Review Article

Vol.9 | No. 1 | November, 2012

CD36 in atherosclerosis

Dhruba Acharya
Kathmandu University School of Medical Sciences, Kavre, Nepal

CD36 was described nearly 30 years ago as "glycoprotein IV" the fourth major band of 88KD observed on SDS-PAGE of platelet membrane (1). It is present on many mammalian cell types: microvascular endothelium; professional phagocytes including macrophages, dendritic cells, microglia and retinal pigment-epithellium; erythroid precursors; hepatocytes; adipocytes; cardiac and skeletal myocytes; and specialized epithelia of the breast, kidney and gut (2). As a pattern recognition receptor, CD36 binds a diverse set of ligands, including oxidized low-density lipoprotein (oxLDL)(5), anionic phospholipids (4), long-chain fatty acids, thrombospondin-1, fibrillar -amyloid, and the membrane of cells undergoing apoptosis (3, 5, 6). CD36 has been implicated in a wide variety of normal and pathologic biological functions, including angiogenesis, atherosclerosis, phagocytosis, inflammation, lipid metabolism, and removal of apoptotic cells (3, 5). In 1993, Endemann et al. first identified CD36 as a potential oxLDL receptor (7).Unlike macrophage scavenger receptor A type I and II, CD36 binds LDL that has been exposed to minimally oxidizing condition. The observation that CD36 was an oxLDL receptor was the catalyst for many to prove the role of CD36 in atherosclerosis.

Atherosclerosis is a progressive chronic inflammatory disease characterized by a gradual thickening and hardening of arteries that ultimately leads to the reduction in the lumen diameter and potentially to ischemia following plaque rupture. A first stage of the disease is the presence of dysfunctional endothelial cells which, via adhesion molecules and expressed cytokines, recruit circulating monocytes and a subpopulation of lymphocytes (CD4/CD8) into the intima. Endothelial dysfunction may be induced by oxLDL. Indeed low density lipoprotein (LDL) when infiltration into the intima can be readily oxidized by resident macrophages or endothelial cells. Moreover C-reactive protein (CRP) and oxLDL can act synergistically to increase monocyte inflammatory properties (through MCP-1, PGE-2, MMP-1 production) and attract further circulating monocytes through the release of MCP-1 to adhere to the activated dysfunctional endothelial cells and extravasate to the intima to scavange oxLDL(8).

Receptor mediated endocytosis of modified LDL by macrophage has been implicated in the pathogenesis of atherosclerosis. The uptake of modified lipoprotein by macrophages leads to lipid laden foam cells and fatty streak development in the arterial wall, one of the earliest steps in the progression of the atherosclerotic plaque(9). Further work to define the ligand on oxLDL that was recognized by CD36 implicated the lipid of the lipoprotein. Podrez et al. showed that CD36 can recognize LDL modified by the Myeloperoxidase-hydrogen peroxide-nitrite system of phagocytic cell (MPO-OxLDL) which may have more physiological relevance than copper oxidized of acetylated-low density lipoprotein (acLDL) (10). The same

Correspondence: Dhruba Acharya, email : dhruba099@gmail.com

authors have also shown that CD36 is the major receptor for LDL modified by monocyte generated reactive nitrogen species. MPO-oxLDL dependent foam cell formation can be inhibited by as much as 80% with monoclonal antibodies (mABs) against the CD36 (11).In 2002, Podrez et al. identify specific trauncated fatty acid moieties as a recognition motif for CD36 (12).

The relative importance of SR-A and CD36 in macrophage response to different forms of modified LDL and the compensatory mechanism for lipid uptake in their absence was revealed by Vidya et al. (2002) by generating mice lacking both SR-A and CD36. The binding, uptake and degradation of acLDL as well as MPOoxLDL were determined in wildtype macrophage and in those lacking either one or both receptors. They conclude that SR-A and CD36 were responsible for the preponderance of modified LDL uptake in macrophages and that other scavenger receptors do not compensate for their loss (13).

In 2000, Febbraio et al. showed the role of CD36 in foam cell formation. Incubation of CD36 deficient monocyte/ macrophage with oxLDL results in only 40-60 % as much oxLDL binding, internalization and cholesterol ester accumulation as is seen in CD36 expressing cells. The study of CD36 null mouse has the most compelling data to support the critical role of CD36 in foam cell formation where macrophages isolated from the CD36 null mouse were profoundly defective in uptake of oxLDL and foam cell formation (14).

