Chapter 10
Scavenger Receptor and Targeting Strategies

Amit S. Lokhande, Priyanka Jahagirdar, Prajakta Dandekar, and Padma V. Devarajan

Abstract Scavenger receptors constitute a group of receptors on the cell surface that attach to various ligands and remove the targets that are non-self or altered. Signaling, transport, endocytosis, phagocytosis, and adhesion resulting in the removal of harmful and degraded substances are some functions of these receptors. Scavenger receptors bind a large repertoire of ligands indicating their involvement in homeostasis and multiple disease pathologies. In this chapter, we describe the role of scavenger receptor group in the pathogenesis of infections and cancer. In addition, we present a variety of ligands with their scavenger receptor binding strategies through different examples of targeted drug delivery systems.

Keywords Cancer · Infections · Nanosystems · Polyanionic ligand · Scavenger receptor · Targeted drug delivery

Abbreviations

AcLDL	Acylated low-density lipoprotein
Aco-HSA	Polyaconitylated-human serum albumin
AGE	Advanced glycation end products
AgNPs	Silver nanoparticles
BBB	Blood–brain barrier
BSA	Bovine serum albumin

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CFUs	Colony-forming units
CR	Cysteine rich
CXC	Chemokine receptor 16
DCP	Dicetylphosphate
DCs	Dendritic cells
EDCs	Endothelial cells
EGF	Epidermal growth factor
Fe_2O_3	Iron oxide
FEEL	Fasciclin EGF-like, and lamin-type EGF-like domains
GPI	Glycosyl-phosphatidylinositol
HDL	High-density lipoprotein
Hsp	Heat shock proteins
LAMP	Lysosome-associated membrane glycoprotein
LCO	Lithocholic oleate
LDL	Low-density lipoprotein
LDLR	Low-density lipoprotein receptor
LOX-1	Lectin-like oxidized LDL receptor-1
LPS	Lipopolysaccharide
LTA	Lipoteichoic acid
MARCO	Macrophage receptor with collagenous structure
MBSA	Maleylated albumin
MTX	Methotrexate
NMs	Nanomedicines
NK cells	Natural Killer cells
OxLDL	Oxidized low-density lipoprotein
PAS	p-amino salicylic acid
PC	Phosphatidylcholine
PG	Phosphatidylglycerol
POPC	Palmitoyloleoyl-phosphatidylcholine
PS	Phosphatidylserine
RBCs	Red blood cells
ROS	Reactive oxygen species
S_1-CLP	Stabilin-1 interacting chitinase-like protein
SCARA-5	Scavenger receptor class A member 5
SiRNA	Small interfering ribonucleic acid
SNP	Single nucleotide polymorphism
SPARC	Secreted protein acidic and rich in cysteine
SR	Scavenger receptor
SRCL	Scavenger receptors with C-type lectin
SRPSOX	Scavenger receptor that binds phosphatidylserine and oxidized lipids
TAMs	Tumor-associated macrophages
TiO_2	Titanium dioxide
UGPR	Uteroglobin-related protein
VLDL	Very low-density lipoproteins
ZnO	Zinc oxide

1 Introduction

Scavenge means to clear, accordingly the role played by the scavenger receptors is clearing the body of a variety of moieties, for instance, modified low-density lipoprotein (LDL), bacteria or infected RBCs, apoptotic cells, etc. [1]. The receptor was first identified by Brown and Goldstein in macrophages and they observed that while the receptor internalized and degraded modified and oxidized low-density lipoprotein (OxLDL) or acetylated LDL, native LDL was spared by these receptors. Intracellular internalization of modified LDL may be due to foam cell formation [2]. Such foam cells loaded with cholesterol are integral to the atherosclerotic plaques and are also located in the lesions of blood vessel walls [3, 4]. While the scavenger receptors play a crucial physiological role, they can also perform as mediators in various pathologies. This chapter details the receptor with special emphasis on exploiting the endocytic property of this receptor in the targeted therapy of various diseases.

2 Scavenger Receptors

Scavenger receptors encompass a group of membrane proteins along with isoforms and soluble secreted extracellular domain isoforms. Although scavenger receptors are divided into 12 classes A-L (Fig.10.1), a term superfamily is not bestowed, as the receptors reveal no structural homology among the different classes [5]. They are more aptly termed as a supergroup [6]. Though structurally dissimilar, the scavenger receptors show affinity for similar ligands comprising of polyions including

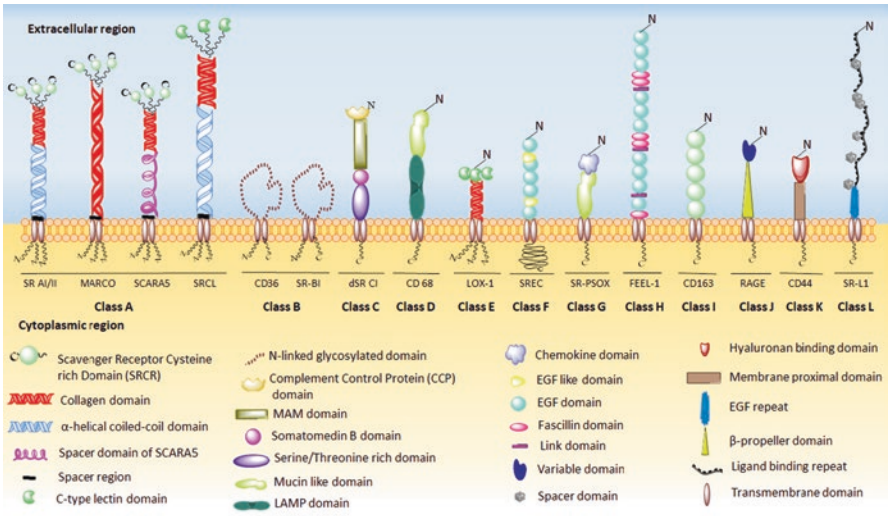

Fig. 10.1 Schematic representation of scavenger receptor classes and their recognition domains

