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Role of Heparanase Inhibition in Atherosclerosis Prevention. A Potential Novel Therapeutic Strategy

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Abbreviations: AS: Atherosclerosis; Ox-LDL: Oxidized LDL; ECM: Extra-Cellular Matrix; OS: Oxidative Stress; HSPGs: Heparan Sulfate Proteoglycans; HFD: High Fat Diet; AKI: Acute Kidney Injury; TFPI: Tissue Factor Pathway Inhibitor

ABSTRACT

Atherosclerosis is a progressive process that leads to ischemic injury to body organs. The basis of the disease is lipid accumulation in the arterial wall that results in narrowing of the artery lumen. Several pathogenetic mechanisms are involved in the development of atherosclerosis. Chronic inflammation and increased oxidative stress induce structural and functional damage of the vascular endothelium and contribute to atherosclerosis progression, where several antioxidants exert varying extents of anti-atherogenic effects. Heparan sulfate proteoglycans are cell surface and extracellular matrix macromolecules that play a key role in maintaining tissue integrity, besides cellular-extracellular matrix communication, towards keeping adequate structure and function of tissues and organs. These macromolecules undergo cleavage by the enzyme heparanase- the enzyme responsible for the degradation of heparan sulfate chains. Recent studies implicated heparanase in atherosclerosis development and progression, and pathophysiologic pathways have been suggested.

In this manuscript, we shed light on the knowledge regarding involvement of heparanase in atherosclerosis and focus on how heparanase inhibition may constitute an effective strategy to attenuate atherosclerosis progression.

Keywords: Heparanase; Heparan Sulfate Proteoglycans; Atherosclerosis; Oxidative Stress; E_0 Mice

Atherosclerosis- Knowledge and Pathogenesis

Atherosclerosis (AS) is the process in which lipid particles, mainly oxidized LDL (Ox-LDL) accumulate in the luminal side of the arterial walls, then enclosed with a fibrous cap, which is composed of hypertrophic endothelial cells, collagen and extra-cellular matrix (ECM) proteins. Together, the lipid core and the surrounding fibrous cap form the atherosclerotic plaques, which cause progressive narrowing of the arterial lumen, resulting in impaired blood flow and oxygen supply, leading to ischemic injury in the affected organs [1]. Being a multifactorial process, AS is accelerated in the presence of several cardiovascular risk factors, such as diabetes mellitus, hypertension, hyperlipidemia, complex genetic susceptibility to the disease, and tobacco abuse. In these diseases, higher levels of oxidative stress (OS) occur frequently, which lead to advanced disease and a higher rate of target organ damage and disease-related complications. OS augments the inflammatory response in the vascular endothelium, which results in vascular endothelial structural and functional damage, thus leading to accelerated AS [2,3].

A proof for the role of OS in the progression of AS is that multiple endogenous and exogenous antioxidants had been proven to attenuate AS progression [4-6]. Heparan sulfate proteoglycans (HSPGs) are macromolecules that are composed of glycosaminoglycan chains covalently bound to a protein core and are either embedded in cell membranes or located in the ECM [7]. HSPGs exert important functions in cell-ECM interaction [8-10] and play key roles both in normal biologic processes [11-16]

as well as in several pathologic processes [7,11,12,17-23], and their normal structure and function are crucial for maintaining normal tissue structure, integrity and function [24]. Heparan sulfate endoglycosidase heparanase (Heparanse), the only enzyme in mammalians that degrades HS chains in the HSPGs [19,25-27], is implicated in the tight regulation of HSPG turnover, through both intracellular and extracellular roles [28-30]. As HSPGs exist in all the body organs and systems, heparanase inhibition is under extensive investigation in various diseases. Recent studies implicate heparanase in AS development and progression. In their study, Blich, et al. demonstrated intense staining for heparanase in the intima of vulnerable atherosclerotic plaques in human coronary arteries compared to a weak staining in stable plaques [31].

