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Review Article

# From Health to Disease: Functional Insights of Scavenger Receptor Class B Type I in Lipid Metabolism and Disease Pathogenesis

**[1]Sujina Simon Sailet, [1]Poornima Ajay Manjrekar, [2]Santosh Rai, [3]Bailuru Vishwanath Tantry and [1]Deenadhayalan Ashok**

*[1]Department of Biochemistry, Kasturba Medical College Mangalore, Manipal Academy of Higher Education, Karnataka Manipal, India*
*[2]Department of Radiodiagnosis, Kasturba Medical College Mangalore, Manipal Academy of Higher Education, Karnataka, Manipal, India*
*[3]Department of Gastroenterology, Kasturba Medical College Mangalore, Manipal Academy of Higher Education, Karnataka, Manipal, India*

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Corresponding Author:
Poornima Ajay Manjrekar
Department of Biochemistry, Kasturba Medical College Mangalore, Manipal Academy of Higher Education, Karnataka Manipal, India
Email: poornima.manjrekar@manipal.edu

**Abstract:** Scavenger receptor class B type I (SR-B1) has caught considerable interest among the scientific community due to its pivotal role in several biological and pathological processes. It is a multifunctional integral membrane protein and multiligand receptor encoded by the SCARB1 gene. SR-B1 has a wide distribution, primarily in the liver as well as steroidogenic organs including the gonads and adrenal glands, and a reduced expression is noted in macrophages, adipocytes, lung tissue and endothelial cells. Its expression across different tissues reflects its diversity in various physiological processes. Alongside, defects can alter the normal rhythm of the body's functioning, leading to the pathogenesis of various diseases. In cholesterol-demanding cells, SR-B1 highlights its significant role in cholesterol homeostasis. This paper explores the multifaced role of SR-B1 in regulating cholesterol handling, its involvement in inflammatory signaling pathways, and its interactions with various transcription factors, inflammatory mediators, and as a therapeutic target across various disease contexts.

**Keywords:** Cholesterol Homeostasis, High-Density Lipoprotein (HDL), Multiligand Receptor, Reverse Cholesterol Transport (RCT), Scavenger Receptor Class B Type I (SR-B1, SCARB1), Steroid Hormones

## Introduction

Scavenger receptor class B type I (SR-B1) is a multifunctional integral membrane receptor encoded by the SCARB1 gene, capable of binding multiple ligands was first discovered by Acton *et al.* (1994) from Chinese hamster ovary. It has caught significant attention in the scientific community due to its pivotal role in cholesterol metabolism, particularly in mediating the selective uptake of High-Density Lipoprotein (HDL) cholesterol in the liver and steroidogenic tissues. While SR-B1's function in lipid transport and metabolism has been extensively studied, its role in other physiological and pathological contexts remains underexplored. Emerging evidence suggests that SR-B1 is not merely a lipid transporter but also a key player in immune regulation, inflammation, and cancer progression. This study aims to reframe SR-B1 in a new context, comparing its roles in health and disease in the currently available knowledge and identifying gaps in our knowledge.

### *Structure of SR-B1 Receptor*

SR-B1 is classified as a family member of structurally similar proteins called the cluster determinant 36 (CD36) superfamily. SR-B1 was first identified as a homolog of CD36. A subsequent phylogenetic study revealed that these genes diverged early in evolution from a common ancestor gene (Acton *et al.*, 1994; Rigotti *et al.*, 2003; Calvo *et al.*, 1995). SR-B1 is characterized to be an ~82 kDa cell surface glycoprotein, built of 509 Amino Acids (AA), attached to the plasma membrane with both N and C terminals extended towards the cytoplasm (Figure 1). It consists of a large extracellular domain, including several sites for N-linked glycosylation and a cysteine-rich region of 408 amino acids, two transmembrane spanning domains

containing 22 and 23 amino acids, a first and short N-terminal intracellular domain consisting of 9 amino acids and finally a second intracellular C- terminal domain of 44 amino acids (Rigotti *et al.*, 2003; Viñals *et al.*, 2003; Shen *et al.*, 2018).