lipoproteins, phospholipids, cholesterol ester, apoptotic cells, carbohydrates, proteoglycans, and ferritin. A structural similarity is evident among different members of a class. Owing to their diverse ligand binding ability, the scavenger receptors represent a significant part of the pattern recognition receptors [7, 8]. A schematic representation of scavenger receptor classes and their recognition domains is depicted in Fig.10.1. A major focus of this chapter is on Class A and B scavenger receptors, the receptors that play a role in infections and cancer.

2.1 Scavenger Receptors' Recognition Domains

2.1.1 Class A

Class A scavenger receptor comprises of type II transmembrane proteins. A cytoplasmic N-terminal domain (40–55 amino acids) is linked to the transmembrane region (26 amino acids). The extracellular domain comprises of three domains, namely, α-helical coiled-coil, C-terminal cysteine-rich (CR), and collagen-like domain and mediates ligand recognition. The unique collagen-like domain has positively charged amino acid residues that bind to polyanions [9–11]. The SR-AI/II, MARCO, SCARA5, and SRCL are most widely studied members of this class (Fig.10.1). SR-AI and AII display identical affinity for collagen-rich region [12]. MARCO exhibits an extended collagen-rich domain and expresses cysteine-rich domain as ligand-binding site [13]. SCARA-5 and MARCO receptors reveal a similar ligand binding. The coiled-coil domain is absent in these two receptors [14]. SRCL comprises of a C-terminal lectin-type domain while it lacks cysteine-rich domain [15].

2.1.2 Class B

The members of this class usually contain type III transmembrane proteins of 450–500 amino acid residues. They mainly express 2 transmembrane regions which contain closely placed short intracellular N- and C-terminals with the central extracellular loop comprising N-linked glycosylated domain of 400–450 amino acid residues, involved in ligand recognition [6]. The CD36 and SR-BI are two major members, which are largely glycosylated and fatty acylated [16, 17].

The structural dissimilarity is evident among different classes of scavenger receptors. Class C is not expressed in humans [18]. Class D scavenger receptors contain lysosome-associated membrane glycoprotein (LAMP) domains and mucin-like domains [19], whereas lectin-like LDLR-1, the only member of class E, shows C-type lectin domain. The C-terminal of this domain is connected by transmembrane domain to the cytoplasmic domain of N-terminal [20]. Class F scavenger receptors revealed growth factor domains, while class G receptors exhibit along with a chemokine domain and a mucin-like glycosylated stem as extracellular domain for ligand binding [21]. Class H scavenger receptors comprise of fascillin,

epidermal growth factor (EGF) like, and lamin-type EGF-like (FEEL) domain [22]. While class I scavenger receptors consist of multiple group B cysteine-rich domains in their extracellular domain [23], class J contains a single transmembrane domain that connects the amino-terminal ligand recognition and binding ectodomain with a short cytoplasmic domain [24]. The class K scavenger receptor consists of hyaluronan binding domain [25, 26] and class L scavenger receptor consists of ligand-binding repeat, EGF repeat, and β propeller domain [27, 28]. A detailed description of these classes can be accessed from the literature [1, 5, 29].

3 Ligand Binding

Although majority of polyanionic ligands bind to scavenger receptors, their specificity depends on scavenger receptor domains. The broad range of specificity of the scavenger receptors prompted scientists to study the active site of these receptors. The positively charged C-terminal of the collagenous domain is essential for binding of ligands. Binding studies suggest that the collagenous domain is responsible for the broad specificity of the receptor [30]. A sticky surface is provided by the collagenous domain that enables selective binding of polyanions with high affinity. The positively charged residues of this domain are important for binding of polyanions. Presence of few negatively charged residues repels polyanions with low affinity and binds only those with high affinity. A direct or indirect effect on ligand binding is shown by other extracellular domains [31].

Although structurally homologous, SR-A1 and MARCO exhibit ligand uptake by discrete mechanisms. Studies suggest that removal of the cysteine-rich domain of MARCO curbs the internalization, whereas an enhanced uptake was seen following CR domain deletion of SR-A1 [32]. A difference in domain charge may have resulted in this consequence. A negatively charged CR domain is predicted by in silico studies. However, some studies report a mixed positive and negative charge for CR domain in MARCO. Such differences in charges could impact the recognition of pathogens and particulate carriers. Ligand receptor binding of MARCO is dependent on metal ions like calcium. Calcium binding and reduced electrostatic potential at the acidic amino acids enable interaction of MARCO with polyanions [33]. Electrostatic potential changes can also alter the stationing of MARCO domains, in turn affecting ligand binding. A high affinity of CD36 of class B to long-chain fatty acids enables fatty acid transport [29, 34].

