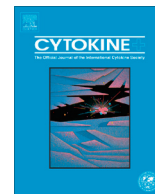




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## Emerging roles for scavenger receptor SREC-I in immunity

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## ABSTRACT

SREC-I is a class F scavenger receptor with key role in the immune response, particularly in antigen presenting cell (APC) such as macrophages and dendritic cells (DC). This receptor is able to mediate engulfment of dead cells as well as endocytosis of heat shock protein (HSP)–antigen complexes. SREC-I could thus potentially mediate the tolerizing influence of apoptotic cells or the immunostimulatory effects of HSP–peptide complexes, depending on context. This receptor was able to mediate presentation of external antigens, bound to HSPs through both the class II pathway as well as cross presentation via MHC class I complexes. In addition to its recently established role in adaptive immunity, emerging studies are indicating a broad role in innate immunity and regulation of cell signaling through Toll Like Receptors (TLR). SREC-I may thus play a key role in APC function by coordinating immune responses to internal and external antigens in APC.

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## 1. Introduction

Scavenger receptors are a family of receptors that have in common the ability to bind to covalently modified proteins, most notably oxidized low density lipoprotein (oxidized LDL). The scavenging of oxidized LDL by endothelial cells plays a significant role in sparing organisms from pathologies such as atherosclerosis [1]. Interestingly the scavenger receptor family is grouped along functional lines and most such proteins have little sequence similarity [2,10]. One mystery associated with this protein family is that, although there is minimal homology in primary structures among scavenger receptor families, they can associate with a similar and equally diverse group of ligands [1,3]. SREC-I (Scavenger Receptor expressed by Endothelial cells), a member of the class F scavenger receptor family, 85.7 kD protein was first cloned from HUVEC (Human Umbilical Vein Endothelial Cells) cells and termed as scavenger receptor expressed by endothelial cells [2,26,31]. The primary structure of this scavenger receptor had minimal similarity with those of most other scavenger receptors previously characterized, although SREC-II which is a member of this same family was shown to have some common features in terms of the extracellular domains [12,26]. The extracellular domain of SREC is also similar to that of Fecl-1 [22]. The extended extracellular domain (ED) of the class F receptors is comprised of epidermal

growth factor like cysteine rich motifs (EGF repeats) while the unusually long intracellular domain contains a serine–proline rich region [25]. SREC-1, particularly in the ED, has significant homology with the *Caenorhabditis elegans* protein CED-1, a polypeptide involved in the uptake of apoptotic bodies [27]. Additional cell corpse engulfing proteins such as MEGF10, MEGF11 and MEGF12 are also CED-1 paralogs and, like SREC-I contain multiple EGF repeats within the ED [20,27]. Like other scavenger receptors the class F family are defined by their ability to bind, internalize and metabolize modified LDL species, such as acetylated (Ac) LDL, oxidized (Ox) LDL, a process involved in the pathogenesis of atherosclerosis [15,25,28]. It was also characterized as an endocytic receptor for calreticulin [4]. In addition to their roles in binding and internalizing these modified lipids, SREC-I was also shown to participate in other cellular functions such as cell–cell adhesion, antigen cross presentation, engulfment of apoptotic cells and innate immunity. The cell adhesion properties may involve SREC-I interaction with SREC-II counter-receptors on the partner cell [26]. SREC-I can also cooperate with pattern recognition receptor function in innate immunity (see below). This receptor has an additional role in mediating morphological changes when overexpressed in a fibroblasts suggesting its participation in morphogenesis of cells (A. Murshid, unpublished studies). The intracellular domain of SREC-1, which is extensive compared with that of other scavenger receptors, is largely uncharacterized. However, it has been shown that this cytosolic domain is capable of interacting with protein phosphatase 1 $\alpha$  (PP1  $\alpha$ ) in L cells and thus mediating morphological changes [13].

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## 2. SREC-I and antigen cross presentation

SREC-I has been shown to be a key receptor for heat shock proteins [8,29]. The physiological significance of extracellular HSPs is not entirely clear, although they are known to play key roles in the immune response [7]. HSPs can be immunostimulatory when associated with tumor antigens, transporting the chaperoned antigens into AP. In contrast, in different contexts, HSPs can play immunoregulatory roles and suppress T cell mediated immunity in inflammatory diseases [5,24]. We have attempted to discover physiologically relevant HSP receptors. We carried out forced expression of candidate receptors in a cell line, CHO that is null for HSP binding then assayed binding of fluorescently labeled Hsp70 or Hsp90 to those receptors expressing cell. Hsp70 was found to bind Class E receptor Lox-1, Class F receptor SREC-I and Class H receptor Feel-1/stabilin-1 [29]. In addition, Hsp70 was found to bind to some NK receptors found on the surface of natural killer cells [29]. As most of our studies have centered on SREC-I we will discuss this receptor in more detail in this review. SREC-I, in common with another scavenger receptor, LOX-I can bind with high avidity to HSPs, including Hsp70, Hsp90, Grp94, Hsp110 and Grp170 with or without associated antigens and appears to be an important common receptor for these proteins [3,19,21]. In addition, among all the scavenger receptors that have been characterized so far, we found that SREC-I and LOX-1 each appeared to mediate the majority of the cross presentation of the Ova SIINFEKL epitope chaperoned by Hsp90 or Hsp70 in BMDC [21].