OxLDL has been shown to bind to macrophage CD36 via its lipid moiety and to other receptors via its apoptotic moiety (15). Using computational modeling, oxLDL binding domain on CD36 was shown to contain a structure with a positively charged groove formed by a lysine cluster which specifically interact with negatively charged ligands such as oxLDL (16). OxLDL bound to CD36 is than endocytosed through a raff mediated pathway that appears to be independent form cavoile, caveolin 1 and clathrin mediated internalization (17). Following oxLDL stimulation,transcriptional factor PPARgamma is transactivated via a P38 MAP kinase dependent pathway (18) and heterodimerised with retinoid X receptor(RXR). The PPARgamma-RXRalphacomplex binds directly to PPAR response elements (PPRES) in the CD36 promotors and induces an increase of CD36 expression (19). Moreover OxLDL mediated CD36 upregulation was reported to be involve initial activation of protein kinase C (PKC) with subsequent PPARgamma activation (20).

Although PPAR activation is clearly an important component of CD36 signalling in monocyte and macrophages, most of the responces to CD36 ligands can not be accounted for by a transcriptional mechanism. For example, internalization of large particulate ligands require rapid induction of intracellular signals to effect cytoskeletal reorganization and direct internalized ligands to specific intracellular compartments but doesn't require new protein synthesis. Similarly the rapid proinflammatory, prothrombotic responses are mostly non transcriptional (21).

Flow chart showing CD36 mediated macrophage foam cell formation (22)

1. Extracellur enjury leads to the transmigration of macrophage and LDL into subendothelial space.

2. Inflammatory stimuli insists endothelial cells and macrophages to secrete oxidative products like Nitric oxide, hydrogen peroxide and myeloperoxidase.

3. These oxidative products act upon LDL particles to convert them into CD36 specific ligands or lagands for other scavenger receptors

4. After internalization of OxLDL via CD36, various lipid biproducts are generated(9-HODE, 13- HODE and PGJ-2) mediated by lipoxigenase or other pathways.

5. These lipid biproducts provide ligands for the transcription factor PPARgamma which enables PPAARgamma to dimerise with binding partner such as RXR and charges the complex for nuclear translocation and activation of transcription of target genes. This arrises the positive feedback loop.

6. The increased expression of CD36 promotes further oxidized LDL uptake perpetuating the cycle resulting in accumulation of cholesterol ester by macrophage and eventually in foam cell formation.

Laungrath et al. has provided important potential in vivo relevance for the previously defined interactions of CD36 with LDL. They show evidences for appreciable expression of CD36 in isolated hepatocytes though it was previously believed that the expression of hepatocytes CD36 was low because in liver, major cell types, hepatocytes, endothelial cells and kupffer cells also express CD36. The significant expression of CD36 in hepatocytes was supported by complementary data in vitro to invo work. Using mice deficient in CD36, SR-BI or both and holoparticles or cholesterol ester radiolabelling, their studies demonstrate a role for CD36 in retardation of LDL clearance by hepatocytes and significant role of CD36 in oxLDL clearance (23). In contrast, de Villers et al. (2001) has shown that CD36 doesn't play a direct role in HDL or LDL metabolism. It was shown by using an overexpression adenovirus strategy but examining only lipoprotein profile (24).

Conclusion:

CD36, a class B scavenger receptor protein is also known as FAT (Fatty Acid Translocase), SCARB3 (Scavenger receptor B 3), GP88 (Glycoprotein 88), GPIV (Glycoprotein IV) and

GP IIIB (Glycoprotein III B).Dimerisation has been purposed to play an important role in CD36 signal transduction. On binding with the ligand, the protein and ligands are internalized which is independent of macropinocytosis and occurs by an actin dependent mechanism requiring the activation of Src Family Kinases, JNK and Rho-family GTPase.

oxLDL, Thromspondin 1, collagen, Long Chain Fatty Acid, apoptotic cell membrane, oxidized phospholipids, Fibrilliar beta amyloid and erythrocyte parasitized with Plasmodium falciparum are ligands for CD36. They are omnipresence more commonly found in microvascular endothelium, platelets, monocytes, cardiac and skeletal muscle, skin microdermal cells, microglia, macrophages and adipocytes. Apart from angiogenesis, lipid metabolism, phagocytosis, and inflammation, CD 36 has an important implication in atherosclerosis. Specific trauncated fatty acid moieties in oxLDL are the recognition motif for CD36. The uptake of modified lipoprotein by macrophages leads to lipid laden foam cells and fatty streak development in the arterial wall. Transcription factor PPARgamma plays important role in receptor mediated endocytosis which is transactivated via a P38 MAP kinase.

Recent study by Laungrath et al (2008) demonstrated a role of CD36 in retardation of LDL clearance by hepatocytes and significant role of CD36 in oxLDL clearance. Whereas it was already shown that CD36 didn't play direct role in HDL and LDL metabolism. What is the proper mechanism for the uptake of LDL and oxLDL by CD36? This is the question yet to be answered properly. In atherosclerosis, much has been said and done on the superficial mechanism of macrophage foam cell formation, one of the early steps in atherosclerosis. But still the development of therapeutics and their application is not defined clearly.

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