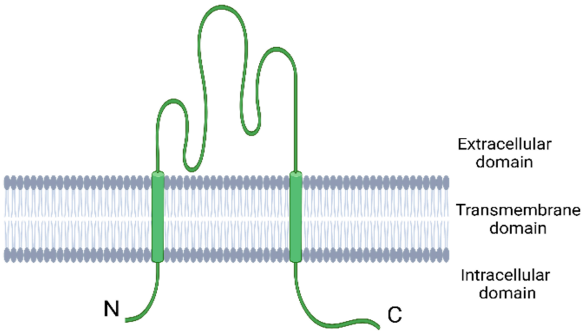


**Fig. 1:** General structure of SR-B1

The SCARB1 gene coding for SR-B1 is positioned on chromosome 12, yielding five different forms of proteins called isoforms through alternate splicing. SR-B1 with 508 AA residues was first identified as isoform 1 (Q8WTV0-2). Isoform 2(Q8WTV0-3) and Isoform 4 (Q8WTV0-4/ SR-BIII) have the identical C-terminal as isoform 1 and 409 residues, but they differ at 43–142 AAs and 474 residues with a distinct N-terminal at 1-42 AAs respectively. Isoform 3(Q8WTV0-1) with 552 residues is the longest and it is different from isoform one at the C-terminal from AAs 468-552. Isoform 5 (Q8WTV0-5/ SR-BII/ SR-B1.1) has 506 residues, with a distinct C-terminal at AA sequence from 468–552 (Shen *et al.*, 2018; Webb *et al.*, 1997).

Initially, OxLDL was considered the primary ligand for SR-B1 (Acton *et al.*, 1996). However, subsequent studies confirmed that SR-B1 has a higher affinity for native High-Density Lipoprotein (HDL) (Hoekstra, 2017). Some variations of SR-B1 transfer lipids in a selective manner between HDL and cells, albeit at lesser efficiency (Webb *et al.*, 1998).

### *SR-B1: A Multiligand Receptor*

Other than OxLDL, Acetylated LDL (AcLDL) (Out *et al.*, 2004; Racanelli and Rehermann, 2006) and native HDL (Ganesan *et al.*, 2016; Pandey *et al.*, 2020) Advanced Glycation End products -Bovine Serum Albumin (AGE-BSA) and methylated BSA can bind with SR-B1 receptors (Acton *et al.*, 1994; Gillotte-Taylor *et al.*, 2001)and AGE-modified proteins (Cai *et al.*, 2005; Tsugita *et al.*, 2017). Oxidative stress and accumulation of oxidized phospholipids can reduce reverse cholesterol transport by inhibiting SR-B1 (Acton *et al.*, 1994; Ohgami *et al.*, 2001). It can also be bound with reconstituted phospholipid/ unesterified cholesterol containing HDL apolipoproteins: ApoA-I, apoA-II, apoC-III and apoE (Marsche *et al.*, 2002; 2003; Ashraf *et al.*, 2008), anionic phospholipids (Gao *et al.*, 2015), negatively charged liposomes (Xu *et al.*, 1997), serum Amyloid A (SAA) (Li *et al.*, 2002), silica (de Beer *et al.*, 2001) and apoptotic cells (Xu *et al.*, 1997; Rigotti *et al.*, 1995; Fukasawa *et al.*, 1996) Native LDL and VLDL have a high affinity toward SR-B1 receptors (Svensson *et al.*, 1999; Imachi *et al.*, 2000). The binding properties of hypochlorite-modified HDL (HOCl-HDL) to SR-B1 are well-studied in Chinese hamster ovary cells. The in-vitro studies concluded that HOCL-modified HDL significantly changed the inherent properties of the native HDL. HOCl- HDL blocks SR-BI-mediated contact with native HDL (Acton *et al.*, 1996). In contrast, HOCl- LDL is not recognized by SR-B1 receptors (Krieger, 1999). Various ligands for SR-B1 and their functional roles are summarized in Table (1).

