Biomedical & Pharmacology Journal, June 2024. Vol. **17**(2), p. 699-712

Scavenger Receptors: Different Classes and their Role in the Uptake of Oxidized Low-Density Lipoproteins

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https://dx.doi.org/10.13005/bpj/2897

(Received: 25 April 2024; accepted: 23 May 2024)

Oxidation of lipoproteins marks a fundamental early phase in atherosclerosis development, a condition distinguished by plaque build-up in the arteries. It is widely accepted that the oxidation of low-density lipoprotein (LDL) plays a pivotal role in atherosclerosis progression. Oxidized LDL (Ox-LDL) exhibits numerous atherogenic characteristics, leading to endothelial dysfunction, the creation of foam cells, and inflammation in the arterial wall. The crucial interaction between Ox-LDL and specific receptors on endothelial cells is key to initiating these processes. In this article, we're going to delve into the various LDL receptors that play a crucial part in the uptake and metabolism of LDL, emphasizing their significance in the development of atherosclerosis. The Cochrane database, Embase, PubMed, Scopus, Google Scholar, Ovid, and other databases were thoroughly searched for works addressing scavenger receptors to explore how both native LDL (nLDL) and Ox-LDL engage with these receptors, facilitating the formation and progression of atherosclerotic plaques. We'll then proceed to a more detailed examination of the complex role scavenger receptors play in the uptake and internalization of oxidized low-density lipoproteins (Ox-LDL), and their vital role in the onset of diseases. The review will further cover the identification, categorization, and roles of scavenger receptors, along with their molecular mechanisms. Grasping the complexity of these receptor-ligand interactions is critical for the creation of focused treatments to fight against pathologic conditions such as atherosclerosis and its related health scenarios.

Keywords: Atherosclerosis; Foam Cell; Oxidative Stress; Ox-LDL receptors.

Oxidized Low Density Lipoproteins (Ox-LDL)

Oxidized LDLs have been studied for decades regarding their role in developing cardiovascular events, when free radicals generated from various sources such as smoking or inflammation react with native LDL (nLDL) particles causing modifications in their structure [1]. The classical LDL receptor (LDLR) is a type of receptor in the cell surface that recognizes and internalizes native LDL (nLDL) particles. LDLR is commonly expressed in hepatocytes and plays a crucial role in the clearance of circulating LDL from the bloodstream. LDLR-mediated endocytosis of nLDL involves the binding of apolipoprotein B (apoB), the protein component of LDL, to the receptor. Upon binding, nLDL enter the cells via clathrin-coated pits, then delivered to endosomes [2]. In the acidic environment of the endosomes, LDLR undergoes conformational changes, releasing LDL particles from the receptor. The released LDL is

then directed to lysosomes, where it is degraded, leading to the release of free cholesterol.

Oxidative stress can be induced by inflammation, diabetes, and an inadequate intake of dietary antioxidants [3], which in turn can lead to the modification of lipoproteins through processes such as oxidation, glycation, alkylation, and nitration [4]. The lipoproteins that have been altered are identified and internalized by scavenger receptors, which are synthesized by a cluster of genes. The elimination of these modified lipoproteins mainly takes place in macrophages and other immune cells located in the liver such as dendritic and kupffer cells. Nevertheless, scavenger receptors can also be detected in various other cell categories, such as cells of endothelium [5,6]. This indicates that scavenger receptors within nonprofessional phagocytes might play a part in eliminating oxidized low-density lipoprotein leading to inflammatory reactions locally. Failure to efficiently break down the process of Ox-LDL uptake and unregulated expression of scavenger receptors can result in cellular dysfunction, programmed cell death, and may lead to formation of foam cells [7]. Conditions linked to the lipoprotein oxidation, like diabetes, atherosclerosis, potentially age-related lipofuscin accumulation, and other degenerative diseases could have a shared etiologic cause [8-10].

Oxidized Low Density Lipoproteins and Atherogenesis

Oxidized low-density lipoprotein (LDL) has been widely acknowledged as a significant contributor to the development of atherosclerosis. However, only recently have researchers started to unravel the intricate involvement of oxidized LDL receptors in this pathological process. The identification of these receptors presents new opportunities for comprehending and potentially managing atherosclerosis. By investigating how these receptors recognize and internalize oxidized LDL particles, scientists aspire to devise targeted therapies that aim to diminish plaque formation and stabilize existing plaques. This groundbreaking discovery has the potential to revolutionize current treatment approaches, which primarily concentrate on reducing cholesterol levels. In the subsequent sections of this review, we delve into a comprehensive discussion of these receptors, including their classification, characterization, and their pivotal role in capturing oxidized LDL.

