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Metalloproteinases, Sialidases and NADPH Oxidases as Key Enzymes involved in Atherosclerosis Development

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Abstract

Background: Atherosclerosis and related cardiovascular diseases remain the leading cause of mortality and morbidity worldwide. Atherosclerosis development involves several pathological processes, including alterations of the blood lipid profile, chronic inflammation and thrombogenesis. The existing therapies for atherosclerosis are aimed at normalization of the lipid profile, reduction of cardiovascular risks and inflammation and alleviation of symptoms. Despite the certain progress made in the field, more efficient and direct approaches are needed to battle the disease effectively. Enzymes that are up-regulated or play key roles in various pathologies are traditionally regarded as potential therapeutic targets.

Methods and findings: We searched MEDLINE for recent articles reporting on the three enzymes that are involved in atherosclerosis development: matrix metallo-proteinases, neuraminidase/sialidases and NADPH oxidases. These enzymes participate in matrix remodeling, atherogenic modifications of LDL particles, and oxidative stress correspondingly.

Conclusion: The enzymes involved in atherosclerosis development, such as metalloproteinases, sialidases, and NADPH oxidases, appear to be potential therapeutic targets for the disease prevention and/or treatment. However, more selective and potent inhibitors of these enzymes need to be discovered before they become relevant for clinical treatment of atherosclerosis.

Keywords: Atherosclerosis; Sialidase; Metalloproteinase; NADH oxidase; Neuraminidase

Introduction

Atherosclerosis underlies a large part of cardiovascular diseases that remain the leading cause of morbidity and mortality worldwide. The main pathological feature of atherosclerosis is the formation of atherosclerotic plaques in the vessel wall. Atherosclerotic lesions are induced by local disturbances of vascular endothelium that often occur in atheroprone sites, such as bifurcations or bends of the vessel [1]. In these sites, endothelium becomes activated, which increases its permeability and stimulates the recruitment of circulating immune cells. Consequently, accumulation of cells and lipids takes place in the subendothelial layer of the vessel wall, resulting in its significant thickening. Growing plaques can reduce the vessel lumen and provoke ischemia by themselves, but more dangerous are so-called unstable plaques that trigger thrombogenesis on their surface. Thrombus formation in the major arteries can lead to sudden and fatal events [2,3]. Pathogenesis of atherosclerosis is a multifactorial process that includes inflammatory response, oxidative stress, and changes in lipid metabolism. Atherosclerosis is associated with alterations of blood lipid profile, with increased levels of Low-Density Lipoprotein (LDL) cholesterol, which serves as the major source of lipid accumulation in the arterial wall. Inflammatory process is another pillar of the pathology, with immune cells participating in lipid storage giving rise to foam cells that constitute the cellular mass of the growing plaque. During the recent years, numerous signaling proteins, enzymes, biomarkers and genes involved in the pathology have been identified, and the list is steadily growing [4-6].

Enzymes are traditionally regarded as potential therapeutic targets, since can often be selectively inhibited or inactivated by small molecules. In the case of atherosclerosis, inhibition of cholesterol biosynthesis by blocking 3-methylglutaryl-CoA with statins is widely used in current clinical practice [7]. Statins are known to possess not only cholesterol-lowering, but also anti-

inflammatory properties, and were shown to stabilize and even regress atherosclerotic plaques. However, they prove not to be sufficient for effective reversal of the atherosclerotic process once it is established, and novel therapies are urgently needed to act at the level of the arterial wall and atherosclerotic lesions. Several enzymes are known to be involved in atherosclerosis initiation and progression at the level of the arterial wall, including metalloproteinases [8], neuraminidases/sialidases [9,10] and NADPH oxidases [11]. In this review, we attempted to summarize the existing information on these enzyme types based on recent articles indexed in MEDLINE.