4 Intracellular Internalization

Scavenger receptors based on their class exhibit different endocytic mechanisms. While SR-A receptors follow clathrin-dependent pathways, LOX-1 proceeds via clathrin-independent pathways. Lipid raft-mediated mechanisms are shown by class

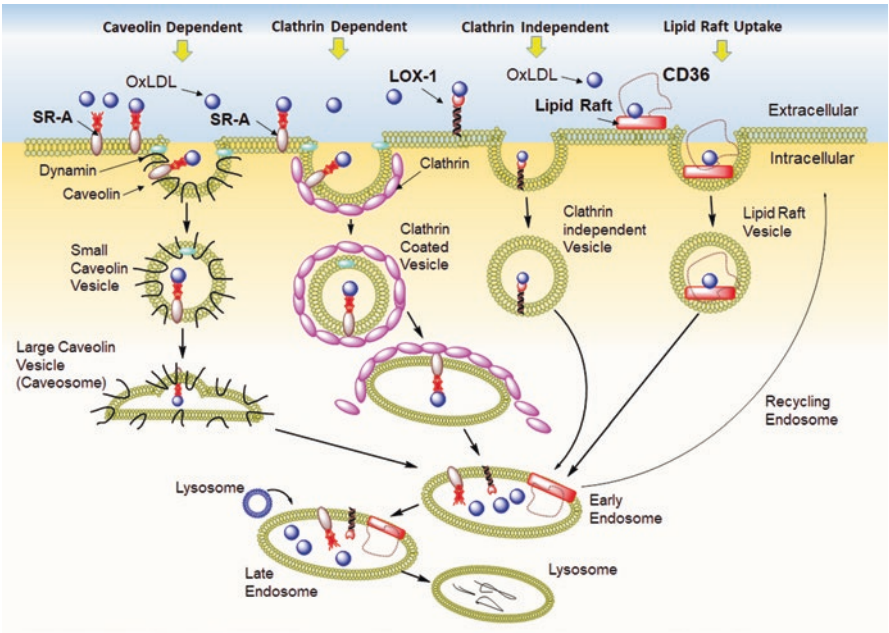

Fig. 10.2 Schematic overview of scavenger receptor-mediated endocytic pathways

B scavenger receptors (Fig.10.2). This endocytosis diversity of scavenger receptors is mainly associated with their sequence diversity and a wide variety of endocytic motifs present in cytoplasmic domains of each scavenger receptor.

The ligand binding to scavenger receptor mediates receptor-mediated endocytosis of this scavenger receptor–ligand complex, followed by intracellular trafficking via endosome lysosome system resulting in the metabolism of ligand. Scavenger receptor-mediated endocytosis of ligands stimulates the cascade of intracellular signaling. This leads to apoptosis, lipid peroxidation, and endothelial cell dysfunction. Monocyte infiltration accompanied by differentiation, which leads to foam cell formation, suggest a role in atherosclerotic plaque formation [6].

4.1 Caveolae/Clathrin-Dependent Pathway

A phagocytic cascade is triggered following internalization of modified LDL by SR-A. In the absence of ligands, unlike LDL receptor, the SR-A does not follow continuous cycling through a metabolic pathway. N-terminal cytoplasmic domain of SR-A contains di-leucine motif at amino acid residues 31 and 32, phosphorylation sites have been involved in ligand internalization and adhesion. This internalization of ligands follows classical coated pit pathway (Fig.10.2) [35].

4.2 Clathrin-Independent Pathway

The class E scavenger receptor LOX-1 binds to OxLDL, apoptotic bodies, and phospholipids and endocytoses via clathrin-independent pathway [36].

4.3 Lipid Raft Uptake

Class B scavenger receptor CD36 follows lipid rafts/caveolae-dependent pathway. Lipid rafts are mainly membrane domains containing lipids such as cholesterol, sphingolipids, glycosyl-phosphatidylinositol (GPI)-anchored proteins, and protein-tyrosine kinases of acylated src family. Caveolae present specialized raft subdomain for uptake mechanisms in some cells [37, 38].

5 Scavenger Receptor Location, Expression, and Function

Scavenger receptors are expressed mainly in endothelial cells (EDCs) and myeloid cells, but others are also expressed in epithelial cells. The SR-AI and AII are mostly expressed on macrophages, EDCs, epithelial cells, astrocytes, dendritic cells (DCs), mast cells, smooth muscle cells and mediates lipid metabolism, clearance of modified host components, pathogens, apoptotic cells, B cell–macrophage interactions, antigen presentation, binding of macrophages to extracellular matrix, and intracellular signaling [39–41]. MARCO is expressed by macrophages, EDCs, DCs, and astrocytes. Infectious stimuli express MARCO in most tissue macrophages. In DCs, antitumor response induces high-level expression of MARCO. MARCO also regulates the clearance of pathogens, necrotic dead cells, unopsonized particles, and enhances B cell–macrophage interaction [42]. SRCLI/II is mostly expressed by EDCs, stromal cells, astrocytes, and microglia, but not by macrophages. SRCL induces adherence of Lewis X-positive cells to vascular endothelium and elicits clearance of desialylated glycoproteins and β-amyloid [15]. Moreover, SCARA-5, a class A receptor is mostly expressed on epithelial cells of testis, airways, thymus, and adrenal glands. SCARA-5 lacks ability to recognize modified LDL and thus not involved in its endocytosis [14].

