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Review

# Role of scavenger receptors in dendritic cell function

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ABSTRACT

Dendritic cells (DCs), the most potent of the antigen-presenting cells, are crucial in initiating and shaping innate and adaptive immune responses. DCs discriminate unmodified self antigens from non-self and altered/modified self antigens via a large family of receptors called pattern-recognition receptors, which include Toll-like receptors and scavenger receptors (SRs). Recent findings underscore the critical role of SRs on DCs in pathogen clearance, atherosclerosis, apoptotic cell recognition, diesel exhaust particle recognition, etc. These new findings present SRs as an unexplored therapeutic target that warrants further basic and applied research, and have implications for vaccine development. This review highlights recent insights into the emerging role of these receptors in DC-mediated immune responses.


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## 1. Introduction

Dendritic cells (DCs), the most potent of the antigen-presenting cells (APCs), are crucial for initiating and shaping innate and adaptive immune responses [1]. DCs play different roles in immunity, such as the activation and regulation of adaptive immune responses, restoration of the resting state, maintenance of self-tolerance, and anergy [2]. DCs can discriminate unmodified self antigens from non-self and altered/modified self antigens via a large family of receptors called pattern-recognition receptors, which include signaling receptors (such as Toll-like receptors [TLRs]) and endocytic receptors (such as scavenger receptors [SRs]) [3,4]. Upon stimulation of pattern-recognition receptors by non-self and altered/modified self signals, DCs undergo activation/maturation to an immunogenic phenotype, resulting in the overexpression of major histocompatibility complex (MHC), costimulatory molecules (CD80, CD86), and cytokines, and promoting the activation of naive T-cells [5]. This process ensures the transfer of molecular information collected in the periphery to other immune cell types such as neutrophil granulocytes, T-lymphocytes, B-lymphocytes, natural killer (NK), and NKT cells. DCs play

*Abbreviations:* DCs, dendritic cells; APCs, antigen-presenting cells; TLR, Toll like receptors; SR, scavenger receptors; SR-A, scavenger receptor; HCV, hepatitis C virus; oxLDL, oxidized LDL; mBSA, maleylated bovine serum albumin; DEP, diesel exhaust particles; LPS, lipopolysaccharide.

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a pivotal role in inflammatory diseases, autoimmune diseases, and cancer as well as in the designing of new types of vaccines based on DC biology. Investigating the underlying mechanisms of DC–pathogen interactions may help us to better comprehend the immune response in physiological and pathological events and to identify new targets for therapeutic intervention.

SRs were first defined by Goldstein and Brown, and were originally identified by their ability to recognize and remove modified lipoproteins involved in cholesterol and lipoprotein metabolism [6]. However, several reports have showed that some SRs can also recognize unmodified lipoproteins, and studies have supported the role of SR-mediated endocytosis of modified low-density lipoprotein (LDL) in foam cell formation and atherosclerosis [7]. Recent studies have demonstrated the critical role of SRs (CD36 and SR type B, class I [SR-BI]) in platelet hyperreactivity in dyslipidemia and atherosclerosis progression [8]. SR-BI deficiency in mice results in enhanced lymphocyte proliferation and altered cytokine production [9]. SRs carry out a striking and broad range of functions, such as pathogen clearance, apoptotic cell clearance, lipid transport, cellular adhesion, intracellular cargo transport, and even taste perception [8,10–15].

Currently, SRs are recognized to be a large family of structurally diverse, transmembrane and cell-surface glycoproteins restricted to macrophages, DCs, endothelial cells, and a few other cell types [16]. DCs are unique APCs that have the ability to stimulate naive T-cells [17]. The priming and expansion of naive T-cells depend on efficient antigen presentation by the surface receptors on DCs. A recent study reported that cell-surface SR-BI expression is very low or undetectable on human monocytes, T-cells, and B-cells, but high on human DCs and primary human hepatocytes [18]. SR-BI expression is induced during the differentiation of monocytes into DCs [18,19]. These findings indicate that SRs might play a specific role in DC function. Therefore, in this review, we highlight recent insights into the emerging roles of SRs on DCs in the initiation and shaping of innate and adaptive immune responses, notably, in pathogen clearance and atherosclerosis formation.

## 2. Pathogen clearance

DCs are pivotal in the initiation of immune responses to control and eliminate viral and microbial infections. SRs have been reported to play crucial physiological roles in innate immune defense by recognizing several different microbial structures and microbial-surface proteins [12,20,21]. SRs act as phagocytic receptors mediating direct, non-opsonic phagocytosis of pathogenic microbes by macrophages and DCs, and some SRs (such as CD36) have been shown to act as coreceptors for TLRs in responses to microbial diacylglycerides [8,22].