Metalloproteinases

Metalloproteinases have a metal (zinc) atom in the catalytic center and a conversed methionine in the catalytic domain. Three families of metalloproteinases have been described: A Disintegrin and Metalloproteinases (ADAMs), A Disintegrin and Metalloproteinases with Thrombospondin Motifs (ADAMTSs) and Matrix Metalloproteases (MMPs) [12]. The big family of human MMPs consists of 23 members, including 14 that are expressed in the vascular system [13]. MMPs are commonly classified based on the substrates they cleave to collagenases, gelatinases, martrilysins, stromeolysins and others. Membrane-type MMPs have a transmembrane domain or GPI anchor and are therefore attached to cellular membranes. MMPs play an important role in tissue remodeling and regeneration, as well as in organ formation. In the adult organism, MMPs take part in such processes as neovascularization. By cleaving extracellular matrix constituents, they ensure recycling of matrix proteins. However, MMPs also participate in a wide range of pathologies, including cancer and atherosclerosis, and therefore represent interesting therapeutic targets [14].

In atherosclerosis, MMPs play a special role, since they process the components of extracellular matrix in the plaque. Different members of MMP family are playing varying roles in atherosclerosis progression. Studies have shown that gelatinases MMP-2 and MMP-9 and stromelysin MMP-3 contribute to vascular smooth muscle cell migration and plaque growth, and are associated with increased carotid Intima-media Thickness (cIMT) [15]. At the same time, martrilysin MMP-7, metalloelastase MMP-12, collagenase MMP-13 and a membrane type metalloproteinase MMP-14 are associated with the activity of monocytes and macrophages and contribute to the loss of extracellular matrix proteins from the fibrous cap of the atherosclerotic plaque, apoptosis of cells present in the cap, and plaque destabilization [8,15,16]. However, for some MMPs, such as MMP-3 and MMP-9, protective functions have been demonstrated in mouse models of atherosclerosis [16].

Enhanced expression and elevated activity of MMP-1, MMP-8 and MMP-13 were demonstrated in atherosclerotic plaques, associated with Endothelial Cells (ECs), smooth muscle cells and macrophages [17-19]. Polymorphisms in the promoters of the genes encoding these enzymes are associated with aortic, carotid and coronary atherosclerosis [20-23]. Moreover, in unstable plaques, increased collagenolytic activity has been observed, that could be attributed to MMP-1, MMP-8 and MMP-13 [17,19]. Enhanced level of MMP-8 in plaques and plasma were predictive of systemic cardiovascular events [24].

Despite being attractive potential therapeutic targets, MMPs have only limited clinical relevance so far. Synthetic MMP inhibitors have been evaluated in clinical trials in patients with cancer and rheumatoid diseases, but were found to be associated with significant toxicity. One MMP inhibitor relevant for cardiovascular diseases that received FDA approval is doxycycline, which down-regulates several MMPs and allows attenuating cardiac inflammation and abnormal tissue remodeling after myocardial infarction [25,26]. Its application is, however, limited to short-term treatment. Further efforts should be focused on identification and evaluation of more selective MMP inhibitors, that might have a better safety profile and more targeted mode of action in atherosclerosis [27].

ADAM metalloproteinases were also found to play a role in atherosclerosis development. These membrane-bound proteinases are responsible for shedding, or release of various peptides and proteins from the cell surface to the extracellular space, and for cleavage of different substrates present in the cell membrane, including adhesion and signaling proteins. Increased levels of ADAM9, ADAM10, ADAM15, ADAM17, and ADAM33 were observed in atherosclerotic plaques [28,29]. ADAM10 was shown to play an important regulatory role in vascular permeability and transmigration of T-cells [30]. ADAM17 is known to be involved in the pathogenesis of various inflammatory diseases, including atherosclerosis, by cleaving membrane-bound signaling molecules. This metalloproteinase has been identified as an attractive potential therapeutic target [31]. ADAMTs are capable to cleave proteoglycans, which makes them important players in atherosclerotic lesion development [32]. Pre-atherosclerotic adaptive intimal thickenings and early lesions are enriched with proteoglycans that facilitate monocytes and macrophages recruitment to the growing lesion and increase lipid retention in the subendothelial space [33]. ADAMs, especially ADAM10 and ADAM17, have been considered as potential therapeutic targets for many years already, and numerous inhibitors were tested in pre-clinical settings. However, all of them, except one, failed to enter the level of clinical trials [34]. Future studies should focus on the development of novel ADAM inhibitors with improved potency and tolerability.