Similarly, Osterholm, et al. demonstrated a 6.6 fold increased heparanase mRNA levels in atherosclerotic plaques in human carotid arteries in comparison to non-atherosclerotic iliac arteries [23]. Likewise, Baker, et al. documented elevated heparanase levels and activity associated with coronary atherosclerosis progression in diabetic hyperlipidemic swine [22]. In their review, Vlodavsky, et al. reported in detail the role of heparanase in atherosclerosis and other vessel wall pathologies [32]. In line with these studies, we demonstrated in apolipoprotein E deficient (E0) mice that heparanase inhibition by PG545 (Pixatimod) significantly decreased serum OS and lowered plasma lipid levels [33]. In addition, we demonstrated in E0 mice placed on high fat diet (HFD) that heparanase inhibition by PG545 significantly decreased serum OS, along decreasing aortic wall thickness and atherosclerotic plaque surface area. In the same study, we demonstrated that PG545 significantly diminished the development of liver steatosis, an issue under current investigation [34].

In biochemical staining and western blotting studies, we demonstrated that PG545 caused significant reduction of IL-1, TNF-α, and aKT, together with increasing FGF-2 and LC-III expression, reflecting the fact that heparanase inhibition resulted in anti-inflammatory effects, besides augmenting regeneration process and increased autophagy, in an attempt of the liver to repair injured liver tissue. All these effects, together with lowering serum OS and lipid levels, can be suggested as the pathogenetic mechanisms by which heparanase inhibition exerts the beneficial anti-atherosclerotic and anti-steatosis effects (Figure 1). Moreover, we also studied the effect of Roneparstat (SST0001) on OS, AS, and liver steatosis in E0 mice placed on HFD for eight weeks. SST0001 showed metabolic effects similar to PG545 (decreased serum lipids levels and OS, and significantly attenuated the development of liver steatosis), but had no effect against the development of atherosclerosis in the aortas of the mice. Like PG545, also SST0001 demonstrated neither heptotoxicity nor renal toxicity, and did not affect blood pressure. In contrast to PG545, which caused prominent weight loss in mice despite minimal effect on food intake, SST0001 affected neither food intake nor mice body weight (data not published).

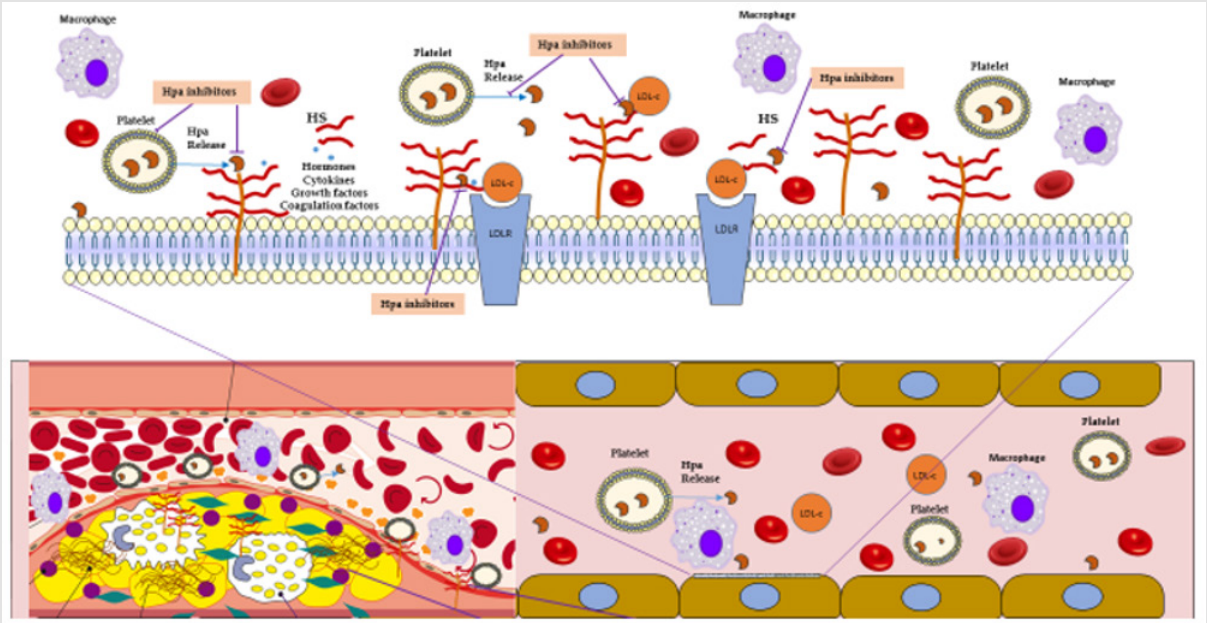

Figure 1: A schematic presentation presenting a long-cut view for an artery. Endothelial cell layer are shown, with a magnification of the luminal endothelia cell membrane, showing components of cell wall- including embedded LDL receptors and heparan sulfate proteoglycan molecules, as well as heparanase molecules and intra-luminal blood cellular components.