CD36 is mostly expressed by myeloid cells, platelets, adipocytes, and EDCs. Monocyte differentiation upregulates CD36 level, a mechanism similar to SR-A. The class B receptors induce lipid transfer activity, clearance of apoptotic cells, and *P. falciparum*-infected erythrocytes. SR-BI is found on monocytes, DCs, liver cells, and adrenal glands [43]. Class C is not found in humans and expressed on macrophages of the Drosophila and Mosquitoes [44]. The class D CD68 scavenger receptor shows intracellular expression in macrophages, and surface expression on dendritic cells and osteoclasts [45]. Moreover, scavenger receptor class E (LOX-1)

is mostly found on EDCs, in various diseased conditions is expressed in smooth muscle cells. Furthermore, LOX-1 is involved in induction of apoptosis of EDCs, monocyte adhesion to EDCs, release of proinflammatory cytokines, and increase in ROS production [46]. The class F receptors are expressed over EDCs, macrophages and are involved in clearance of modified host components, antigen clearance and cross-presentation [47]. The class G scavenger receptors are expressed over macrophages, dendritic cells, and also expressed in multiple organs [48]. The class H scavenger receptors are mostly expressed in EDCs of liver, spleen, and lymphatic system, whereas macrophages only express FEEL-1. The class H facilitates lymphocyte adhesion and transmigration, clearance of modified lipoproteins and apoptotic cells, induces angiogenesis, and is involved in intracellular trafficking [49]. However, Class I CD163 receptor is mainly expressed on myeloid cells and mediates clearance of hemoglobin (Hb):haptoglobin (Hp) complexes, and aids erythroblast adhesion to macrophages [6]. Other classes of scavenger receptors such as class J, K, and L are still in research stage, in which class J is mainly expressed on neurons, class K on macrophages, and class L on kidney proximal tubule cells, lung, thyroid, gallbladder, neuroepithelium, epididymis, prostate, ovaries, uterus, and blood–brain barrier. They are mainly involved in the clearance of extracellular matrix ligands [5]. Although different types of scavenger receptors are expressed at the same site, they show diversity in intracellular trafficking and consequently elicit different responses.

6 Pathophysiological Features

SR-AI/II plays a major role in innate immunity against bacterial infections, where they recognize polyanionic cell wall products of bacteria including lipopolysaccharide (LPS) and lipoteichoic acid (LTA). They mediate unopsonized phagocytosis of Gram-positive bacteria. This innate immune response stimulates scavenger receptor and enhances recognition and rapid internalization of pathogenic materials, thereby playing a role in the host defense mechanism [50].

SR-BI is involved in several processes such as apoptosis, binding and internalization of pathogens, and signaling for induction of anti-inflammatory response. Microorganisms supported by anti-inflammatory activity of SR-BI undergo internalization via multimolecular pathways. This was elucidated based on observations in infectious diseases caused by Gram-positive and -negative bacteria, as also infections caused by dengue virus, hepatitis C virus, *Plasmodium* species, and many other infectious agents. SR-BI is also involved in the clearance of microbial end products. Binding of SR-BI to lipopolysaccharide is reported [50].

Involvement of scavenger receptors in the regulation of cancer tumor growth and associated immune reactions is reported. Tumor-associated macrophages (TAMs) show elevated levels of SR-A. An overexpression of SR-BI on cancer cell lines is observed. This results in increased lipid uptake in tumor cells, thus promoting growth [51]. Yet another interesting mechanism by which SR-BI increases tumor

proliferation is the intracellular signaling cascade involving activation of the PI3K/AKT pathway, thereby causing tumor growth [52, 53].

Scavenger receptors are extensively studied in atherosclerosis, where SR-A and CD36 induce modified LDL uptake which is associated with foam cell formation [54]. On the other hand, SR-BI mediates cholesterol transport which is responsible for its anti-atherogenic role [55]. Although cells present in atherosclerotic lesions expressed LOX-1 and CD68, their exact role in response to atherogenesis is yet to be confirmed.

Interestingly, scavenger receptors are reported to play an important role in the pathophysiology of Alzheimer's disease, where they exhibited potential endocytosis of β-amyloid fibrils [56].

7 Ligands

Majority of scavenger receptors are able to bind bacteria, virus, and cell surface components. They showed effective binding with polynucleotides, sulfated polysaccharides, and long-chain fatty acids [40]. Almost all scavenger receptors mediate modified LDL uptake. The members of this supergroup such as SR-A, SR-B, and SR-E show efficient binding to both OxLDL and AcLDL, whereas SR-H only mediate AcLDL uptake. Among all, class B receptors bind to unmodified LDL, HDL, and VLDL. Such differential binding dictates their functional diversity in the clearance of modified LDL. The scavenger receptor expresses positively charged amino acids cluster (arginine or lysine) which thereby facilitates ionic interaction with negatively charged polyanionic ligands, lipoprotein particles, and pathogenic materials such as lipopolysaccharide and lipoteichoic acid. The ligand-binding potential of scavenger receptors increases with enhanced oligomer expression [29, 31, 41]. The numerous ligands for different scavenger receptor classes are summarized in Table 10.1.

