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Review Article

Mechanistic Pathways of Atherosclerosis – Vasa Vasorum, Endothelial Progenitor Cells (Epcs) – and the Effects of 3-Hydroxy-3-Methylglutaryl-Coenzyme A (HMG-Co A) Reductase Inhibitors

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Abstract

HMG-Coa reductase inhibitors (statins) have gained a tremendous effect on huge populations. Changing life expectancy and changing natural history of natural humans, considered at risk to develop cardiovascular disease, and patients with known cardiovascular disease. Over the years it has become clear that the major clinical effect induced by statins is not solely due to a lipid profile positive change, but also due to other effects known as the "paleographic effects" of statins (all the beneficial effects of statins besides the lipid lowering effect). A better understanding of statins of mechanistic pathways strengthened even more the paleographic significance of the beneficial effects of statins, and some even suggest that the lipid lowering effect could be actually a marker of the other, more significant effects-like the effects of statins on vascular inflammation and plaque stabilization, immune modulation, on circulating endothelial progenitor cells and endothelial cells, up-regulation of endothelial nitric oxide synthase (e-NOS) modulation of thrombosis and coagulation. All the activities and effects of statins have been discovered in the last decade and are dependent on regulation of nuclear factor K B (NF-k-B), cell adhesion molecules' activation, PI3k-Akt pathway, Rhs/Rho-kinase and activation of Akt.

Keywords: HMG-CoA reductase inhibitors; e-NOS; Endothelial function; EPCs

Introduction

Atherosclerosis is considered today as a long standing inflammatory process. It is well known that an inflammatory process occurs in the arterial wall at the site of plaque formation [1-3]. The response to injury mechanism is considered the traditional pathway of atherosclerosis that leads to the development of the dangerous plaques and plaque rupture. Plaque angiogenesis plays a fundamental role in the development of atherosclerosis, providing nutrients to the developing intimae and also a potentially unstable hemorrhagic condition prone to rupture [4,5]. Intimal micro vessels are related directly to the stage of the developing plaque. In atherosclerosis, intimal neovascularization arises from the network of adventitial blood vessels close to the plaque and not from the main artery.

Understanding the Basic Steps - Vasa Vasorum and New Blood Vessels Formation

Arteries get their nourishment by diffusion from the lumen of the vessel or from vasa vasorum [6]. Blood vessels with thin walls of less than 29 smooth muscle cell layers don't have vasa vasorum blood supply [7], and also blood vessels that are less than 0.5 mm in diameter [8]. However, most of the larger vessels (coronary and carotid arteries) have vasa vasorum, feeding penetrating vessels as far as the inner layers of the media [9]. Vasa vasorum are considered functional end arteries [10,11]. Traditionally there are 3 types of vasa vasorum–the vasa vasorum externa, vasa vasorum interna, that supply the arterial wall with oxygenated blood, and the venous vasa vasorum, that drain the arterial blood pool [12]. Atherosclerosis is a dynamic process, and the vasa vasorumsupport atherosclerosis development, including plaque neovascularization. The extensive network of small blood vessels that supply the walls of the medium and large sized arteries function as a conduit for macrophages and inflammatory cells and factors that promote the progression of angiogenesis and plaque build-up [13].

Vasa Vasorum and the Atherosclerotic Plaque

A new paradigm was born from the understanding of the vasa vasorum network, and that is the concept of "outside-in" hypothesis claiming that vascular inflammation is initiated in the adventitia and progresses inward to the media and intima [14-16]. There is a positive correlation between the adventitial vasa vasorum and the development of atherosclerosis. Animal studies have demonstrated lower vasa vasorum density in animals with low incidence of atherosclerosis [17,18]. Another close relationship has been demonstrated between intra plaque hemorrhage and plaque neo-vascularity. Galili found that the smaller micro vessels among the vasa vasorum blood vessels are less mature and are more susceptible to rupture and to bleed [19]. The growth of vasa vasorum is related to plaque neovascularization and plaque development [20,21].