Earlier it was demonstrated that HSP–antigen complexes could be bound to SREC-I and internalized in antigen presenting cells such as dendritic cells (DC) and macrophages (as well as a large variety of tissue culture cell lines [21]). An Hsp90–antigen–SREC-I internalization pathway was characterized in these cell types which was similar to a previously described mechanism involving *tubule like vesicles formation upon uptake of ligand–receptor complex* and known as CLIC (Clathrin independent carriers) or GEEC (GPI anchored protein-enriched endocytic compartments) [9,10]. This pathway is distinct from endocytic mechanisms involving Clathrin and is heavily utilized by GPI-anchored proteins [32]. Although the significance of entry of HSP–SREC-I complexes through the CLIC/GEEC pathway is not entirely clear, this mechanism does appear to permit regulation of antigen cross presentation by signal transducing molecules as discussed below. Hsp90–polypeptide–SREC-I complexes were able to mediate cross presentation of external chaperoned antigens, mediating processing in both endosomal and proteasomal compartments.

It is not clear to what degree the antigen presentation pathways involved with HSP-chaperoned antigens are similar to those used by other forms of antigens. For free, unchaperoned antigens, dedicated receptors have been shown to direct antigens to either the MHC class II pathway or to cross-presentation via the MHC class I complexes [6,11]. We have demonstrated that antigens bound to Hsp90 could be internalized via SREC-I and later processed. Internalized antigens could be loaded onto either MHC class I (cross presentation) or MHC class II molecules (class II presentation). It is not known whether the scavenger receptor mediates triage between the two MHC pathways or whether the choice of pathways is stochastic. Antigen presentation then led to specific activation of both CD8<sup>+</sup> and CD4<sup>+</sup> T cells. In these parallel MHCI and MHCII antigen presentation pathways, SREC-I engagement by Hsp90-bound antigens increased Cdc42 GTPase activity, regulating actin assembly and polymerization and other signaling pathways such as Src kinase signaling [33,41].

Receptor mediated internalization of Hsp90 bound antigens rather than non-specific internalization of free antigens has two potential advantages. Such HSP chaperoned antigens can be

protected from proteolysis during trafficking through the cell compartments and thus reduced amount of antigen would be required to initiate both CD4<sup>+</sup> and CD8<sup>+</sup> T cell priming [23]. It is however clear that we understand chaperone mediated antigen cross priming only in outline so far and that considerable further investigations are required in order to understand the basic mechanisms involved. SREC-I thus plays a key role in receptor-mediated uptake of chaperone-bound antigen presentation, protecting and transporting its charges to the key intracellular sites.

## 3. Role of SREC-I in apoptotic cells engulfment

The elimination of defective and unwanted cells by apoptosis is an essential process for maintenance of tissue homeostasis as well as contributing to tumor regression in cytotoxic therapies. A rapid and immunologically clean removal of these apoptotic cells is crucial for evading inflammation, immune tolerance and homeostasis [34]. Phagocytic cells recognize and engulf these dying cells through several surface receptors expressed by these cells or by the interaction of bridging soluble proteins that recognize “find-me” and “eat-me” signals presented in apoptotic cells, as lipid lysophosphatidylcholine (LPC) and phosphatidylserine (PS) [35].

The first suggestion that SREC-I could participate in the recognition and engulfment of apoptotic cells was when the transmembrane protein CED-1 from *C. elegans* was identified as an ortholog of human SREC-I. CED-1 was reported to be responsible for the recognition and internalization of apoptotic cells by *C. elegans*. This receptor has a sequence similarity and shares a similar overall structure with SREC-I [36]. Using GFP under control of *ced-1* promoter, it was demonstrated that CED-1 is expressed at high levels in cells that can act as endocytic cells along the surface of cell corpses but not in the dying cell. Mutations in the *ced-1* gene that cause loss of protein function resulted in a phenotype characterized by cell corpse retention, indicating that CED-1 is required for identification and engulfment of apoptotic cells in *C. elegans* [36].

More recently it was demonstrated that DC, macrophages and endothelial cells expressing SREC-I could bind phosphatidyl serine moieties exposed on the apoptotic cell surface [37]. Additionally, the same group demonstrated that CD8 $\alpha$ <sup>+</sup> DCs expressing higher levels of SREC-I were more capable of engulfing dying cells or apoptotic cells than those of SREC-I<sup>−/−</sup> mice. Forced expression of SREC-I in these SREC-I<sup>−/−</sup> DCs reversed the phenotypes and enhanced uptake of dying cells. These findings indicated a role of SREC-I in apoptotic cell engulfment and removing dying cells. Additionally these knock-out mice had a spontaneous lupus-like disease, with the presence of autoantibodies, indicating that impairment in the SREC-I-mediated clearance of apoptotic cells contributes to development of this autoimmune disorder [37].

## 4. Signaling through SREC-I

In addition to internalizing HSP-bound peptides, ligand-bound SRECI appears to play a significant role in cell signaling. These signaling properties appear to be related to the appearance of SREC-I in lipid rafts after binding ligands such as Hsp90 [21]. Lipid rafts are cholesterol and sphingolipid-rich membrane microdomains, floating in the bulk membrane, that can concentrate molecules involved in cell signaling [18]. Although lacking the glycerophosphoinositide anchor domain motifs found in many raft-associated membrane proteins, SREC-I contains other motifs that would permit it to associate with lipid rafts [22]. The S-acylation of cysteine residues close to the transmembrane domain, with highly saturated palmitate residues, that can dissolve in the environment of the lipid raft has been associated with the ability of cells without

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