The class A macrophage SR (SR-A) on DCs may dampen the pro-inflammatory response or products to pathogenic microbes. Becker et al. showed that the expression of murine SR-A is restricted to specific subpopulations of $CD11b^{+}DEC\text{-}205^{+}MHCII^{+}$ bone marrow-derived DCs (BM-DCs) and $CD11b^{+}CD4^{-}B220^{-}CD80^{int}CD86^{hi}$ splenic DCs [23]. They demonstrated that the receptor significantly limited DC maturation in response to endotoxin; $SR\text{-}A^{-}$/dyslipidemia BM-DCs display enhanced expression of the costimulatory molecule CD40 and increased production of the pro-inflammatory cytokine tumor necrosis factor-α (TNF-α) upon lipopolysaccharide (LPS)-driven maturation. In another study, phagocytosis and uptake of *Neisseria meningitidis* by human DCs via SR-A were shown to increase the release of TNF-α, interleukin (IL)-1β, and IL-6; the enhanced secretion of IL-8 after recognition was not dependent on phagocytosis [24].

Malaria is a devastating disease that inflicts enormous morbidity and mortality, and is caused by the protozoan parasites, *Plasmodium* species [25]. Although several *Plasmodium* species cause malaria, *Plasmodium falciparum* accounts for the majority of malarial deaths in humans [26]. Studies have demonstrated that CD36 mediates the binding of *P. falciparum*-infected red blood cells (iRBCs) to human monocyte-derived DCs and reduces the production of TNF-α and IL-12 [27]. Gowda et al. recently determined the levels of CD36-adherent iRBCs internalized by and the levels of pro-inflammatory cytokines produced by human DCs treated with anti-CD36 antibody and by CD36-deficient murine DCs [28]. Their results confirmed that CD36 contributes significantly to the uptake of iRBCs and the production of pro-inflammatory cytokines by DCs; moreover, DCs with internalized iRBCs could activate NK and T-cells to produce interferon (IFN)-γ. Furthermore, they implied that the effect of CD36 on the anti-malarial immunity conferred by DCs is imprinted early during infection when the parasite load is low [28].

Among the blood-borne viruses, hepatitis C virus (HCV) is a major cause of chronic liver inflammation worldwide. Over 75% cases of HCV infection develop into persistent disease that can ultimately progress to cirrhosis and hepatocellular carcinoma [29,30]. DCs play crucial roles in the initiation of antiviral immunity. Although the role of DCs in HCV infection has been extensively studied, the molecular mechanisms of HCV antigen uptake and processing by blood DCs are poorly understood. Some groups have proposed that SRs play a role in HCV-related adaptive immune responses by DCs [31,32].

SR-BI has been demonstrated to play a prominent role in HCV binding and uptake by human monocyte-derived DCs [18]. SR-BI expression was found to continuously increase during the differentiation of monocytes into DCs, and correlate with the initiation of the binding of HCV-like particles (HCV-LPs). These findings indicate that SR-BI may target HCV antigens in the cytosol, where the antigens gain access to the MHC class I presentation pathway; this is followed by efficient cross-presentation to HCV-specific $CD8^{+}$ T-cells. This novel function of SR-BI is further supported by the observation that high-density lipoprotein (HDL) enhances and anti-SR-BI markedly inhibits the binding of HCV-LPs to DCs. Finally, very low expression of SR-BI was observed on both the myeloid and plasmacytoid subsets of DCs, compared to the expression on in vitro-generated monocyte-derived DCs [18]. In addition, the same group reported in a later work that the acquisition of HCV in cell culture by ex vivo, isolated human myeloid DCs was not markedly altered in the presence of SR-BI antibody [33]. These findings were supported by Marukian et al. who reported that the level of SR-BI RNA expression in human blood DC subsets was >3-log lower than the expression level in in vitro-generated monocyte-derived DCs [34]. Beauvillain et al. [35] demonstrated that maleylated-bovine serum albumin, a ligand of most SRs, inhibited HCV nonstructural protein 3 (NS3) binding to human DCs. Furthermore, by using SR-expressing Chinese hamster ovary (CHO) cells, they observed that NS3 bound to SR-A1- and SR expressed on endothelial cells-I (SREC-I)-transfected CHO cells but not to CHO cells expressing other SRs. Moreover, both SRs and TLR2 contributed to NS3-induced myeloid cell activation [35]. In addition, SR-A and SREC-I participated in the cross presentation of NS3 by DCs, via a mechanism involving the endocytosis of exogenous antigens from infected dying or dead cells by peripheral or intrahepatic DCs, antigen processing in the cytosol/endosomal compartment, and "cross routing" to the MHC I pathway [36,37]. These data are very relevant to increase our knowledge of the mechanisms involved in HCV infection and facilitate the development of effective vaccines against HCV infection [38].

Furthermore, it has been shown that antigens complexed to heat shock protein 90 (Hsp90) can be specifically bound by SREC-I, endocytosed, and MHC-I cross-presented by murine BM-DCs [39]. It has also been observed that SREC-I can bind and