**Table 1:** Multiligand for SR-B1

| Ligand | Year of discovery | Functional role |
|---|---|---|
| OxLDL and AcLDL | 1994, 2001 | SR-B1-mediated uptake contributes to foam cell formation in macrophages, a key event in atherosclerosis |
| AGE- BSA, methylated-BSA, and AGE-modified proteins | 1994, 2001, 2003 | They clear glycated proteins which are associated with diabetic complications and inflammatory responses |
| LDL | 1994, 1997 | Relevant to atherosclerosis and lipid homeostasis |
| VLDL | 1997 | SR-B1 serves a crutial role in VLDL metabolism and lipid transport |
| HDL | 1996,1999 | Maintaining lipid homeostasis and preventing atherosclerosis |
| Negatively charged liposomes | 1996 | Mimics the charge properties of HDL |
| Apoptotic cells | 1996,1999,2000 | Clearance of apoptotic cells |
| Pathogenic microorganisms | 2003 | SR-B1 facilitates viral entry into macrophages and its removal |
| HDL apolipoproteins (apoA-I, apoA-II, apoC-III, and apoE) reconstituted into phospholipid/ unesterified cholesterol complexes. | 1997,2001,2002 | They mimic HDL and facilitate cholesterol efflux and transport |
| Hypochlorite-modified HDL (HOCl-HDL) | 2002 | Associated with oxidative stress and inflammation in cardiovascular diseases |
| Serum amyloid A (SAA) | 2005 | Interacts with HDL metabolism and promotes inflammation |
| Oxidized phospholipids | 2008,2014 | Implicated in the pathogenesis of atherosclerosis |
| Silica | 2017 | Relevant in the context of environmental exposure, potentially modulating its function in lipid metabolism and immune responses |

### *SR-B1 in Health*

SR-B1 has a wide distribution, primarily in the liver and other steroidogenic organs, including adrenal glands and gonads, with decreased expression noted in macrophages, adipocytes, endothelial cells, and lung tissue. The widespread expression of SR-B1 across different tissues highlights its diverse physiological functions. Alongside, defects can alter the normal rhythm of the body's functioning, leading to various diseases. In cholesterol-demanding cells, SR-B1 highlights its significant role in cholesterol homeostasis.