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Vascular Walls and EPCs

Several studies have demonstrated that the vascular walls serve as a peri vascular niche for stem/progenitor cells that play a key role in vascular repair, fibrosis and atherosclerosis [22,23]. Pericytes, known also as vascular mural cells, surround endothelial cells in capillaries and in micro vessels [24,25]. A subpopulation of pericytes have the ability to behave as multi-potent cells that can differentiate into mesodermal and ectodermic cell lineage, including smooth muscle cells, osteoblasts, adipocytes, and skeletal muscle cells [26-28]. Endothelial progenitor cells (EPCs) also exist within populations of tissue resident endothelial cells [29]. A sub population of endothelial stem cells was found, marked as CD31+ cells that are located at the inner surface of preexisting micro vessels and macro vessels [30]. It seems that the vasa vasorum has an important function not just as a blood and nutrient conduit tube but also as a stem cell reservoir. Blocking vasa vasorumangiogenesis with angiostatin reduced macrophage accumulation in and around plaques and inhibited progression of atherosclerosis [31]. Anti-angiogenic factor PAI-1_{23} also inhibited plaque formation and atherosclerosis progression in hypercholesterolemia mice through plasmin dependent mechanism [32,33].

3-Hydroxy-3-Methylglutaryl-Coenzyme a (HMG-Coa) Reductase Inhibitors, Epcs and Atherosclerosis

HMG-CoA reductase inhibitions (statins) have gained a tremendous effect on huge populations. Changing life expectancy and changing natural history of natural humans, considered at risk to develop cardiovascular disease, and patients with known cardiovascular disease. Over the years it has become clear that the major clinical effect induced by statins is not solely due to a lipid profile positive change, but also due to other effects known as the "pleotrophic effects" of statins (all the beneficial effects of statins besides the lipid lowering effect). A better understanding of the mechanistic pathways of statins strengthened even more the pleotrophic significant effects of statins, and some even suggest that the lipid lowering effect could be actually a marker of the other, more significant effects, like the effects of statins on vascular inflammation and plaque stabilization [34], immunomodulation [35], on circulating EPCs and endothelial cells,[36]up-regulation of endothelial nitric oxide synthase (e-NOS) [37], modulation of thrombosis and coagulation [38]. All these activities and effects of statins have been discovered in the last decade and are dependent on regulation of Nuclear factor K B (NFKB), adhesion molecules' activation, PI3k-Akt pathway, Rhs/Rho-kinase and activation of Akt [39]. Statins also inhibited the development of adventitial vasa vasorum and the progression of atherosclerosis [40].

Circulating EPCs have been documented as important partners in the process of neovascularization of ischemic tissues. The general belief is that these cells are recruited from bone marrow when they are needed, induce and enhance new blood vessels formation (angiogenesis) without an effect on the lipid profile [39]. A marked enhancement in EPCs recruitment has been documented in wild type mice that experienced myocardial infarction, and have been shown to improve, though neovascularization, the left ventricular function [41]. Bone marrow EPCs have been shown to incorporate into foci of neovascularization in the border zone surrounding the necrotic area of the myocardial infarction [42]. Those recruited EPCs are believed to enhance myocardial revascularization at the border zone and prevent further necrosis, thus, help to prevent expansion of the necrotic area and improve the left ventricular function [43,44]. A basic fundamental necessity for this process is nitric oxide (NO), manufactured by endothelial nitric oxide synthase (e-NOS) [45].

It has been shown that statins enhance NO bioavailability through increased e NOS activity, leading to direct and indirect activation of cell adhesion molecules on EPCs and on endothelial cells and blood cells improving the "fine tuning" of "smooth" communication between cells [46], statins have been shown also to reduce senescence of EPCs and to inhibit expression of growth inhibitors [47], with reduction of the myocardial fibrosis and secondary "remodeling" of the affected failing heart. Again, all these processes were dependent on the intact activity of e NOS. Lipid lowering gene transfer in mice increased EPC number and function [48], improved myocardial vascularity with improved diastolic function [49,50].