Heparanase Inhibition in Acute Kidney Injury

In ischemia-reperfusion acute kidney injury (AKI) rat model, pre-treatment with PG545 significantly attenuated the development of AKI, which was expressed by lower serum creatinine and blood urea nitrogen levels in the treated mice. Histologic studies of the kidneys in the sham-control mice revealed the development of acute tubular necrosis, with tubular lysis, loss of brush border and the accumulation of debris in the tubular lumen. Electron microscopy analyses revealed mitochondrial distortion in the sham-control mice, compared to normal ultrastructure of the mitochondria in mice pre-treated with the heparanase inhibitor [35].

Heparanase Inhibition in Malignant Diseases

The role of heparanase in the development of malignant diseases was well established, and the effect of heparanase inhibition in the treatment of different malignancies has been extensively studied. Recent studies demonstrated favorable effects of the heparanase inhibitor SST0001 (Roneparstat) when added to standard treatment protocols in patients with multiple myeloma [36-38] or in different kinds of human pediatric osteosarcoma and other sarcoma models [39,40], as well as in cases of mesothelioma [41] and different pediatric malignancies [42], and thus heparanase inhibitors are under consideration as an additional modality for treating malignant diseases [43-45].

Heparanase Inhibitors and the Coagulation System

Impaired endothelial dysfunction is an early feature of formation of the atherosclerotic lesion. Acute cardiac ischemic syndromes, such as unstable angina pectoris or myocardial infarctions, occur following the abrupt rupture of an atherosclerotic plaque, an event that leads to exposure of the highly thrombogenic lipid core constituents of the plaque to the intra-vascular content, resulting in activation of the coagulation system, which further accelerates the atherosclerotic plaque formation [46-48]. Heparan sulfate molecules play key roles in activation of the coagulation system.

In a book chapter, Nadir Y. had described in detail the role of heparanase in the activation of the coagulation system and reported increased heparanase level and activity in several clinical settings associated with hypercoagulability, such as in women using oral contraceptives, cases of diabetic foot, women at delivery, after orthopedic surgeries, and in patients with lung cancers and other malignancies [49]. Former studies have reported in detail the role of heparanase in increasing coagulation via three mechanisms, including enhancement of tissue factor activity, upregulation of tissue factor expression in endothelial cells, and by releasing the single chain polypeptide tissue factor pathway inhibitor (TFPI) from cell surface [50], and heparanase inhibition by peptides derived from TFPI-2 was proved to inhibit the procoagulant activity of heparanase and to attenuate sepsis in mouse model [51].

Conclusion

There is a large evidence regarding the involvement of heparanase in several disease processes, supported by the fact that higher heparanase levels and activity are associated with more advanced and complicated diseases, as was shown in several malignancies, diabetes mellitus, nephropathies of variable etiologies, and infectious and inflammatory processes. Likewise, several recent studies had implicated heparanase in atherosclerosis development and progression. Many basic science and clinical studies were held and others being ongoing, to explore the effect of heparanase inhibition on malignant diseases. Conversely, only few studies have reported the effect of heparanase inhibition on atherosclerosis formation and progression. Undoubtedly, heparanase inhibition exerts favorable effect towards attenuating atherosclerosis progression, in spite of the contradictory results obtained so far.

The effect of heparanase inhibition on AS is expressed by significant attenuation in the development of aortic atherosclerotic plaques and reducing aortic wall thickness, through several possible mechanisms, which include lowering of serum lipid values, decreasing serum oxidative stress, and anti-inflammatory effects. However, lack of pathogenic mechanism and effect of long term use of heparanase inhibitors in humans limit the possibility to apply using heparanase inhibitors in humans for prevention or treating atherosclerosis, and further research is absolutely warranted. In the literature, additional heparanase inhibitors are available, where their effect was not examined neither on AS nor on liver steatosis. In face of the existing non-consistent results demonstrated so far, it is highly warranted that the effect of additional heparanase inhibitors on atherosclerosis prevention and treatment be studied.

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