Sialidases

Sialidases, or neuraminidases, are glycosidases that catalyze the removal of α-glycoside bonds that link terminal sialic acid residues to carbohydrate chains of glycoproteins and glycolipids [35,36]. Neuraminidases are commonly present on the surface of bacteria and viruses that use these enzymes to facilitate interaction with host cells. Viral neuraminidases have different sensitivity to inhibitors than mammalian neuraminidases, and are widely used as therapeutic targets. In mammals, four types of sialidases have been described: NEU1 (lysosomal sialidase), NEU2 (cytosolic sialidase), NEU3 (membrane sialidase) and NEU4 (mitochondrial sialidase). These enzymes are encoded by different genes and also have different properties, such as subcellular localization, pH-optimum, substrate specificity and

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stability [36,37]. Altered activity of human sialidases is implicated in various pathologies, including cancer, which remains the best studied to date [38], neurological and cardiovascular diseases. Modulation of human sialidase activity is therefore regarded as potentially valuable therapeutic approach for treatment of several disorders, including atherosclerosis [39,40]. In atherosclerotic plaques, NEU1 was shown to be involved in atherogenesis through generation of elastin-derived peptides that attract immune cells and promote the local inflammatory response [41]. The information on the involvement of other mammalian neuraminidases in atherosclerosis development remains very limited. However, there is accumulating evidence that desialylation of LDL particles in the blood plasma performed either by trans-sialidases may play a crucial role in the pathology.

Studies of atherogenic modifications of LDL that provoke lipid accumulation in the arterial wall cells resulted in the discovery of desialylated LDL present in circulation [42]. The enzyme responsible for this modification has been identified as trans-sialidase, which is present and active in human blood plasma [43]. Incubation of native LDL samples with purified trans-sialidase *in vitro* resulted in LDL desialylation and increase of atherogenicity. Reduced level of sialic acids was also demonstrated in LDL samples treated with bacterial silidase. Desialylated LDL corresponds by its characteristics to small dense electronegative LDL, which is also prone to oxidation and is known to be associated with atherosclerosis [44]. Desialylation of LDL is associated with enhanced cholesterol uptake by macrophages and in lipid accumulation in human aortic smooth muscle cells [45]. It is likely that desialylation is an early even in the cascade of atherogenic modifications of LDL that include oxidation. Sialic acid has been demonstrated to serve as a potent free radical scavenger, therefore playing an important role in regulating oxidative stress [46,47]. Interestingly, administration of exogenous sialic acid had a protective effect in a mouse apoE-/- model of atherosclerosis, reducing the plaque formation and the level of plasma triglycerides and cholesterol [48]. These findings highlight the link between desialylation and oxidative stress associated with atherosclerosis.

Human trans-sialidase transfers sialic acid residues from sialoglycoconjugates to various acceptor glycoconjugates. Trans-sialidase is able to cleave residues of sialic acid from glycoconjugates present in LDL, Intermediate Density Lipoprotein (IDL), Very Low-Density Lipoproteins (VLDL) and High-Density Lipoprotein (HDL), and to transfer them to a range of acceptors that are present in blood plasma [49,50]. Physiological role of trans-sialidase in human plasma remains unclear [51]. It was shown that sialidases can modify properties of a range of blood cells types and lipoproteins [52]. Data obtained on C57Bl/6 mice demonstrated that expression of hypomorphic sialidase influenced lipoprotein metabolism. Such expression, specifically in blood cells, was sufficient to attenuate atherogenesis. Moreover, treatment with sialidase inhibitor, 2-deoxy-2,3-dehydro-N-Acetylneuraminic acid (DANA) resulted in attenuated atherosclerosis development in apoE-/- mice. Hypomorphic sialidase expression was associated with increased monocytic cholesterol uptake and macrophage cholesterol efflux to High-Density Lipoprotein (HDL). Therefore, hypomorphic sialidase expression appeared to be atheroprotective in C57Bl/6, apoE-deficient and ldlr-deficient mouse models [52].