Class A recognizes lipidic and apolipoprotein functionalities expressed by modified LDL [57]. This class of scavenger receptors exhibits neuronal cytotoxicity by mediating the uptake of β-amyloid fibrils in microglia and thereby contributes to the pathophysiology of Alzheimer's disease [58]. The affinity of extracellular ligands biglycan and decorin to SR-A induces association of macrophages in the extracellular matrix of smooth muscle cells involved in atherosclerotic plaque formation. Similarly, advanced glycation end products (AGE) efficiently endocytosed by SR-A are released during inflammation. On the other hand, SR-A also mediates uptake of glycated proteins such as glycated collagen IV. Expression of SR-A on adenocarcinoma cells mediates internalization of T-cell tumor antigen and thus plays an important role in cancer pathology. During lung inflammation, MARCO mediates uptake of uteroglobin-related protein-1 (UGRP-1). Besides MARCO another member of class A, SRCL-I recognizes Lewis-X trisaccharides with high affinity and dictates its role in recognizing desialylated glycoproteins. SRCL-I also recognizes β-amyloid peptide in Alzheimer's patients [5].

Table 10.1 Scavenger receptor class and their ligand molecules

Class	Receptor	Endogenous ligands	Pathogenic ligands	Exogenous ligands
A	SR-AI/II	AcLDL, OxLDL, lysophosphatidylcholine, ApoA-I, Apo E, cholesterol, modified collagen type I, III, and IV, biglycan, decorin, AGE-BSA, β-amyloid fibrils, calreticulin, gp96, Hsp70, CpG DNA	*N. meningitidis* surface proteins, Gram-positive and -negative bacteria, C-reactive protein, hepatitis C virus, LPS, LTA	Polyacrylic acid, phosphatidic acid-modified albumin, calciprotein particles, maleylated LDL
A	MARCO	AcLDL, OxLDL	*N. meningitidis* surface proteins, Gram-positive and -negative bacteria, LPS	TiO_2, Fe_2O_3, Latex beads, and $CSiO_2$
A	SCARA5	L-ferritin, haptoglobin, hemoglobin	Gram-positive and -negative bacteria	Fe_2O_3
A	SRCL	OxLDL, β-amyloid, desialylated Lewis X-containing glycoproteins, Lacto-ferrin, matrix metalloproteinases 8, 9	Yeast, Gram-positive and -negative bacteria	Fe_2O_3, modified glycoproteins, modified polysachharides
B	CD36	AcLDL, OxLDL	Gram-negative bacteria, *Cryptococcus neoformans* and *P. falciparum*, LTA	Phosphatidylserine, β-glucan, A diacylated, lipopeptides
B	SR-BI	AcLDL, OxLDL, native LDL, native HDL, VLDL, apoptotic cells	Gram bacteria, *M. fortuitum*, hepatitis C virus, *P. falciparum*, LPS	Sulfated polysaccharides
D	CD68/ Macrosialin	OxLDL	ICAM-L (Leishmania surface protein)	Phosphatidylserine-rich liposomes
E	LOX-1	OxLDL, acLDL, fibronectin, and pancreatic bile salt-dependent lipase Hsp60, Hsp70	Gram-negative and -positive bacteria	Modified LDL, lipoprotein particle, phospholipids, sulfated polysaccharides, poly(I), AGEs
F	SRECI/II	AcLDL, OxLDL, glucose-regulated protein 170, Hsp70, Hsp90, Hsp110	Gram bacteria, hepatitis C virus, fungal pathogens, zymogen granule protein 2	Carbamylated LDL, calreticulin
G	SRPSOX/ CXCL16	OxLDL	Bacteria	Phosphatidylserine

(continued)

Table 10.1 (continued)

Class	Receptor	Endogenous ligands	Pathogenic ligands	Exogenous ligands
H	FEEL-1/ Stabilin1/ CLEVER1	AcLDL, AGE, SPARC, Hsp70, SICLP, Placental lactogen, and GDF-15	Gram-negative and -positive bacteria	Phosphatidylserine, heparin sulfate
H	FEEL-2/ stabilin-2/ HARE	AcLDL, AGE, and GDF-15	Gram-negative and -positive bacteria	Procollagen, hyaluronic acid, phosphatidylserine, heparin
I	CD163	Hb:Hp, TWEAK a TNF superfamily cytokine	Gram-positive and -negative bacteria	Not known
J	RAGE	AGEs, HMGB, S-100 protein	Not known	Modified AGE
K	CD44	Hyaluronan, growth factors, cytokines, and matrix metalloproteinases	Bacteria, proteoglycans	Hyaluronic acid, glycosaminoglycans
L	SR-L1	Cholesterol, Apo-EI	Not known	Not known
L	SR-L2	Leptin, insulin, and amyloid β peptide	Not known	Not known

Class B receptors show diverse ligand specificity where they bind native lipoprotein particles and hypochlorite modified LDL which are found in atherosclerotic lesions. CD36 present in vascular endothelial cells mediates hexarelin uptake and causes vasoconstriction. Furthermore, this CD36 also binds collagen type I, AGE-modified BSA, and β-amyloid fibrils. It also recognizes oxidized phospholipids expressed on apoptotic cells, thereby mediating macrophage clearance. SRBI receptor of class B, binds AcLDL with greater affinity. It also mediates uptake of native lipoprotein particles and recognizes expressed apolipoprotein components. It also binds AGE-BSA and β-amyloid fibers [5, 29, 57, 58].