Scavenger Receptors

Role in Atherosclerosis

There are two primary types of receptors responsible for removing LDL from circulation: low-density lipoprotein receptor (LDLR) and scavenger receptors, figure-1. The LDLR functions as a gatekeeper, facilitating the endocytosis of LDL particles into cells for additional processing. In contrast, scavenger receptors are less selective and can attach to not only oxidized LDL but also other altered forms of lipoproteins [11]. These receptors are commonly located on macrophages in arterial walls and play a significant role in the formation of foam cells, a key feature of early atherosclerotic lesions.

Scavenger receptors (SRs), encompass a wide array of cell-surface receptors. with structural variations that play various biological roles. These receptors are classified into different classes based on their characteristics. One of the main functions of SRs is binding to a broad spectrum of ligands, which aid in their removal. The processes involved in clearing damaging substances include phagocytosis which involves the engulfment of particles, endocytosis which refers to the process of internalizing substances into the cell, adhesion that plays a role in cell attachment, and signaling [6]. Understanding the interaction between different types of LDL receptors and oxidized LDL is essential to grasp the mechanisms behind the development of atherosclerosis. Various attempts have been made to discover novel therapeutic strategies aimed at preventing or reversing the adverse effects of cardiovascular disease through the exploration of the intricate connection among oxidative stress, receptor functionality, and plaque formation. Nevertheless, challenges like the limited understanding of the molecular structure, exact function, and mode of operation of scavenger receptors have impeded these endeavors. Hence, additional research and the creation of targeted interventions to regulate scavenger receptor activity are imperative to tackle the impact of atherosclerosis on cardiovascular diseases.

Characterization of Scavenger Receptors

The groundbreaking work of Michael Brown and Joseph Goldstein in 1979 led to the discovery of scavenger receptors (SRs) [2]. They

discovered receptors in macrophages that could bind and also lead to internalization of low-density lipoprotein (LDL) which undergoes structural modifications such as acetylation or oxidation, through their earlier studies on the natural LDLR. However, these receptors did not recognize and internalize native LDL [6]. Over time, several scavenger receptors, including SR-AI/II and SR-B, have been identified as potential targets for therapeutic intervention in atherosclerosis. Additionally, recent studies have suggested that Ox-LDL may activate toll-like receptors (TLRs), which play a significant role in innate immunity and being involved in the inflammatory cascade in atherosclerosis. Therefore, understanding the mechanisms of Ox-LDL-mediated signaling pathways and their interactions with various receptors is crucial for developing effective strategies to prevent or treat atherosclerosis. Dysfunction in these scavenger receptors can result in hypercholesterolemia, a condition characterized by high cholesterol levels in the blood, ultimately contributing to the development of atherosclerosis and other heart diseases.

Numerous strategies have been developed to address scavenger receptors, including CD36, in pre-clinical investigations and advanced clinical trials as targets of therapy [12,13]. Considering the significant involvement of CD36 in cancer and the development of metabolic disorders like atherosclerosis, diabetes, and non-alcoholic fatty liver disease, the potential clinical applications of CD36-targeted therapy extend far beyond cancer [12]. Moreover, anti-hyperlipidemic, anti-atherosclerotic, anti-cancerous, and anti-diabetic properties of medicinal plants confirmed in clinical trials and computational studies can be investigated in targeting scavenger receptors as therapeutic approaches [14-16]. In addition, Koen and his team suggested that anti-SR-BI receptor therapy could be an effective way to prevent HCV infection in a liver transplant setting [17].

Classes of Scavenger Receptors

Importance of Systematic Classification

A standardized nomenclature has been developed to address the existing communication ambiguities surrounding specific scavenger receptors and promote collaboration across diverse fields [18]. This comprehensive classification and naming system was established through the collection of feedback at three expert meetings, effectively removing a significant obstacle for researchers. By working together, a consensus was successfully reached on the precise definition of scavenger receptors, leading to the proposal of a standardized nomenclature [6,18]. As a result, the scavenger receptors were systematically categorized into 12 distinct classes. According to this classification, the nomenclature for the scavenger receptor is denoted as "SR-" followed by the assigned letter for the class (A, B, C, etc.) and an Arabic number indicating the order within the class. Additionally, a dot is used to separate the Arabic number that specifies the alternatively spliced form (e.g., SR-B1.1) [18].

