Atherosclerosis 221 (2012) 303–310

Contents lists available at SciVerse ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Review

Lipid rafts: A signalling platform linking lipoprotein metabolism to atherogenesis

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ARTICLE INFO

Article history:
Received 8 June 2011
Received in revised form
22 September 2011
Accepted 12 October 2011
Available online 20 October 2011

Keywords:
Atherosclerosis
Cholesterol
Lipid raft
Lipoprotein
Oxysterol
Signal transduction

ABSTRACT

Lipid rafts are microdomains of the plasma membrane which are enriched in cholesterol and sphingolipids. They serve as a platform for signal transduction, in particular during immune and inflammatory responses. As hypercholesterolemia and inflammation are two key elements of atherogenesis, it is conceivable that the cholesterol and cholesterol oxide content of lipid rafts might influence the inflammatory signalling pathways, thus modulating the development of atherosclerosis. In support of this emerging view, lipid rafts have been shown to be involved in several key steps of atherogenesis, such as the oxysterol-mediated apoptosis of vascular cells, the blunted ability of high density lipoproteins (HDL) to exert anti-inflammatory effects, and the exacerbated secretion of pro-inflammatory cytokines by immune cells. Additional studies are now required to address the relative contribution of lipid raft abnormalities to the pathophysiology of atherosclerosis and cardiovascular disease.

Contents

1. Lipid rafts: a platform for signalling

Over the last decade, many reports have pointed out the existence of particular micro-domains at the plasma membrane: lipid rafts. As compared to the surrounding plasma membrane, these microdomains are enriched with cholesterol and sphingolipids which self-associate to form an ordered structure with weaker fluidity [1,2]. The packing of lipids found in lipid rafts allows them to be isolated as membrane fractions that are insoluble in non-ionic detergents, also called detergent-resistant membrane (DRM) [3]. Although the lipid raft concept might not be fully encompassed within the DRM structures as they can be isolated in the laboratory [4–6], it has been widely assumed that both rafts and DRMs are closely related.

The observation that numerous membrane proteins involved in cell signalling, cell adhesion, and cell migration are located within rafts, together with the evidence of dynamic nano-assemblies of sterols, sphingolipids and proteins in living cells [7] has increased interest in the biological functions of lipid rafts [8,9], in

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doi:10.1016/j.atherosclerosis.2011.10.016

particular, the role of lipid rafts in inflammation and immune responses [10,11]. Thus, lipid rafts were found to facilitate the T cell receptor (TCR)-mediated activation of T cells and to participate in the inflammation process [12]. Interestingly, Toll-like receptors (TLR) and interleukin receptors are found within the lipid rafts of cells treated with pro-inflammatory lipopolysaccharides (LPS) [10,13,14]. In fact, it has been shown that rafts serve as signalling platforms where the proteins involved in a signalling pathway transiently co-localize to allow signal transduction. The binding of hormones or cytokines to their receptors has been shown to lead to the recruitment of receptor–ligand complexes in rafts which allows the triggering of the signalling pathway [15]. In contrast, the recruitment of a protein within rafts may also block the activation of a signalling pathway through the exclusion of the triggering proteins from rafts [16]. Overall, it appears that ligand-induced changes in the localization of receptors in raft or non-raft domains of the plasma membrane can regulate signal transduction [3].

It should be emphasized that the lipid composition of the plasma membrane per se is actually a major determinant of the localization of proteins within lipid raft domains, and subtle changes in the lipid composition of the plasma membrane, and particularly in the cholesterol content may result in the modification of the overall signal transduction cascade. As an example, cholesterol depletion of lipid rafts using methyl-β-cyclodextrin or lovastatin was found to inhibit the insulin receptor signalling pathway, as was platelet-derived growth factor (PDGF)-mediated stimulation of phosphatidyl inositol-3-kinase (PI3-kinase) [17,18].

Within lipid rafts, caveolae are flask-like invaginations of the plasma membrane which are visible in electron microscopy [19]. Caveolae contain caveolin-1 as a main protein which exhibits several functional domains. Among these domains, the caveolin scaffolding domain (CSD) appears particularly important for the interaction with proteins involved in signalling pathways. Caveolae and caveolin-1 could be involved in several important steps of atherogenesis, including in particular the transport of low density lipoproteins (LDL) from the blood vessel lumen to the subendothelial space [20], the control of vascular smooth muscle cell proliferation, and the inflammation process. Caveolae also play an important role in cardiovascular signalling [21] and particularly in redox signalling because endothelial nitric oxide synthase (eNOS) is negatively regulated through its interaction with caveolin-1 (Fig. 1 – steps 4 and 5) [22].