Class C receptor binds to AcLDL and pathogens, whereas class D (CD68) binds to OxLDL and negatively charged phosphatidylserine-rich liposomes. The Class E (LOX-1) binds to OxLDL, fibronectin, phosphatidylserine, AGE-modified protein and clears apoptotic cells. LOX-1 mediates Hsp70 internalization in dendritic cells, which is not endocytosed by class A & class B receptors. Both Class F receptors, SREC-I and SREC-II, are involved in the uptake of modified LDL, and mediate recognition of other ligands such as calreticulin, molecular chaperones, gp96, and tumor released heat shock proteins (Hsp70), whereas they lack recognition for AGE-modified proteins.

Class G (SRPSOX) receptor-like LOX1 (Class E) binds to OxLDL but not to AcLDL and it also acts as chemokine ligand for CXC chemokine receptor 16, thereby mediating adhesion of DCs to T cells and NK cells. In class H, FEEL-1 receptor binds to extracellular SPARC (secreted protein acidic and rich in cysteine) glycoprotein and SI-CLP (stabilin-1 interacting chitinase-like protein) sorted in macrophages and Hsp70, while they show poor recognition for AGE-BSA. However, FEEL-2 recognizes hyaluronic acid and AGE-BSA with high affinity [5, 6, 29].

Scavenger receptors bind to foreign ligands including bacteria, fungi, virus, and parasites. In case of pathogens, their extracellular expression containing lipopolysaccharides, lipoteichoic acid, C-reactive protein, endotoxins, and numerous other surface proteins are recognized by these receptors [59]. Researchers have studied various other ligands based on functionality for scavenger receptor targeting, which is summarized in Table 10.2.

Table 10.2 List of scavenger receptor ligands based on functionality

Ligand functionality	Ligands	Reference
Polyacids	Polyacrylic acid	[60]
	Polyitaconic acid	[61]
	Poly-D glutamic acid	[62]
Phospholipids	Phosphatidylserine	[63]
	Phosphatidylglycerol	[64]
	Phosphatidylinositol	[37]
	Phosphatidic acid	[37]
	Oxidized phospholipids	[65]
	Cardiolipin	[66]
Polysaccharides	Dextran sulfate	[67, 68]
	Heparin and heparan sulfate	[69, 70]
	Keratan sulfate	[71]
	Dermatan sulfate	[72]
	Chondroitin sulfate	[73]
	Glucoronate oligosaccharide	[74]
	Hyaluronate	[75]
	Carrageenan	[68, 76]
	Carboxymethyl dextran	[77, 78]
	Carboxymethyl cellulose	[79, 80]
	Fucoidan	[81, 82]
	Glycosaminoglycans	[83]
Polynucleotides	Polyinosinic acid poly (I)	[84]
	Poly (G), poly (G:I), polyxanthinylic acid, telomere models $[d(G_4T_4)_5]$	[85]
Fatty acids	Stearic acid	[86]
	Myristic acid, polyunsaturated fatty acids	[87]
Inorganic particles	Fe_2O_3	[33, 88]
	TiO_2, ZnO	[89]
	Silica	[90]
	Asbestos crocidolite	[91, 92]
Modified Proteins	Maleylated BSA	[93, 94]
	Malonaldehyde LDL	[95]
	Calciprotein	[96]
	Procollagen propeptides	[97]
	Heat shock proteins (Hsp)	[98]
	Major vault protein (MVP)	[99]
Others	Bovine sulfatides	[100]

8 Receptor-Mediated Targeting Strategies

Endocytic uptake mechanism of scavenger receptor suggests a simplistic way of receptor-mediated targeted drug delivery. The drug gets released intracellularly after efficient internalization of the ligand–receptor complex. This interaction also induces the cascade of inflammatory responses. Although there exist many different scavenger receptor classes, till date, only A and B scavenger receptors have been studied for nanomedicine-mediated response. These scavenger receptors serve as a unique nanomedicine target also for many theranostic applications. Research directed towards site-specific targeted drug delivery through scavenger receptor using various nanoformulations relies on receptor-specific ligands carrier compositions mainly involving polyanions [101].

8.1 Drug–Ligand Conjugates

The chemical coupling of a suitable drug to a scavenger receptor-specific ligand such as maleylated albumin (MBSA) increases recognition by scavenger receptors for high-affinity binding, thereafter it undergoes internalization and metabolically degraded in lysosomes to release free drug for activity. Almost 100-fold enhanced efficacy was observed with such drug–ligand conjugate when studied in leishmaniasis, tuberculosis, and neoplastic conditions. Coupling of methotrexate (MTX) to MBSA exhibited rapid internalization inside leishmania-infected hamster peritoneal macrophages and demonstrated 100-fold antileishmanial effect compared to free drug. It also eliminated intracellular amastigotes of *L. donovani* and L. mexicana *amazonesis*. However, in case of *M. tuberculosis*-infected macrophages the targeting of anti-tubercular drug p-amino salicylic acid (PAS) and MBSA conjugate resulted in only 50% reduction of colony-forming units (CFUs). However, compared to free drug which exhibited CFU reduction of 0.5%, the enhancement in efficacy was nearly 100-fold. In neoplastic condition, the conjugation of drug Daunomycin with MBSA exhibited 100-fold cytotoxicity over free Daunomycin when tested at low concentration of 0.1 μM. Similar cytotoxic results were found with Doxorubicin-MBSA conjugate when tested on human histiocytic lymphoma cells [102].