Scavenger Receptors Class A (SR-A)

SR-A is a trimeric integral membrane glycoprotein expressed on various tissue macrophages, including those found in atherosclerotic plaques. Research using mouse models has shed light on the function of SR-A in atherogenesis [19]. Studies involving bone marrow transplantation with transgenic donor material have shown that overexpression of SR-A in macrophages did not significantly alter the progression of atherosclerosis in hyperlipidemic mice when they are lacking (apoE) or (LDLR) [20]. On the other hand, deletion of the SR-A gene in mice consistently resulted in reduced atherosclerosis in hyperlipidemic conditions [21]. Both apoE-deficient and LDLR-deficient mice lacking SR-A showed decreased lesion formation compared to control mice. Class A receptors have been characterized as proteins with a remarkable binding affinity for acetylated LDL (acLDL). Notably, these receptors do not bind native LDL and are prominently expressed in vital organs such as the liver, adrenal gland, spleen, and lung [22]. Both SR-AI and AII have been revealed as trimeric membrane glycoproteins, differing solely in their cysteine-rich C-terminal domain - figure 2. In SR-AI, this domain encompasses 110-amino acids, while in SR-AII, it is replaced by a shorter sequence of 6-amino acids [23,24]. Despite this disparity, both receptors exhibit comparable affinities for acLDL. Furthermore, it is noteworthy that SRA receptors are not limited to macrophages alone, as they have also been detected in liver and smooth muscle cells (SMC) [25]. The SR-AIII receptor, distinguished by its absence of specific amino acids derived from

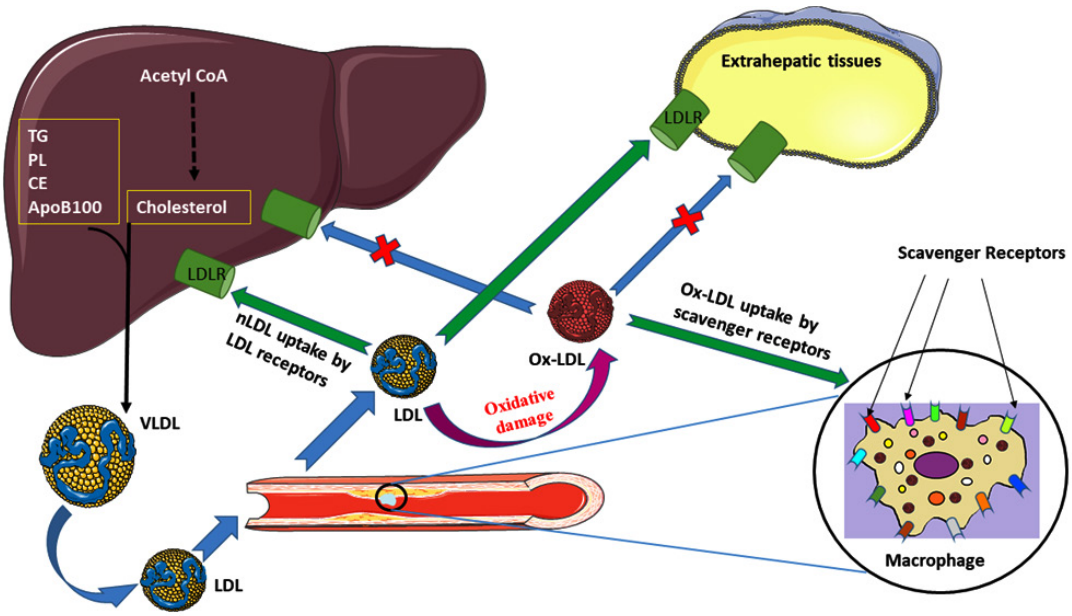

Fig. 1. Receptors for Low Density Lipoproteins (LDL). LDLRs will no longer recognize oxidized forms of low density lipoproteins, resulting in their uptake by scavenger receptors. TG: Triglycerides, PL: Phospholipids, CE: Cholesteryl ester, ApoB100: Apoprotein B100, nLDL: Native LDL, Ox-LDL: Oxidized LDL.

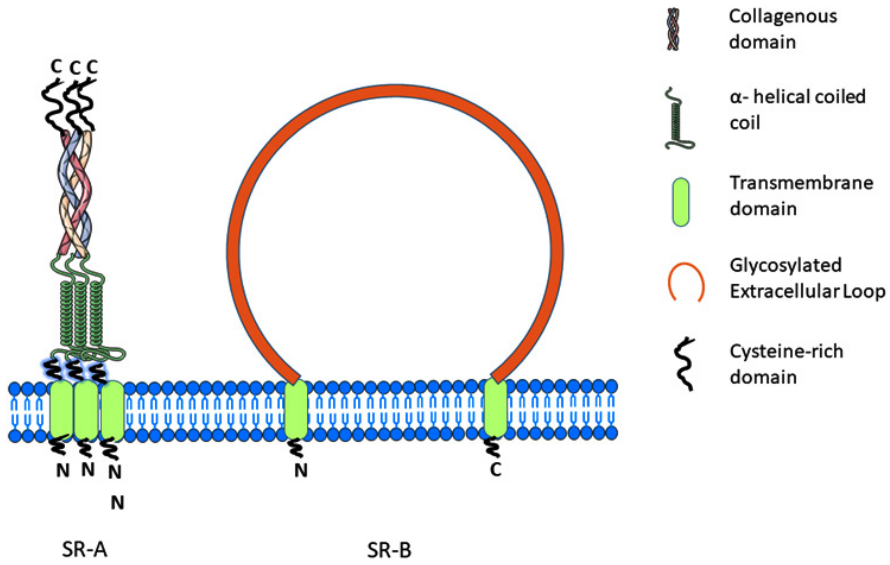

Fig. 2. Scavenger Receptors Class A and Class B. Class B scavenger receptors consist of two transmembrane domains that surround an extracellular loop.