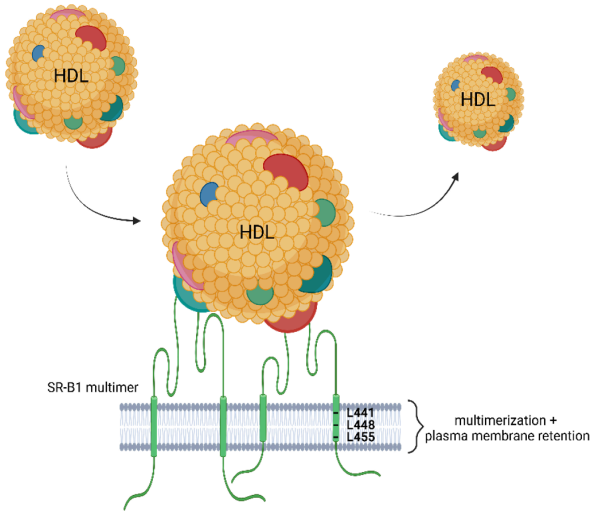


**Fig. 2:** Selective CE uptake by SR-B1 multimers

### *SR-B1 and Hepatocytes*

Hepatocytes, the principal Parenchymal Cells (PC), comprise 70-80% of the liver volume and 60% of the liver cell population and play a pivotal role in metabolism, detoxification, endocrine and exocrine functions (Viñals *et al.*, 2003). As regards metabolism, the liver plays a vital role in lipid metabolism, leading to energy homeostasis. Triacylglycerol (TG) and Cholesterol Ester (CE) are the storage forms of lipids. Other than the de-novo synthesis and degradation of surplus cholesterol into bile acids, the in and outflow of cholesterol via lipoproteins plays a pivotal role in the overall handling of lipids by the liver. The spare cholesterol is transported from peripheral tissues by High-Density Lipoprotein (HDL), which is then delivered to the liver for further disposal. As the chief HDL receptor, SR-B1 enables the bi-directional flow of cholesterol among the cells and HDL (Shen *et al.*, 2018). Various in-vitro and in-vivo studies have revealed that the SR-B1 regulates both selective docking of HDL and -intake of the HDL-associated Cholesterol Esters (CE) by the hepatocytes (Acton *et al.*, 1996; Hoekstra, 2017). Mechanisms controlling SR-B1 dynamics in terms of multimerization and its retention at the cell surface seek the C- C-C-terminal leucine zipper of SR-B1 and an actin cytoskeleton integrity (Figure 2), where it performs its selective lipid uptake as studied by Marques *et al.* (2019). Oligomerization of SR-B1 increases its efficiency (Shen *et al.*, 2018). Whilst SR-B1 also effluxes cholesterol to lipoproteins, it depends on the ligand binding to this receptor (Acton *et al.*, 1996). The SR-B1mediated influx and efflux of HDL-CE by hepatocytes make it a vital target for therapeutic benefits in managing cholesterol levels with Reverse Cholesterol Transport (RCT) (Brundert *et al.*, 2005). RCT is the process of the overall transfer of cholesterol via HDL and LDL/ VLDL from peripheral tissues to the liver, where it is further metabolized into bile acids/ steroid hormones for its excretion. In the liver, after delivering CE from the mature HDL, lipid-depleted HDL re-enters the circulation to participate in RCT (Figure 3).

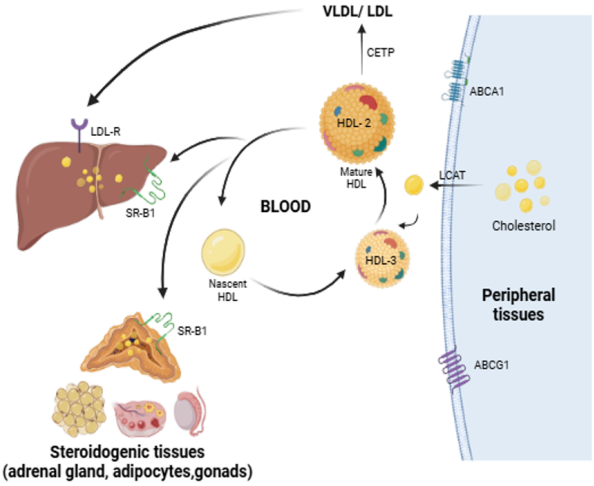


**Fig. 3:** Reverse cholesterol transport

*LDL-R: low density lipoprotein receptor; SR-B1: scavenger receptor class B type 1; HDL: high density lipoprotein; VLDL: very low-density lipoprotein; CETP: cholesterol ester transfer protein; LCAT: lecithin- cholesterol acyltransferase; ABCA1: ATP- binding cassette transporter A1; ABCG1: ATP-binding cassette subfamily G member 1*

Since SR-B1 is a receptor for both HDL and LDL (Krieger, 2001), it plays an essential role in the turnover of both LDL and HDL, bringing the total lipid homeostasis together. Many studies have been undertaken to determine the sub-cellular liver localization of SR-B1. Non-Parenchymal Cells (NPC), such as stellate cells, Kupffer cells, and sinusoidal endothelial cells, make up the remaining 20-40% of the liver volume in addition to PC. There is also evidence supporting the function and expression of SR-B1 in NPC in preserving hepatic homeostasis (Marques *et al.*, 2019; Gu *et al.*, 1998; 2000).

### *SR-B1 and Adrenal Gland*

Landschulz *et al.* (1996) localized SR-B1 on the resurfaces of steroidogenic cells in the zona fasciculata and zona reticularis of the adrenal gland by the immunofluorescence technique. Cholesterol, a precursor