8.2 Liposomes

Negatively charged phospholipids such as phosphatidylserine (PS) and phosphatidylglycerol (PG) are efficiently recognized by macrophages [103]. The studies confirmed that negatively charged liposomes are efficiently taken up by macrophage scavenger receptors over neutral or cationic liposomes [104–107]. When macrophage cells which expressed scavenger receptor were treated with negatively charged PS-liposomes and neutral PC-liposomes, the former exhibited 5.3-fold

enhanced macrophage uptake over PC liposomes [108]. Incorporation of dicetylphosphate (DCP) also induced net negative surface charge over liposomes [109]. Polyaconitylated-human serum albumin (Aco-HSA) surface anchored liposomes showed effective anti-HIV 1 activity due to high uptake by scavenger receptors expressed on sinusoidal cells. This conjugation of Aco-HSA to liposomes enhanced liver uptake 17-fold, as compared with control liposomes, and the Aco-HSA liposomes were mostly found in liver EDCs and kupffer cells. Further, in this study, reduced liver uptake (24%) of Aco-HSA was found post-injection of polyinosinic acid, which is a known SR ligand [110].

In case of stealth liposomes, endocytic CD163 scavenger receptor enhanced uptake of monoclonal antibody loaded pegylated liposomes in CD163 transfected cells and macrophages [111]. Palmitoyloleoyl-phosphatidylcholine (POPC)-apoE liposomes functionalized using different apoE proteins (apoE2, apoE3, apoE4, apoE165, apoE202, apoE229, and apoE259) enhanced scavenger receptor B binding affinity and were thought to regulate brain cholesterol metabolism [112]. Liposomes carrying fluorescently labeled cholesterol when tested on HepG2 cells (model system for human hepatocytes) showed 20% binding for class B scavenger receptor and only 10% recognition was confined to low-density lipoprotein receptor (LDLR) which provided additional insights for scavenger receptor-mediated uptake of liposomes [113]. It was reported that, in certain cells, liposome uptake is not inhibited by known scavenger receptor ligands suggesting their uptake was not scavenger receptor-mediated. PS-containing liposomes showed enhanced uptake in an African green monkey kidney cell line (CVI) compared to phosphatidylcholine (PC) liposomes, independent of inhibition by known competitors for scavenger receptor [polyinosinic acid or dextran sulfate]. On the other hand, in case of murine macrophage cell line, PS-liposome uptake was inhibited competitively by polyinosinic acid, but not by polycytidylic acid [114]. The liposomes for targeted scavenger receptor delivery in various diseased conditions are described in Table 10.3.

8.3 Nanoparticles

8.3.1 Lipoprotein Particles

In one study, it was found that OxLDL exhibited stronger CD36 binding and HDL has stronger SR-BI binding ability among all lipoproteins [124]. Synthesized HDL nanoparticles also revealed high affinity for SR-BI-rich cancer cells. Furthermore, HDL nanoparticles mediated delivery of siRNA to the cancer tumors overexpressed with SR-BI. Similarly, these HDL nanoparticles exhibited SR-BI-mediated paclitaxel delivery to prostate cancer cells. Such studies proved the potential of SR-BI-mediated targeting of nanoparticles and their subsequent involvement in many disease states [125]. Administration of acylated LDL particles loaded with muramyl tripeptide mediated antitumor efficacy through the scavenger receptors [126]. In one study, the antinociceptive activity of apo lipoprotein functionalized loperamide-

Table 10.3 Liposomes for scavenger receptor targeting

Active	Ligand	Study outcome	Reference
Tuberculosis			
Rifampicin	Maleylated bovine serum albumin	Higher lung retention in rats compared to free drug	[109]
Rifampicin	Tuftsin	2000-times more effective in lowering lung CFU compared to free drug	[115]
Rifampicin and isoniazid	Dicetylphosphate (DCP)	Decreased bacterial load in lung, liver, and spleen	[116]
Hepatitis			
No drug	L-α-phosphatidylinositol (PI) and L-α-phosphatidylserine (PS)	Improved antiviral efficacy by reducing infected cell cholesterol level	[117]
Leishmaniasis			
Pentavalent antimony	PS	16-fold more efficacy compared to free drug	[118]
Buparvaquone	PS	>90% efficacy in liver and spleen found	[119]
HIV			
No drug	PI and PS	Suppressed mean viral secretion by 22% and infectivity by 55%	[117]
Iminosugar N-butyl-deoxynojirimycin	PI and PS	Decreased viral secretion by 62% and infectivity by 86%	[120]
Cancer			
CPX-351 (cytarabine and daunorubicin 5:1 molar ratio)	PS	SR-BI mediated efficient uptake of CPX-351 in K562 leukemia cells	[121]
Doxorubicin	Polyethylene glycol	CD163-targeted pegylated liposomes showed 50% cell killing over Doxil	[111]
Atherosclerosis			
Fumagillin	1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine-N-7-nitro-2-1, 3-benzoxadiazol-4-yl (DPPE-NBD), and 1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine-N-biotinyl (DPPE-Biotin)	Diminished atherosclerotic lesion	[122]
Dexamethasone	Decadeoxyguanine linked to lithocholic oleate (LCO-dA2dG10)	Enhanced macrophage uptake	[123]

loaded albumin nanoparticles was assessed. Three apo lipoproteins E3, A-I, and B-100 exhibited 95%, 65%, and 50% antinociceptive activity, respectively, whereas plain loperamide solution showed no effect, which showed uptake of such particles through SR-BI receptor expressed at BBB [127].