Therefore, sialidases appear to play an important function at the initial stages of atherosclerosis, most importantly, through participation in the formation of atherogenic modified LDL species and through the possible link with oxidative stress. Development of selective and efficient inhibitors of sialidase activity in the blood plasma could provide an interesting therapeutic opportunity for atherosclerosis prevention.

NADPH Oxidases

As described above, oxidative stress plays an important role in atherosclerosis progression [53]. One of the best studied effects is the formation of oxidized LDL during oxidative stress and therefore generation of atherogenic LDL species [11,54]. Integral membrane proteins NADPH oxidases (NOX) are major producers of Reactive Oxygen Species (ROS). They are widely expressed in the vasculature and are present in platelets. In humans, 7 NOX enzymes are known (NOX 1-5, DUOX1 and DUOX2), all of them sharing a common mechanism of action, but possessing distinct regulatory mechanisms [55]. NOX were first identified in the membranes of "professional" phagocytic cells of the immune system. In these cells, ROS play an important role participating in host defense and mediating killing of pathogens [56]. Later, presence of NOX enzymes was revealed in non-phagocytic blood cells and other cell types, including endothelial cells and smooth muscular cells. In non-phagocytic cells, ROS play primarily signaling role and NOX expression and ROS generation are maintained at low levels. However, NOX expression can be up-regulated in response to mitogenic and transforming growth factors, as well as under some pathological conditions, such as hyperlipidemia or hyperglycemia [57,58]. In the vascular system, NOX 1, NOX 2, NOX 4, and NOX 5 are expressed in the endothelium, vascular smooth muscle cells, fibroblasts and perivascular adipocytes. Other isoforms either are present at very low levels or have not been found and their significance has not been determined [57].

In atherosclerosis, NOX were shown to contribute to virtually every stage of pathology development, including atherogenic modification of LDL, endothelial dysfunction, recruitment of the immune cells to the growing lesion and thrombogenesis on the surface of unstable plaques [58]. Calcium-dependent NOX5 is a major source of ROS in atherosclerosis and is involved in the oxidative damage associated with the disorder. Levels of NOX5 mRNA and protein are significantly increased in coronary arteries obtained from patients that suffered from coronary artery disease compared to healthy arteries, and these data correlate with the Ca_{2+}-dependent NADPH oxidase activity in the arteries. Expression of NOX5 was found in the endothelium of early-stage lesions and in vascular smooth muscle cells in the intima of advanced coronary lesions [59]. ROS generated by NOX2 is predominantly detected in the endothelium and adventitia, while NOX1 and NOX4 are important for vascular smooth muscle cells functioning due to the fact that expression and activity consequently vary with the disease progression. The differential way of ROS generation by functionally distinct NOX

isoforms that are expressed in different vascular cell types may be used as a therapeutic advantage [60]. Inhibitors of NOX family members can be considered for the development of future anti-atherosclerosis therapies [61]. Over the years, several candidate inhibitors of NOX (besides the agents that enhance NO generation and therefore act indirectly) have been identified. However, few of them made it into clinical practice [62]. One of the promising NOX inhibitors extracted from plants, apocynin, is also characterized by low toxicity, and therefore appears to be interesting for the development of therapies against cardiovascular diseases [63]. More studies are needed to develop safe and specific ways of NOX inhibition for long-term treatment of atherosclerosis and related disorders.

Conclusion

Several human enzymes with very distinct properties have been demonstrated to play important roles in atherosclerosis development. In this review, we focused on three groups of enzymes: MMPs, sialidases and NOX, all of them currently considered as relevant therapeutic targets. Although certain progress has been achieved in the development of selective inhibitors of these enzymes relevant for clinical practice, more studies are needed to improve the characteristics of these molecules and reduce their toxicity. Better understanding of the role of each enzyme isoform in the development of different stages of atherosclerosis will inform the search for selective inhibitors.

Conflict of Interest

The authors declare no conflict of interest.

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