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Molecules in focus

Scavenger receptors: Implications in atherothrombotic disorders

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ABSTRACT

Scavenger receptors are modified lipoprotein binding receptors, expressed on the surface of a variety of cells including endothelial, macrophages and platelets. The most extensively studied class B scavenger receptors comprise of CD36 and SR-BI and have been found to bind to native and modified LDL. Interaction of modified LDL to CD36 accelerates foam cell formation, the key step in atherosclerotic plaque deposition. Recently scavenger receptors have also been implicated in thrombosis. Platelet CD36 serves as a sensor of oxidative stress and modulator of platelet reactivity under hyperlipidemic conditions thus, inducing prothrombotic signals. In contrast, targeting platelet SR-BI corresponds to reduce platelet hyperreactivity in hyperlipidemia suggesting that targeting these receptors could be a promising strategy for the treatment of atherothrombotic disorders.

1. Introduction

Scavenger receptors are modified lipoprotein binding receptors that are involved in cholesterol and lipoprotein metabolism. Scavenger receptors were first identified on activated macrophages and were found to bind and internalize modified lipoproteins. Scavenger receptors found on macrophages range from class A to G that share the defining feature of being able to bind the modified forms of LDL (Fig. 1). Some of them are multi-ligand receptors while others may have pattern recognition property. Scavenger receptor–ligand interaction initiates signaling cascades that regulate macrophage activation, lipid metabolism and inflammatory pathways which may influence the development and stability of atherosclerotic plaque. Recent studies have demonstrated the expression of scavenger receptors especially CD36 and SR-BI on platelets suggesting their critical role in platelet hyper-reactivity in dyslipidemia and atheroprogression. The present review focuses mainly on scavenger receptors class-B; one of the major receptors involved in atherosclerosis, thrombosis and other cardiovascular complications.

2. Structure

CD36 first identified as the platelet glycoprotein III b/IV, is an 88 kDa heavily glycosylated transmembrane protein that belongs to scavenger receptor class B family (Fig. 1). Class B scavenger receptors-BI (SR-BI) belongs to the evolutionarily conserved CD36 family of protein, thus sharing 30% sequence homology with CD36 (Acton et al., 1994). SR-BI, an 82-kDa membrane glycoprotein contains a large extracellular domain and two transmembrane domains with a short cytoplasmic amino- and carboxyl-terminal tail (Fig. 1) (Krieger, 1999). Lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) is a ~50 kDa surface protein that belongs to class E scavenger receptor (Fig. 1). While scavenger receptor class A (SR-A) is a 77 kDa trimeric protein (Fig. 1).

3. Expression, activation and turnover

Apart from platelets, CD36 is also present on the surface of skeletal and cardiac myocytes, adipocytes, monocytes and microvascular endothelial cells (Knowles et al., 1984). The diverse group of ligands that bind to CD36 consists of oxidized phospholipids (Endemann et al., 1993), thrombospondin-1, collagen, various microbial pathogens, apoptotic cells, fatty acids and microbial diacylglycerides (Hoebe et al., 2005; Podrez et al., 2002; Silverstein et al., 2010). The expression of CD36 on platelets has also appeared to play an important role in atherothrombotic events (Podrez et al., 2007). Other major class B scavenger receptor SR-BI is expressed on the surface of stereodigenic tissues mainly in the adrenals, ovary, hepatocytes and to some extent on endothelial cells (Krieger, 1999). Like CD36, it also binds to a variety of ligands including native lipoproteins, oxidized lipoproteins, advanced glycation end products and anionic phospholipids (Krieger, 1999) and plays a pivotal role in cholesterol metabolism.

Lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) is expressed on the surface of endothelial cells, macrophages,

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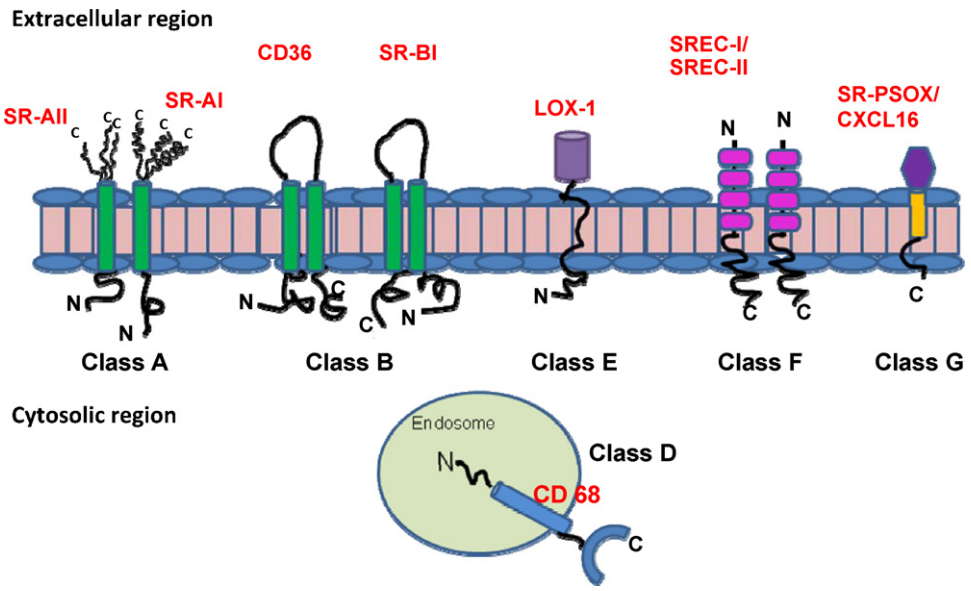