8.3.2 Inorganic Nanoparticles

Dextran sulfate-mediated macrophage uptake of silver nanoparticles (AgNPs) through scavenger receptor is reported. Scavenger receptor-mediated uptake of AgNPs resulted in their intracellular accumulation and thereby apoptosis [128]. Furthermore, protein functionalization of AgNPs reduced its uptake due to decreased surface charge [129, 130]. Inhalation of ZnO nanoparticles induced enhanced expression of both SR-A and SR-B and thereby influenced atherosclerotic disease progression. However, TiO_2 nanoparticles did not exhibit the same mechanism [89]. The macrophage phagocytic activity was diminished when subjected to superparamagnetic iron oxide nanoparticles exposure. These iron oxide nanoparticles inhibited macrophage activation for M1 to M2 state and enhanced TNF-α production [33, 88].

8.3.3 Miscellaneous

Gadolinium-containing nanomedicines with anti-CD36 antibodies were efficiently taken up by macrophages in vitro compared to nanomedicines without CD36 antibodies [131]. The scavenger receptor A class member MARCO also exhibited interaction with carbon nanotubes [132] and polystyrene nanoparticles [133]. Furthermore, when scavenger receptor A was overexpressed in human embryonic kidney 293 (HEK293) cells, a cell line which is normally devoid of scavenger receptor expression, elicited enhanced uptake of amorphous silica nanoparticles, demonstrating role of scavenger receptor in uptake of nanomedicines [101,134]. The miscellaneous nanoparticles targeting scavenger receptors are given in Table 10.4.

Table 10.4 Other nanosystems for scavenger receptor targeting

Nanomaterials	Study outcome	Reference
Inorganic		
Dextran-coated superparamagnetic iron oxide nanoparticles (SPIO)	Promotes SPIO uptake by embryonic kidney cells (HEK293T) overexpressing SR-AI and MARCO	[33]
Silver nanoparticles	Inhibition of SR-BI caused reduced uptake of AgNPs in endothelial and epithelial cells	[129]
Silver nanoparticles	Decreased uptake in MARCO-deficient alveolar macrophages	[135]
Miscellaneous		
Multiwalled carbon nanotubes	Efficient binding to MARCO in macrophages	[132]
Fluorescent labeled polystyrene particles	Enhanced macrophage association of nanoparticles through MARCO	[133]
Silica nanoparticles	Enhanced nanoparticles uptake by human embryonic kidney 293 (HEK293) cells with overexpression of SR-A	[134]

9 Clinical Trials

Although targeting to scavenger receptor is still in its nascent stage, very few scavenger receptor-mediated delivery systems have reached clinical trials. Herein we discuss such clinical studies with their outcome, demonstrating the role of scavenger receptors and targeting strategies. A study exploring targeting of pegylated interferon α2 plus ribavirin therapy to SR-BI receptor encoded by SCARB1 gene for hepatitis C virus studied the association of single nucleotide polymorphism (SNP) of SCARB1 gene and its response to therapy, where they found SNP may increase antiviral therapy outcome [136, 137]. Interestingly another study was conducted to understand underlying molecular mechanisms causing disruption to HDL regulation through scavenger receptor (SR-BI) in various metabolic diseases including atherosclerosis, where genotype modification affects HDL metabolism and cholesterol homeostasis [138]. One study was conducted to assess the role of scavenger receptor ligands as biomarkers for cardiovascular disease diagnosis, where oxidized phospholipids and apolipoprotein B identification by antibodies can be detected to predict cardiovascular disease state 15 years in advance. The receptor studied here was CD36 [139]. Studies were also conducted for anti-hepatitis C virus efficacy testing of a new molecule ITX 5061 by blocking the virus uptake through scavenger receptor (SR-BI) expressed on hepatocytes to reduce the infection chances in liver transplant patients [140]. No clinical trials are however evident on scavenger receptor-targeted drug delivery.

10 Advantages and Limitations

Targeting scavenger receptors offers great promise for improved therapeutic efficacy. This receptor has recognition specificity for pathogenic materials and plays an important role in various disease conditions. Intracellular delivery of actives can be achieved through scavenger receptor-mediated drug delivery, as the majority of infections are intracellular.

The major limitation of targeting these receptors is their broad ligand binding and recognition including both endogenous and exogenous molecules, which will compete for receptor-mediated endocytosis. Another major challenge is immunogenicity as these receptors are involved in inflammation and expressed on immune cells. Furthermore, they are widely expressed on majority of cell types; hence, specificity is a challenge.

11 Future Perspectives

Recently, newer classes of scavenger receptors were found and many more are still to be discovered, hence targeting to these receptors can provide newer avenues in site-specific drug delivery. Exploitation of scavenger receptor-mediated drug delivery

is an option of the future. SR-BI due to its overexpression is reported as biomarker for human nasopharyngeal carcinoma [141]. The role of scavenger receptor as a biomarker for diagnosing various other disease conditions needs to be explored.

12 Conclusion

Scavenger receptors play a multifaceted and dynamic role in various cell-signaling pathways in the human body and are involved in metabolic regulation of macrophages for improved immune response. Scavenger receptors facilitate uptake of a broad spectrum of ligands including endogenous and foreign molecules. However, this receptor poses a challenge in stealth delivery of nanomedicines due to its inherent ability of scavenging numerous components. Targeted drug delivery using scavenger receptor is still in its nascent stage and can be further exploited for the treatment of infections and cancer.

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