exon 10 of the SR-A gene, displays an incapability to facilitate ligand uptake. Moreover, it assumes the role of a prevailing inhibitory regulator within the trimeric SR-A molecule [26], this role may protect cells from excessive uptake of Ox-LDL in advanced atherosclerotic lesions. The SR-AI/II receptors possess a significant characteristic of wide-ranging specificity towards various ligands. These ligands encompass diverse forms of modified particles of lipoproteins, an assortment of non-lipoprotein ligands with negative charge, as well as bacteria. Various research studies have provided evidence that SR-AI/II receptors have the ability to bind with both acLDL and Ox-LDL. It is important to note that there exist notable variations between these two modified forms of LDL regarding their binding affinities. The remarkable capacity to recognize different forms of LDL was observed when several alterations to the LDL protein were identified, including acetylation, succinylation, acetoacetylation, and malondialdehyde treatment. These modifications target the lysine residues, highlighting the intricate nature of LDL's recognition ability. However, the mechanisms underlying the binding process seem to be intricate and multifaceted [11,22]. It has been proposed that the recognition of LDL by SR-A receptors involves chemical modifications that counteract the positive charges on the protein, similar to the effects of oxidation [27]. In order to be recognized by these receptors, a significant portion of the lysine residues in the apo-B protein needed to be neutralized, and as the modifications increased, the binding and degradation of LDL also increased. In order to achieve maximum uptake, more than 60% of the lysine residues needed to be modified through acetylation or succinylation [28]. Another receptor belonging to the SRA class, called scavenger receptor with C-type lectin (SRCL), also known as collectin placenta 1 (CL-P1), has also been discovered. Like SRAI/II, CL-P1 recognizes low density lipoproteins with extensive oxidation. .Additionally, CL-P1 has the ability to bind to yeast and bacteria such as S. aureus [29].

In conclusion, scavenger receptors class A (SR-A), play a significant role in the initiation and modulation of atherosclerosis. SR-A contributes to the formation and progression of atherosclerotic lesions by promoting the uptake of modified lipoproteins by macrophages. Its involvement in innate immunity and metabolic disorders further underscores its multifaceted role in disease pathogenesis. Understanding the intricate mechanisms underlying SR-A function may lay the groundwork for the advancement of innovative therapeutic approaches to combat atherosclerosis and related cardiovascular diseases.

Scavenger Receptors Class B (SR-B)

The family of class B scavenger receptors (SR-B), which includes SR-BI, SR-BII (referred to as CLA-1 and CLA-2), CD36 thrombospondin receptor, and lysosomal integral membrane protein II, consists of a set of integral membrane proteins. While lysosomal integral membrane protein II is the only one not found on the surface of the cells, the remaining receptors have been demonstrated to engage with a variety of ligands that play roles in numerous biological processes. These processes encompass atherosclerosis, inflammation, host defense mechanisms, angiogenesis, viral antigen presentation, as well as the elimination of apoptotic cells from the system [30].

Scavenger receptors BI/BII and CD36 share several same characteristics such as similarity in molecular structure and caveolae-like domains on the plasma membrane. Structurally, these receptors possess a distinctive characteristic as they consist of two transmembrane domains that surround an extracellular loop – figure 2. Additionally, they have cytoplasmic amino and C termini [31]. These characteristics serve to enhance the process of lipid transfer between cells and also play an important role in communication between cells through signaling molecules. This exchange of lipids contributes significantly to the maintenance of cellular functions and the regulation of various physiological processes. Additionally, these receptors have overlapping ligands which includes bacteria, viruses, and modified lipoproteins. In terms of lipid metabolism, SR-BI/II are crucial as they mediate both selective uptake of cholesteryl ester from HDL and HDL-mediated efflux of cholesterol. They also facilitate the uptake of whole HDL particles. On the other hand, CD36 is well-known as a receptor for lipoproteins and a transporter for long chain fatty acids. However, the precise role of CD36 in recognition of various pathogens is yet to be fully understood [30-33]. The CD36 is a glycoprotein (88 kilo Dalton), expressed in platelets, macrophages, as well as endothelial

cells. It is the first member of all SR-B receptors family to be identified for Ox-LDL [34]. Like SR-A receptors, the CD36 was found to internalize Ox-LDL but not nLDL. However, unlike SR-A receptors, the binding of Ox-LDL to CD36 was not inhibited by acLDL [35,36]. Nevertheless, other research has indicated that CD36 possesses the capability to bind to acLDL as well.[37]