for steroid hormones production, is derived from multiple sources: (1) de novo lipogenesis of cholesterol, (2) mobilization of Cholesterol Esters (CEs) from lipid droplets and (3) lipoproteins derived CE influx via SR-B1 and Low-Density Lipoprotein Receptors (LDL-R). Anterior pituitary releases, Adrenocorticotropic Hormone (ACTH) in response to corticotropin-releasing hormone from the hypothalamus and is found to modulate the expression of SR-B1 in the adrenal gland during the process of steroidogenesis (Figure 4). Various animal models and in-vivo studies demonstrated that the stimulation of ACTH significantly increases SR-BI expression in adrenal cells, which enhances cholesterol uptake and steroidogenesis, likely mediated by the secondary messenger's cAMP (Shen *et al.*, 2016). ACTH-treated mice exhibited a dual regulatory mechanism for SR-B1 expression involving both hormonal and depleted cellular cholesterol stores as metabolic stimuli to increase its expression and, therefore, to increase the cholesterol uptake and maintain cholesterol repository for steroidogenesis (Sun *et al.*, 1999). Acute and chronic ACTH treatments monitor the expression of SR-B1 through its phosphorylation, oligomerization, and its interaction with other accessory proteins such as cAMP-dependent protein kinase (PKA) signaling cascade, Salt-Inducible Kinase 1 (SIK1), and a serine/threonine kinase (Shen *et al.*, 2016).

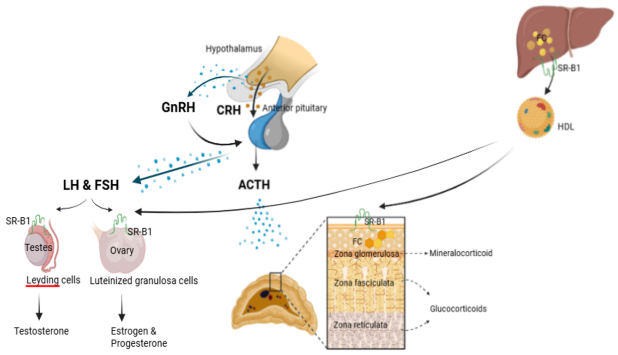


**Fig. 4:** Anterior- Pituitary- Adrenal (APA) and Anterior-Pituitary- Gonadal (APG) axis in steroidogenesis. CRH, corticotropic releasing hormone

*ACTH: Adrenocorticotropic hormone; SR-B1: scavenger receptor type B class 1; FC: free cholesterol; HDL: high-density lipoprotein*

## *SR-B1 and Gonads*

In the ovary, SR-B1 is expressed in the corpus luteal cells (Landschulz *et al.*, 1996). It serves as a primary receptor for HDL, aiding the uptake of cholesterol esters, essential for synthesizing steroid hormones, such as progesterone and estrogen, crucial for ovarian function and follicular development. Studies in rats using Immunohistochemistry (IHC) demonstrate that SR-B1 is primarily localized in the oocytes, theca interna cells of follicles, interstitial cells, and corpus luteum during the estrous cycle, but not in granulosa cells (Svensson *et al.*, 1999; Landschulz *et al.*, 1996). Weak staining was seen in stromal cells and it was discovered that uterine SR-B1 was expressed in circular muscle cells, glandular epithelial cells, and endometrial luminal epithelial cells. During the estrous cycle, ovarian SR-B1 expression varied with stage. It linearly raised from proestrous to metestrous phase, while uterine SR-B1 dropped from proestrous to diestrous (Wang *et al.*, 2015). After receiving estrogen therapy, the ovary's corpus luteal cells showed significantly higher levels of SR-B1 mRNA and protein. Wang *et al.* investigated the significance of sex hormones in relation to ovarian and uterine SR-B1 By administering 17 β-estradiol (E2), progesterone, or their antagonists to immature rats. And they found that; E2 significantly up-regulates the expression of SRB-1 in both the ovary and uterus, which indicates that SR-B1 is involved in follicular maturation as well as uterine and luteal function (Wang *et al.*, 2015).

Expression and microvillar localization of SR-BI in Leydig cells as well as Sertoli cells of testes indicate steroidogenic properties (Landschulz *et al.*, 1996; Shiratsuchi *et al.*, 1999) and play a decisive role in the maintenance of male reproductive function. As the primary receptor responsible for the selective influx of HDL-derived CEs, SR-B1 is essential for providing the necessary cholesterol substrates required for steroidogenesis in the Leydig cells for the biosynthesis of testosterone (Azhar *et al.*, 2003), supporting spermatogenesis. In-vitro studies have shown valuable insights into the functions of SR-B1 in tests. Azhar *et al.* (1998) highlighted that the expression of SR-B1 drastically increased by gonadotropin treatment, which also increases the selective uptake and internalization of lipoprotein-derived CE in Leydig cells- that is observed by HDL-BODIPY-CEs. However, since the SR-B1 knockout mice seem to be fertile, some studies indicate that the expression of SR-B1 is not necessary for male mice fertility (Rigotti *et al.*, 2003; 1997).

