pleiotropic effects of statins. Via KFL-2, the drugs induce atheroprotective connexin 37 [20•], reduce cellular proliferation and also elicit an endothelial anti-inflammatory effect. Importantly, also in cells of the acquired immune-system statins increase KFL-2. This mechanism mediates an anti-inflammatory effect in the mouse myocarditis models [21•]. Giving the central importance of the acquired immune system in atherosclerosis, it can also be inferred that this mechanism may limit plaque inflammation. Statins also have effects on the innate immune-system. They decrease macrophage proliferation and inflammatory activity [22], potentially also via increasing KFL-2 [23]. Recently, in an ApoE-/C57WT mouse atherosclerosis regression model of aortic transplantation, it was reported that statins activate a CCR7-dependent egress pathway for macrophages out of the plaque [24]. This novel mechanism may not only reduce plaque size, but may also contribute to reserve cholesterol transport and the anti-inflammatory effects of statins.

Also vascular smooth muscle cells contribute to the atherosclerotic process. They contribute a substantial part of the

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