Numerous studies have provided significant evidence indicating that CD36 exhibits distinct characteristics compared to SR-A receptors when it comes to its preference for moderately-oxidized LDL. For instance, Endemann and colleagues [35] demonstrated that CD36 receptors have the ability to uptake (Ox-LDL) after a period of 4 hours of oxidation. Interestingly, the maximal uptake of Ox-LDL by CD36 receptors was noted following a 10-hour oxidation period. On the other hand, the SR-A receptors did not exhibit any uptake of Ox-LDL after 4 hours of oxidation, and it took more than 20 hours of oxidation for the SR-A receptors to reach their maximal uptake capacity. However, both CD36 and SR-A receptors demonstrated similar levels of uptake when it came to extensively oxidized LDL.[6,19,38] CD36 receptors have been demonstrated to have a specific affinity for anionic phospholipids, including phosphatidylserine (PS) and phosphatidylinositol (PI). This was observed through experiments where liposomes containing PS and PI were found to compete with acLDL for binding to CD36 receptors [39]. However, Boullier and colleagues [40] demonstrated that CD36 may be inhibited by both Apoprotein B and lipid micro-emulsions derived from (Ox-LDL). Additionally, the researchers discovered that Apoprotein B and the lipoprotein lipids compete for the same location on the CD36 receptor.

In general, accumulating evidence suggesting that CD36 possesses the ability to integrate cell signaling and metabolic pathways through its dual capabilities. Consequently, this ability has the potential to impact the differentiation and activation of immune cells, ultimately playing a role in determining their fate. The expression of CD36, coupled with its dual functions in both innate and adaptive immune cells, contributes to the development of various diseases such as atherosclerosis and tumor progression. As a result, CD36 and its downstream effectors hold promise as potential targets for therapeutic interventions.

Similar to the CD36 receptor, SR-B1 has the ability to bind both Ox-LDL and acLDL. However, unlike the previously identified scavenger receptors, SR-B1 also has the capability to recognize native LDL [32]. What sets SR-B1 apart is its identification as the primary receptor for the HDL, which are abundantly expressed in the liver and steroidogenic tissues. These tissues are crucial for the selective uptake of cholesterol esters (CE) in vivo [31,33]. Studies have shown that the augmentation of SR-BI expression in the LDL receptor deficient mice demonstrates a highly beneficial and safeguarding impact, reducing the mean area of atherosclerotic lesions. Conversely, targeted disruption of SR-BI has been found to have a proatherogenic effect [33]. Additionally, SR-B1 has been observed to internalize oxidized forms of HDL.

In summary, SR-Bs are multi-ligand membrane protein receptors that play a critical role in the regulation of atherosclerosis. They are involved in cholesterol metabolism, selective cholesterol uptake, reverse cholesterol transport, HDL-induced anti-inflammatory responses, and the inhibition of atherosclerotic progression. SR-Bs expressed in hepatocytes, endothelial cells, macrophages, and platelets. These receptors exert both anti-atherosclerotic and pro-atherosclerotic effects, depending on the context and specific cellular functions. Further research is needed to fully understand the mechanisms of SR-Bs in atherosclerosis and develop targeted therapeutic strategies for cardiovascular disease prevention and treatment.

Scavenger Receptors Class C (SR-C)

Scavenger receptors of class C (SR-C), are a group of receptors that play a crucial role in host defense and development. They are involved in the recognition and uptake of a wide range of ligands, including polyanionic ligands and potentially toxic small molecules [41,42]. Drosophila has been found to possess class C scavenger receptors; however, the existence of mammalian class C scavenger receptors remains unknown at present. These receptors, which play a crucial role in cellular communication and immune response modulation, are actively produced and present on the surface

of myeloid cells, and play a key role in regulating vascular function and inflammation within the body, as well as the binding and internalization of microorganisms and their products [43]. In insects, SR-C has been identified as a macrophage-specific scavenger receptor, with high affinity for acetylated low-density lipoprotein (LDL) [41]. The involvement of class C scavenger receptors (SR-C) in various immune mechanisms has been extensively studied. In Drosophila, SR-C has been found to play a crucial role in the phagocytosis of both gram-positive and gram-negative bacteria, as well as viruses in shrimp [44].

Class D scavenger receptors (SR-D) represent a category of receptors found on the surface of cells. They participate in identifying and eliminating different ligands including altered lipoproteins, dying cells, and harmful pathogens. As of today, CD68 (Macrosialin) in mice, is the sole member of class D scavenger receptors. CD68 is a protein that spans the membrane and comprises a mucin-like domain, a center rich in proline, domains associated with the lysosome-associated membrane glycoprotein (LAMP), a single region spanning the membrane, and a minor cytoplasmic tail [45]. CD68 is abundant on immune cells, and is mainly localized in lysosomes and endosomes. It plays a significant role in the clearance of oxidized LDL, and the modulation of inflammatory responses. The extracellular domain of SR-D, which comprises a total of 300 amino acids, is characterized by a high abundance of threonine and serine residues, which play crucial roles as sites for the attachment of carbohydrates [6]. Since class D scavenger receptors play a role in atherosclerosis, inflammation, and host defense mechanisms, this nature of diverse functions make them potential targets for therapeutic interventions in cardiovascular disease and immune-related disorders.