## *SR-B1 in Macrophages and other Tissues*

Macrophages are the paramount components of the innate immune system and play an important role in initiating various adaptive immune responses. Multiligand receptor SR-B1 recognizes a variety of ligands, including modified lipoproteins, pathogenic microorganisms, and apoptotic cells. The binding of these diverse ligands to SR-B1 on macrophages leads to internalization, contributing to the cell debris clearance and initiation of immune response (Rigotti *et al.*, 2003). In addition, SR-B1 has been implicated in the macrophages' preferential absorption of CE from HDL. Various studies revealed that the expression is increased by peroxisome proliferator-activated receptors (PPARs), testosterone and AGEs (Chinetti *et al.*, 2000; Iwashima *et al.*, 2000; Langer *et al.*, 2002) and decreased by Lipopolysaccharide (LPS), Tumor Necrosis Factor- α (TNF-α) and interferon- γ in macrophages (Buechler *et al.*, 1999).

SR-B1 is expressed in the intestine, which is involved in the utilization of dietary cholesterol. In the mouse model, Voshol *et al.* (2001) found that intestinal SR-B1 expression was transcriptionally regulated by bile components. Expression of SR-B1 in the keratinocytes of the skin is increased by simvastatin, an inhibitor of cholesterol synthesis, and decreased by 25-hydroxycholesterol, which suggests expression of SR-B1 in keratinocytes is regulated by cellular cholesterol levels (Tsuruoka *et al.*, 2002).

### *SR-B1 in the Disease States*

Owing to its various functions, SR-B1 has been implicated in a range of diseases, including cardiovascular diseases, metabolic disorders, cancer, and infertility.

### *SR-BI and Cardiovascular Disease*

The intrinsic purpose of SR-B1 in cholesterol homeostasis makes it a tangible target in cardiovascular health. Studies in mouse models have shown that partial or total loss of SR-B1 expression leads to early atherosclerosis (Shen *et al.*, 2018; Braun *et al.*, 2002; Covey *et al.*, 2003). Similarly, overexpression of hepatic SR-B1 has been implicated in decreased atherosclerosis (Komori *et al.*, 2008). SR-B1 regulates endothelial function, promoting HDL signaling for RCT and nitric oxide synthesis, indicating its anti-atherogenic actions (Yu *et al.*, 2021). HDL stimulates endothelial nitric oxide synthase via SR-B1 and its adaptors. PDZ domain-containing protein-1 promotes endothelial repair and anti-inflammatory processes (Li *et al.*, 2002). Conversely, recent studies have identified various non-hepatic mechanisms through which SR-B1 acts as a pro-atherogenic factor. In-vitro and animal models have shown that SR-B1 can deliver LDL and modified lipoproteins into arteries by transcytosis via binding to the 8 amino acid C-terminal domain of SR-B1, leading to their internalization (Yu *et al.*, 2021). The subsequent recruitment of guanine nucleotide exchange factor-dedicator of cytokinesis 4 activates Ras-related C3 botulinum toxin substrate 1 (Rac 1) and forms macrophage foam cells, which can promote atherosclerosis (Rohrer *et al.*, 2009; Huang *et al.*, 2019). SR-B1 expression on macrophages has been associated with the release of inflammatory cytokines, further exacerbating the inflammatory environment within the arterial wall (Tsukui *et al.*, 2023; Gracia-Rubio *et al.*, 2021). Contrarily, the macrophage SR-B1 initially encourages cholesterol efflux and reverse cholesterol transport, lowering macrophage foam cell formation. Crucially, SR-B1 may inhibit plaque formation by mediating macrophage apoptosis as an outcome of cholesterol load. Apoptosis of macrophages is thought to be atheroprotective in early lesions, but it encourages the development of atherosclerosis in later stages (Van *et al.*, 2004). Galle-Treger *et al.* (2020) revealed accelerated aortic atherosclerosis characterized by decreased macrophage apoptosis activity induced by Apoptosis Inhibitor of Macrophage (AIM) in a mouse model. Indeed, phagocytosis of apoptotic cells, including macrophages (efferocytosis), significantly limits the development of plaque necrotic cores in the late atherosclerotic lesions (McCarthy *et al.*, 2009), suggesting macrophage SR-B1 as a new target in CVD.