It is a known phenomenon that statins affect mice through lipid-lowering independent effects because cholesterol in mice is not affected by statins. Several experimental and clinical studies have demonstrated that statins exert positive effects on EPCs mobilization, homing and function [51-53]. Statins enhance EPCs proliferation and differentiation through the Akt pathway [54,55], inhibit oxidative stress induced EPCs apoptosis [56], reduce rate of senesce [57], and improve EPCs' migratory and angiogenic function [55,58]. Other recent studies have shown that statins increased EPCs number, augmented anti-inflammatory polarization traits in the affected EPCs [59], improved mobilization of EPCs and re-endothelialization of denuded arterial segments [51], and restored age related impairment in neovascularization by increasing EPCs numbers [60]. Indirect effects on EPCs are induced by statins through nitric oxide (NO) dependent pathways. Statins enhance endothelial NO bioavailability by increasing NO production in the endothelium and prevent NO degradation [61]. Endothelial derived NO plays an important role in EPCs activation and mobilization.

Effects of Statins on Patients with Cardiovascular Disease

Several studies have demonstrated that higher levels of EPCs (quantified as CD34+/KDR+ cells on flow cytometry) are associated with better clinical outcomes in patients with coronary artery disease (CAD)[62,63]. Patients with heart failure (irrespective of the etiology) have reduced levels of EPCs compared with healthy controls [64]. The number of CD34+ cells was decreased in patients with severe heart failure and increased in proportion to the amelioration of heart failure during hospitalization [65].

The numbers of EPCs increased 1.5 fold following 1 week treatment of CAD patients with statins, and increased 3 fold following 4 weeks' treatment. Statins increased the number of EPCs (CD34+/ kinase insert domain receptor +) and also enhanced their function and activity (assessed by migratory assays) [36]. Patients with an acute ischemic stroke that were treated with statins had significantly higher levels of EPCs compared to placebo [66]. Post-menopausal women who got statins vs. placebo in a double blind fashion for 8 weeks, those who got statins increased the absolute number of EPCs with a

significant reduction of the senescent cells [67]. Another study found that patients who underwent coronary artery bypass graft (CABG) surgery and got statins for 14 days before the operation increased their circulating EPCs pre- and post-operation with a better clinical recovery and with lower levels of C reactive protein (CRP) [68]. Intracoronary infusion of circulating EPCs improved left ventricular remodeling and function in patients with post myocardial infarction heart failure [69].

Statins have been shown to affect mesenchymal stem cells (MSCs) as well, affecting survival and function of these stem cells that have been documented to contribute (animal models and human studies) to affect the failing myocardium inducing reversed remodeling by transforming into EPCs (~20% of them), improving angiogenesis and vasculogenesis [69-71].

Epcsand the Atherosclerotic Plaque

Hypercholesterolemia and vascular inflammation negatively affect EPC number and function and may cause exhaustion and depletion of the EPC bone marrow pool [72-75]. Statins induce cardiovascular risk reduction, lower lipids in patients with cardiovascular disease and are associated with increased number of EPCs in the peripheral blood [76,77] with better homing to sites of vascular injury [78]. A study that examined the effect of EPCs number on atherosclerotic plaques found that after increasing circulating c-kit+Flk1+Cd11b- and CD34+CD133+Flk1+ cells by AMD3100 a significant reduction in plaque burden was observed [79]. More than that, AMD3100 caused significant EPCs mobilization from the bone marrow and decreased lesion burden 2.3 fold. These data may suggest that availability of circulating EPCs may be a rate limiting factor in atherosclerotic plaque lesion progression and regression [79].