Scavenger Receptors Class E (SR-E)

Based on their structure, these proteins are classified as belonging to a specific subgroup within the natural killer cell, family of (C-type lectin-like receptors) [6,46]. The gene complex of NK receptors encodes numerous CLEC-like receptors which are expressed on the NK cells as well as other types of leukocytes [47]. LOX-1 has been associated with the recognition of a diverse array of other ligands such as apoptotic cells, and many types of bacteria, underscoring its multifunctional nature and diverse roles in cellular responses. Despite the extensive research on LOX-1 and its ligand-binding capabilities, there is currently a notable absence of data about the presence of this particular splicing variant in mouse cells, suggesting a gap in our understanding of the receptor's expression and function in this specific context. Further investigations into the expression and functional implications of this splicing variant in mouse cells could provide valuable insights into the broader roles of LOX-1 in different biological systems. The elucidation of the presence or absence of this splicing variant in mouse cells could potentially shed light on novel aspects of LOX-1 biology and its relevance in various pathophysiological conditions. Therefore, future studies focusing on the characterization of this splicing variant in mouse cells are warranted to enhance our comprehension of LOX-1-mediated processes and their potential implications in health and disease [46,47]. Another receptor of this class, called (Dectin-1), primarily found on cells of the myeloid lineage, exhibits a regulation in its expression influenced by various cytokines and stimuli of microbial origin, highlighting the intricate interplay between immune responses and external factors. The (Dectin-1) has garnered renewed interest as of late, primarily because of its involvement in the initiation of trained immunity. The induction of long-term memory in innate immune cells can be activated by â-glucans, this receptor plays a vital role in this process [48].

Mannose receptor (CD206) is another important member of this family, which is known to bind a set of different ligands [49]. It is involved in processes such as phagocytosis of mannose-coated substances, endocytosis of glycoproteins attached to mannose [6]. Mannose receptor is a type of receptor that can identify harmful microorganisms by detecting certain sugars on their surface. It then engulfs and destroys these microorganisms through the process of phagocytosis. Studies have shown that mannose receptor is present on immature dendritic cells, which are found in different tissues including the skin and the lymph nodes. Cells which are involved in inflammation in skin diseases like atopic dermatitis, have also been found to express the mannose receptor [50,51].

The role of the (Asialoglycoprotein receptor 1) has been investigated in various studies, particularly in relation to ethanol-induced impairments and liver disease. It has been observed that ethanol can negatively affect the clearance of apoptotic cells by (ASGPR), potentially leading to an increase in proinflammatory mechanisms during liver disease [52].

Scavenger Receptors Class F (SR-F)

The members of this class known as scavenger receptor expressed by endothelial cell-I (SREC-I) and (SREC-II) are both transmembrane type receptors. Class F scavenger receptors are type of receptors known for having epidermal growth factor–like regions located at their N-terminus, in addition to the transmembrane protein domain and a long tail in cytoplasm. An example of a Class F scavenger receptor is SR-F1, which is situated on human chromosome 17. Another variant, SR-F2, can be found on human chromosome 22. These receptors play a crucial role in various biological processes within the human body. It is believed that these receptors have the ability to trigger signal transduction processes within the cell [53,54]. The level of similarity between these two receptors is 35%, and while they both have the ability to bind the modified forms of LDL, but only SREC-1 is responsible for taking in these ligands for degradation. Research conducted on macrophages has shown that this particular receptor is only accountable for 6% of the overall breakdown of acetylated LDL, indicating its involvement in the formation of foam cells. On the other hand, SREC-II exhibited minimal capability in internalizing modified low density lipoproteins (LDL) compared to SREC-I [55]. Class F scavenger receptors are integral in recognizing and binding to specific molecules in the cellular environment. Through this interaction, they are involved in processes such as immune responses and lipid metabolism. Understanding the function and distribution of these receptors can provide valuable insights into how cells communicate and respond to their surroundings. Research on Class F scavenger receptors continues to expand our knowledge of their significance in maintaining cellular homeostasis and overall health.

Scavenger Receptors Class G (SR-G)

Scavenger receptor for phosphatidylserine and oxidized lipoprotein (SR-PSOX) was initially known for its role in binding to Ox-LDL and later was found to be the same as the membrane-bound chemokine (CXCL16) [54]. Class G scavenger receptors play a crucial role in the development of atherosclerosis, these receptors are present in both human and mouse lesions associated with atherosclerosis. In particular, they are found on smooth muscle cells (SMCs) responsible for maintaining the structural integrity of blood vessels, endothelial cells which form the inner lining of the arteries, and macrophages within the arteries. When these receptors interact with modified lipoproteins such as (Ox-LDL), they trigger a series of events leading to the formation of atherosclerotic plaques.