### *SR-B1 and Metabolic Disorders*

The SR-B1 has also been implicated in the development of metabolic disorders, including Type 2 Diabetes Mellitus (T2DM) and Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD). Polymorphisms in the SR-B1 receptors are associated with the emergence of insulin resistance and T2DM (Tetik Vardarlı *et al.*, 2017; Wamique *et al.*, 2022). Murao *et al.* (2008) reported that activation of p38 Mitogen-Activated Protein Kinase (MAPK)- Specificity Protein-1 (Sp1) pathway regulatory genes mediate the inhibitory effect of hyperglycemia on SR-B1 promoter activity paving the way for accelerated atherosclerosis in diabetic patients (Wamique *et al.*, 2020).

SR-B1 has been linked to the pathogenesis of MASLD, previously termed Metabolic-Associated Fatty Liver Disease (MAFLD). MASLD is defined as the buildup of excess triglycerides in the liver combined with at least one cardiometabolic risk factor, such as type 2 diabetes or being overweight (European Association for the Study of the Liver (EASL) *et al.*, 2024; Higarza *et al.*, 2025). The dysregulation of SR-B1 has been associated with impaired cholesterol trafficking, which can promote the development of fatty liver (steatosis) and the progression to more severe liver diseases, such as Metabolic Dysfunction-Associated Steatohepatitis (MASH) to Hepatocellular Carcinoma (HCC). Several animal models have been studied, which demonstrate the expression of SR-B1 influencing the high-fat diet associated with dyslipidemia, CVD risks, and hepatic steatosis (Rivera *et al.*, 2020; Malhotra *et al.*, 2020). SR-B1 has been linked to controlling inflammatory processes in the liver and its function in lipid metabolism. Recent studies have linked the important role that inflammation and lipid metabolism play in the pathophysiology of MASLD and SR-B1 may be a major mediator of this relationship (Wang *et al.*, 2021). Adipocyte inflammation, a hallmark feature of central obesity, reduces the expression of SR-B1 and ABCA1 which further reduces the cholesterol efflux and, therefore HDL-C (Stadler *et al.*, 2020). Animal models have shown accelerated inflammation of adipose tissue in the high-fat diet-fed SR-B1 knockout mice; however, loss of SR-B1 expression also protected them against the development of hepatic steatosis (Rivera *et al.*, 2021; Hoekstra *et al.*, 2015). Whether the same is reproducible in human subjects needs confirmation. Taken together, by regulating the uptake and metabolism of lipids in the

liver and influencing the inflammatory response, SR-B1 appears to be a promising target for treating this prevalent liver disease.

### *SR-B1 and Cancer*

Emerging evidence suggests that SR-B1 may also play a crucial role in the development and progression of certain types of cancers. Expression of SR-B1 is often upregulated in various cancer cells, including those of prostate, breast, and ovarian origin. This increased expression of SR-B1 has been linked to enhanced cholesterol uptake from circulating lipoproteins, which can promote tumor growth and proliferation (Mooberry *et al.*, 2016). Pandey *et al.* (2021) studied prostate cancer disruption of cholesterol availability via cholesterol regulation through either synthesis or silencing SR-B1 impacts signaling pathways, motility, and proliferation. In-vitro studies have shown similar findings in cellular proliferation, migration, and tumor growth in breast cancer (Danilo *et al.*, 2013). Overexpression of SR-B1, along with the decreased plasma HDL levels in cancer patients compared with healthy controls, indicates that it could be the main source of cholesterol to the cancer cells (Cruz *et al.*, 2013). The potential of SR-B1 to attenuate tumorigenesis has prompted researchers to create reconstituted HDL (rHDL) molecules capable of a selective drug delivery mechanism and suppression of tumor growth (Danilo *et al.*, 2013; Sabnis and Lacko, 2012).