Fig. 1. Schematic representations of different class of scavenger receptors.

smooth-muscle cells and platelets (Sawamura et al., 1997). The ligands to which LOX-1 binds comprise of oxidized LDL, apoptotic cells, activated platelets and bacteria thereby signifying its implication in the pathogenesis of atherosclerotic lesions. LOX-1 expression on the surface of platelets was found to be activation-dependent. During platelet activation fusion of alpha granule membranes with plasma membrane is followed by the translocation of LOX-1 towards the platelet surface. Scavenger receptor class A (SR-A) is expressed on the surface of platelets and monocytes/macrophages. It binds to both oxidized and acetylated lipoproteins.

4. Biological function

4.1. Scavenger receptor CD36

Various studies using CD36 knockout mice have demonstrated their role in many pathophysiological processes including atherosclerosis, innate immune response, apoptosis, diabetes and thrombosis (Podrez et al., 2000). Earlier inhibition studies using the monoclonal antibody (OKM5) have suggested the role of CD36 in platelet activation and aggregation (Knowles et al., 1984). Initial stages of platelet adhesion to fibrillar collagen were also found to be defective in human CD36-deficient platelets. Other studies have also indicated a significant role of CD36 in thrombosis; however the role may be restricted to the dyslipidemic milieu, where enhanced oxidative stress results in the generation of specific ligands for CD36 (Podrez et al., 2007). Binding of oxidized LDL to CD36 induced platelet activation thus contributing to a pro-thrombotic phenotype in the setting of hyperlipidemia (Podrez et al., 2007). This study also found a 40 fold increase in levels of $oxPC_{CD36}$—a group of oxidized choline glycero-phospholipids (Podrez et al., 2007) that mediate CD36-dependent recognition of oxidized LDL in the plasma of hyperlipidemic apoE and LDL receptor knockout mice compared to normolipidemic mice. This effect was linked to platelet hyper reactivity (Podrez et al., 2007). Various platelet transfusion studies have shown that the occurrence of prothrombotic state in hyperlipidemia can be averted by the genetic deletion of platelet CD36 (Podrez et al., 2007).

In another set of experiments it has been found that micro particles; an endothelial cell derivative also bind to platelets in a CD36 dependent manner and facilitate their activation. This binding of micro particles to CD36 was attributed to the presence of phosphatidylserine on their surface (Ghosh et al., 2008). Platelet CD36 is also coupled with non-receptor tyrosine kinases of the src family, which have previously been involved in platelet activation by oxidized LDL (Huang et al., 1991). Recent studies stated that hyperlipidemia *in vivo* and oxidized LDL *in vitro* activate JNK2 and its upstream activator MKK4 in platelets via CD36 (Chen et al., 2008). CD36-dependent phosphorylation of platelet JNK within thrombi was also demonstrated.

4.2. Scavenger receptor-BI

The major physiologic function of SR-BI is to mediate the selective transport of cellular uptake of lipids, especially cholesteryl esters from HDL and the bidirectional flux of unesterified cholesterol between cells and lipoprotein (Krieger, 1999). Hepatic SR-BI regulates plasma lipoprotein metabolism, biliary cholesterol secretion and the structure and composition of plasma HDL particles. Over expression of SR-BI protein in mouse liver has been found to be associated with reduced levels of plasma HDL cholesterol, thus implicating a possible role for SR-BI in the transport of cholesterol from peripheral tissues to liver (Kozarsky et al., 1997). Likewise CD36, SR-BI receptors also play a significant role in atherosclerotic progression in hyperlipidemia. A recently conducted study has demonstrated that specific oxidized phospholipids that accumulate *in vivo* in oxidative stress may inhibit reverse cholesterol transport and contribute to the development of hypercholesterolemia and atherosclerosis (Ashraf et al., 2008).

In addition to liver, SR-BI is also expressed by cells within the arterial wall, including smooth muscle cells, macrophages in human and murine atherosclerotic lesions (Chinetti et al., 2000; Hirano et al., 1999). With regard to atherosclerotic lesion development macrophage SR-BI may be of equal importance. However the results obtained from recent studies related to SR-BI expression on macrophages are quite contradictory. Locally in the arterial wall, SR-BI expression on macrophages may protect against atherosclerosis by stimulating cholesterol efflux and preventing foam cell formation. Experiments conducted using murine bone marrow transplantation models have demonstrated that inactivation of macrophage SR-BI promotes the development of atherosclerosis in apoE-deficient mice. Furthermore, genetically suppressing SR-BI activity in apoE knockout mice dramatically accelerates the onset