Understanding the function of these receptors in different cell types provides valuable insights into the progression of atherosclerosis and potential therapeutic targets to combat this common vascular disease [56]. Currently, it is not fully understood how SR-PSOX contributes to macrophage uptake of Ox-LDL, the foam cells formation, and the atherosclerosis. However, there is evidence suggesting a potential link between a genetic variation in the (CXCL16/SR-PSOX) gene and the severity of coronary artery stenosis [57].

Scavenger Receptors Class H (SR-H)

The SR-H1 (FEEL-1) and SR-H2 (FEEL-2) scavenger receptors contain epidermal growth factor (EGF) and EGF-like domains, alongside with fasciclin and lamin-type EGF-like (FEEL) domains. These receptors are commonly observed either as (Type 1 membrane glycoproteins) or as another form (soluble secreted glycoproteins), possessing a considerable length of up to 2570 residues, showcasing their structural diversity and functional versatility. The cell types that express these proteins encompass spleen cells, lymph nodes cells, macrophages, cells of the bone marrow, foetal liver cells, and endothelial liver cells in adults, indicating a wide distribution and potential functional significance across various tissues and organs [54,58]. The extracellular or soluble regions of SR-H proteins exhibit a complex architecture, comprising three distinct blocks which collectively contribute to the diverse ligand-binding capabilities of these receptors. Furthermore, in close proximity to the transmembrane domain, there exists a singular (Fasciclin) domain, adding another layer of complexity to the structural organization of

SR-H proteins. Both (SR-H1) and (SR-H2) exhibit a remarkable affinity towards binding AcLDL, advanced glycation end-products (AGE), and bacterial components, underscoring their potential roles in mediating a wide array of physiological and pathological processes. Notably, there is emerging evidence suggesting that (SR-H1) on monocytes may serve as a valuable biomarker for predicting an elevated susceptibility to cardiovascular disease (CVD), highlighting the clinical relevance and diagnostic potential of these receptors in the context of cardiovascular health [59].

Scavenger Receptors Class I (SR-I)

Scavenger receptors class I (SR-I) CD163 family is predominantly expressed in various macrophage subtypes including Kupffer cells, cortical, and thymic macrophages the medullary population. The primary function of CD163, which is mainly involved in maintaining homeostasis, is its ability to bind (Hemoglobin:Haptoglobin) complexes. Additionally, there is evidence suggesting that CD163 positive macrophages or the soluble form of CD163 contribute to the resolution of inflammation, as they are abundantly present in inflamed tissues [60]. SR-I receptors exhibit type I transmembrane characteristics, possessing a distinctive extracellular domain consisting of numerous group B SRCR domains. These receptors play a crucial role in recognition of a broad spectrum of ligands, encompassing both endogenous substances and modified host-derived ligands, as well as pathogenic microorganisms. [61]. They are actively involved in various cellular processes such as phagocytosis, which is the engulfing and destruction of foreign particles, adhesion, which is the attachment of cells to one another or to other surfaces, and signaling, which involves the transmission of molecular messages within the cell. Findings from the ligand uptake research indicated that cells which express the short tail variant of CD163 displayed a heightened capability for the process of ligand endocytosis in comparison to those expressing the long tail variants of the protein [62].

Scavenger Receptors Class J (SR-J)

SR-J, is a distinct group that consists of only one member, the receptor for advanced glycation end products (RAGE) [63]. RAGE belongs to the cell surface molecules, the large Ig family which have the ability to interact with a wide range of ligands such as advanced glycation end-products (AGE), and the (S-100 protein) [64]. This receptor consists of a solitary transmembrane domain which links the amino-terminal ectodomain responsible for recognizing ligands with a brief domain in the cytoplasm. Additionally, the part of the receptor located in the extracellular region is composed of three immunoglobulin-like regions [54,63]. RAGE predominantly acts in recognizing the endogenous molecules which are released during infection and chronic inflammation, where signaling plays a role in inflammation, oxidative stress, and the scenarios of apoptosis [63]. These processes can contribute to the development of pathologies such as atherosclerosis and degenerative diseases [65]. In neuronal cells, the generation of ROS induced by RAGE can either promote cell survival and differentiation or lead to cell death by disrupting the redox balance [18,66].