### *SR-B1 and Infertility*

SR-B1-mediated cholesterol uptake from HDL serves as a primary substrate for steroid hormone production in steroidogenic cells, essential at various stages of reproduction and fetal growth, and development. The expression and regulation of SR-B1 have been comprehensively studied in the context of the ovary and uterus for the synthesis of luteal steroid hormones by Jiménez *et al.* (2010). Animal models show that the upregulation of SR-B1 in rat ovary and uterus across the estrous cycle is involved in uterine, luteal function and follicular maturation (Wang *et al.*, 2015). Throughout the oestrous cycle, uterine SR-B1 is abundantly expressed in the stromal cells, glandular epithelial cells, endometrial luminal epithelial cells, and circular muscle cells. This differential expression pattern suggests that SR-B1 may be entailed in various uterine functions, including the provision of cholesterol for the synthesis and maintenance of endometrium, preparation for embryo implantation and its development (Wang *et al.*, 2015). Velasco *et al.* (2006) found a direct association of granulosa SR-B1 expression and estradiols in humans, suggesting its potential impact on female fertility. Supporting evidence from mouse models has shown that; downregulation of SR-B1 receptors along with increased circulating HDL hampers the developmental capacity of the eggs (Arias *et al.*, 2022). While the role of SR-B1 in ovarian physiology is well-established, its significance in testicular function and in male fertility is less clear. Estrogen receptors and androgen receptors are known to regulate critical processes during spermatogenesis and the regulation of their expression by sex steroid hormones is an unexplored area. Table (2) is a comparative table summarizing previous research on SR-B1in various disease aspects.

**Table 2:** Comparative table summarizing previous research on SR-B1's role in various diseases

| Disease states | Key findings | Experimental models | Critical insights |
|---|---|---|---|
| SR-B1 in Cardiovascular disease | SR-B1 facilitates reverse cholesterol transport (RCT), reducing atherosclerosis | SR-B1 knockout mice, human hepatocytes (in-vitro models) | While SR-B1 is protective in RCT, its overexpression in macrophages may promote foam cell formation |
| SR-B1 in Metabolic Disorders | SR-B1 deficiency exacerbates insulin resistance and dyslipidemia | High-fat diet-induced mouse models | SR-B1's role in metabolic health extends beyond lipid transport |
| SR-B1in Cancer | SR-B1 is overexpressed in breast, prostate, and ovarian cancers, promoting tumor growth and metastasis | Cancer cell lines | SR-B1's role in cholesterol uptake may fuel cancer cell proliferation, but its immune-modulatory role is underexplored |
| SR-B1 in Infertility | Downregulation of SR-B1 receptors hampers the developmental capacity of the eggs. | Mice models | While the function of SR-B1 in ovarian physiology is well-established, its significance in testicular function and in male fertility is less clear. |

## Conclusion

Emerging findings highlight the diverse and complex roles of SR-B1 in tissues beyond the traditional areas of lipid metabolism and transport. It has a multifaceted role in the modulation of cholesterol homeostasis, active participation in inflammatory signaling pathways, and its interactions with various transcription factors and inflammatory mediators, making it a subject of intense research. Although current strategies, including small-molecule inhibitors, HDL mimetics, and gene therapy, offer potential, significant challenges persist in terms of specificity, delivery, and safety. Further evidence-based research and clinical trials are needed to explore its potential as a therapeutic target in various disease contexts and its potential as a biomarker for disease risk assessment. The dual role of SR-B-1 in the non-hepatic

mechanisms needs further attention to elicit its role in the pathogenesis of disparate disease states.

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## Author's Contributions

**Sujina Simon Sailet**: Drafting and writing the manuscript.

**Poornima Ajay Manjrekar**: Conceptualization and design.

**Santosh Rai**: Review of the initial version.

**Bailuru Vishwanath Tantry**: Review of the final version.

**Deenadhayalan Ashok**: Collecting articles and drafting.

## Ethics

The submitted manuscript is a review article and does not involve any ethical concerns.

### *Conflict of Interest*

The authors declare that they have no conflicts of interest.

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