2. Lipid rafts: a new frontier in elucidating the molecular mechanisms of atherosclerosis

Although only a few studies have so far dealt with the role of lipid rafts in the pathophysiology of atherosclerosis, lipid rafts might be master regulators of several key events, including transcytosis of LDLs, vascular-wall cell apoptosis, immune cell activation and inflammation, as well as protease activation and plaque (in)stability.

2.1. Transendothelial transport of LDLs and caveolae

Initiation of atherosclerosis involves the accumulation of LDLs in the sub-endothelial space of arteries. Several models have been proposed to explain the transendothelial transport of LDLs from the lumen of the vessel to sub-endothelial space [23]. In the transcytosis model, it has been hypothesized that LDLs may be transferred from the lumen to the intima either by a fluid phase transcytosis or by using a receptor-mediated transcytosis. In both cases, caveolae would be implicated, and it has been recently shown that caveolin-1 deficiency alters transcytosis [24]. Moreover, in apolipoprotein E-deficient mice, caveolin-1 deficiency is associated with a protective effect against atherosclerosis development [25].

2.2. Apoptosis

Apoptosis exerts divergent effects in terms of the progression and severity of atherosclerosis lesions, depending on the lesion stage and the cell type. Apoptosis of endothelial cells, smooth muscle cells or macrophages has been shown to favour the initiation of lesions [26], the rupture of plaque [27,28] or the regression and stabilization of lesions [29]. Better knowledge of the molecular mechanisms of cell death, according to the cell type, the development of the disease, and the lipid environment should lead to better understanding of the lesion outcome. In fact, differences in the lipid composition of the plasma membrane, depending on the cell type and/or on the lipid microenvironment could modulate the raft-embedded signalling pathways involved in the survival and/or death of vascular cells. Interestingly, the death receptor pathway for apoptosis might be involved in atherogenesis [30]. Indeed it has been reported that oxidized LDLs (oxLDLs) are able to activate Fas-mediated endothelial cell apoptosis [31], a death pathway involving the translocation and clustering of Fas into lipid rafts [32]. It is possible that such a mechanism is also involved in the Fas-mediated, oxysterol-induced death of human aorta smooth muscle cells [33].

2.3. Inflammation and immune cells

T cells are found in atherosclerosis lesions, where they modulate the atherogenic proinflammatory response and the plaque development [34]. Thus the presence of activated T cells in human atherosclerotic lesions suggests that T cell receptor (TCR)-mediated signalling pathway, a pathway involving lipid rafts, is activated during atherogenesis. In T cells, several proteins involved in TCR signalling, as TCR itself and the tyrosine kinase lck, colocalize in lipid rafts upon activation [35]. Accordingly, a recent *in vitro* study reported that the 7-ketocholesterol-induced alteration of lipid raft microdomains results in a reduction of T cell receptor signalling during T cell activation [36]. Monocytes/macrophages are key players in the pathophysiology of atherosclerosis, particularly in the inflammation process [37,38]. It has been shown that caveolae and caveolin-1 play a key role in the expression and the localization of the endothelial cell surface adhesion molecules such as VCAM-1 (vascular cell adhesion molecule-1) and E selectin, which are involved in monocyte recruitment at inflammation sites in the artery wall. Caveolin-1-mediated down-regulation of eNOS activity, might be actually responsible for the up-regulation of VCAM-1 expression in endothelial cells [25,39,40]. Finally, caveolae may be important for the leukocyte transmigration into the subendothelial space, a process which might involve leukocyte adhesion and E selectin redistribution in caveolae [41].

It has also been reported that the differentiation of monocytic THP-1 cells into macrophages induces changes in the lipid content of rafts. The plasma membrane of monocytic THP-1 contains a lower proportion of sphingomyelin than do differentiated THP-1 macrophages, suggesting putative consequences in terms of raft-associated signalling pathways [42]. In the same way, it has recently been shown in mouse macrophages that sphingomyelin synthase deficiency is associated with significant decreases in the sphingomyelin content of lipid rafts, thus attenuating NFκB activation and the pro-atherogenic inflammatory process [43].

2.4. Protease activity and plaque stability

A recent study demonstrated that a low level of caveolin-1 is associated with features of plaque instability and particularly with elevated metalloproteinase MMP-9 activity. The study identified