Scavenger Receptors Class K (SR-K)

Scavenger receptors of this class (SR-K) includes CD44, a glycoprotein in the cell surface that is primarily known for its role as a receptor for hyaluronan [67]. Despite lacking structural homology with other scavenger receptors, CD44 shares certain structural features with them. This elegant and persuasive transmembrane protein possesses numerous domains and a humble cytosolic tail, which, although limited in direct signaling capabilities, holds immense potential. At its N-terminal, the extracellular domain serves as a docking site which uptakes multiple ligands [68]. Similar to other scavenger receptors, CD44 can be shed by extracellular proteases which play a pivotal role in generating cleavage products that are widely believed to possess significant biological functionality. Furthermore, CD44 exhibits functional properties that are common to other types of (SRs) [18]. It has a wide range of ligands, including both host molecules and microbial ligands. CD44 also plays a role in pattern recognition and innate immunity. The extent to which CD44 exerts pro- or anti-inflammatory effects varies greatly depending on the particular type of cell and the surrounding environment in which it is present. Similar to other scavenger receptors, In addition to its immunologic functions, CD44 also contributes significantly to cellular processes such as migration, and cellular homeostasis [69,70].

Scavenger Receptors Class L (SR-L)

SR-L include SR-L1 and SR-L2. SR-L1, reported in previous work as (CD91), (LDLR-related protein 1), or (A2-macroglobulin receptor, A2MR), is one of the largest members of the LDLR gene family that mediates the endocytosis of more than 40 structurally and functionally distinct ligands [18,71]. It is the most important receptor for clearance of cholesterol in the plasma. Another member of this class SR-L2, also known as megalin, high expression of this receptor was observed in epithelial cells of proximal tubules. Megalin is suggested to play a crucial role in the reabsorption of nephrotoxic compounds, including antimicrobial drugs like colistin and vancomycin, as well as anticancer drugs such as cisplatin. Additionally, megalin is responsible for the reabsorption of albumin that has been modified by advanced glycation end products or contains fatty acids [72]. The documented literature does not provide detailed and sufficient information about the structure and function of SR-L receptors.

As discussed in this review, the role of scavenger receptors is closely linked to various physiological and pathological processes, including maintaining homeostasis, clearing apoptotic cells, and age-related cardiomyopathy. Notably, scavenger receptors have a significant impact on the development and advancement of atherosclerosis and formation of plaques, making them a promising target for treatment strategies and gene therapy. Currently, most studies on scavenger receptor gene therapy have employed adenoviral vectors [73]. Research investigating the mechanisms of action of the scavenger receptors will greatly enhance the efficacy of interventions aimed at treating atherosclerosis and cardiovascular diseases.

CONCLUSION

This comprehensive review explores the critical role of scavenger receptors in the uptake of oxidized LDL and their substantial contribution to atherosclerosis. Lipoprotein oxidation is a critical early stage in the development of atherosclerosis and the formation of plaque in arterial walls leading to serious pathologic scenarios. It has been well-established that the oxidation of (LDL) represents the key factor in the progression of atherosclerosis. When get oxidized, LDLs will be converted to pathogenic particles (Ox-LDLs) which possesses a range of atherogenic properties, contributing to endothelial dysfunction, foam cell formation, and inflammation within the arterial wall. The interaction between Ox-LDL and specific receptors on endothelial cells and macrophages plays an important and fundamental role in these processes. Understanding the molecular mechanisms and functions of scavenger receptors provides a foundation for potential therapeutic targets and the development of innovative prevention and treatment strategies for atherosclerotic cardiovascular diseases.

Future directions

• The presence of oxidized LDL (Ox-LDL) in atherosclerotic plaques suggests that further research is needed to understand the role of Ox-LDL receptors in different phases of atherosclerosis and plaque formation.

• The potential use of soluble LOX-1 as a biomarker for cardiovascular disease diagnosis, prognosis, and assessing the efficacy of therapy should be explored in future human studies.

• The role of oxidized phospholipids, present in Ox-LDL and apoptotic cells, in the binding of Ox-LDL to scavenger receptors needs to be further elucidated.

• The impact of inhibiting scavenger receptor function on the uptake of Ox-LDL and clearance of apoptotic cells needs to be studied as a potential approach of therapy.

• The significance of LOX-1 polymorphic genes in increasing susceptibility to myocardial diseases should be further investigated.

• The potential therapeutic intervention targeting scavenger receptors in regenerative medicine needs to be explored.

• Development of future therapeutics for treatment of atherosclerotic cardiovascular and cerebrovascular diseases by targeting the Ox-LDL-LOX-1 axis, and/or mechanisms involved in the uptake of ox-LDL by scavenger receptors should be further investigated.

• Specific experimental designs and/or collaborations across disciplines are recommended to enhance the understanding of scavenger receptors and their contribution in different pathologic scenarios.

ACKNOWLEDGEMENT

The author would like to thank Waddah Abdalla from "King Abdulaziz High School" for his valuable help in designing figures..

Conflict of Interests

The author declare that there is no conflict of interest regarding the publication of this paper.

Funding Sources

No fund to be declared for this manuscript.

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