EPCs normally reside in bone marrow niches characterized by low oxygen tension and high levels of CXCL12. They are moving out of the niche in response to EPC-activation factors [80]. EPCs number in the peripheral circulation are used as a surrogate marker for cardiovascular risk. Low levels of circulating EPCs are independent predictors of endothelial dysfunction and progression of atherosclerosis [81,82]. Correction of hyperlipidemia in patients with cardiovascular disease is accompanied by an increase in circulating EPCs with improved cardiovascular risk profile [83]. Long term treatment with bone marrow EPCs from non-atherosclerotic young Apo E-/-mice prevented atherosclerosis progression in adult Apo E-/- recipients even though they still had hypercholesterolemia [84]. It has been shown that the most potent chemokine kigand for the chemokine receptor CXCR2, CXCL1, is up-regulated in the vascular wall in regressing atherosclerotic plaques [85]. This chemokine receptor recruits human circulating EPCs to sites of acute arterial injury [86]. The homing of bone marrow EPCs to ischemic tissues also depends on beta 2 integrin expressed on EPCs, on endothelial expression of ICAM-1,[87] and an interaction between EPC alfa4-beta1 integrin (VLA-4) with VCAM-1 in the vessel wall [88] One hypothesis suggested that the transferred stem cells Tie2-GFP+CD133+Sca-1+Flk1+ EPCs enhance plaqur regression by inducing vasculogenesis. Another hypothesis was suggested that EPCs induce regression of atherosclerotic plaques through secretion of paracrine or just arcane factors that trigger in situ proliferation and migration of pre-existing endothelial cells [79].

Direct EPC treatment and/or indirect EPC mobilization therapy have been suggested in prevention and treatment of atherosclerosis in patients with heart failure and post myocardial infarction [89]. The option of inducing and enhancing endogenous stem cells instead of injecting stem cells from donors looks very attractive. G-CSF can be used for EPCs mobilization from the bone marrow, however, induction of pro-inflammatory cytokines by G-CSF caused side effects, mainly in patients with coronary artery disease due to its effects on the cardiovascular system [90,91] AMD3100 (Mozobil) is a more potent stem cells mobilized [92], without systemic cytokines' secretion and without the significant enhancement of white blood cells [93]. We have demonstrated that CD133+ cells were significantly mobilized from the bone marrow to the circulation following a single injection of CXCR4 antagonist, plexifor (AMD3100; Mozobil), without evidence for systemic activation of inflammation [93].

Summary

Atherosclerosis is a leading cause of death in Western countries. Life style, including diet and exercise are being the main goal of intervention. One of the main aims of modern medicine is to identify markers that could predict the development of atherosclerosis. Endothelial function could serve as a biological non-invasive marker to detect early changes that will lead to the development of atherosclerosis. Different approaches are used among them are the flow-mediated vasodilatation (FMD), antero-posterior abdominal aorta diameter (APAO), intima-media thickness of the common carotid artery (CCA-IMT), and arterial stiffness. However, two main independent factors should be taken into account for vascular evaluation: age and sex. These factors can't be changed but modern medicine and a better understanding of the mechanism of atherosclerosis can help us to have a better management and a better prevention based on our knowledge of different physiological and cellular biology characteristics that are changing with age and are gender oriented [94]. The main focus of intervention and prevention in cardiovascular disease are diet and exercise. It is known that dietary supplements like dietary omega-3 polyunsaturated fatty acids (ω-3 PUFAs) are well-defined in adults; however, no data still exists for the use of dietary supplements like omega 3 in childhood. W-3 PUFA has been shown to play an important role in reducing the metabolic and vascular alterations induced by fat accumulation since young age. Such a relationship could be more important in prevention of future cardiovascular events especially since ω-3 PUFAs has been shown to improve endothelial function during childhood [95].

The new pathways and understanding the importance of vasa vasorum and its role in atherosclerosis and as a niche for stem cells (EPCs) and the understanding that stem cells are important players in the atherosclerotic process may open new horizons in prevention, management, and treatment of cardiovascular disease. Recent publications describe the magic of stem cells' transplantation for cardio-vascular regeneration and myocardial remodeling post myocardial infarction, but there could be other alternatives, like enhancement of self-existing stem cells' reservoirs in the bone marrow and in the vasa vasorum through different approaches, among them are statin therapy, that has been proved as an effective and safe approach to treat and prevent cardiovascular disease through improvement in endothelial function, inhibition of vascular

inflammation, and upgrading stem cells' numbers, function and quality.

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