RESEARCH HIGHLIGHT

# Implications of scavenger receptors in the safe development of nanotherapeutics

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**Nanomaterials (NMs) are being utilized in a variety of biomedical applications including drug delivery, diagnostics, and therapeutic targeting. These applications are made possible due to the unique physicochemical properties that are exhibited at the nanoscale. To ensure safe development of NMs for clinical use, it is necessary to understand their interactions with cells and specifically cell surface receptors, which will facilitate either their toxicity and/or clinical function. Recently our research and others have investigated the role of scavenger receptors in mediating NM-cell interactions and responses. Scavenger receptors are expressed by a variety of cell types that are first to encounter NMs during clinical use such as macrophages and endothelial cells. Scavenger receptors are recognized to facilitate uptake of a wide variety of ligands ranging from foreign substances to endogenous lipids/proteins. While interaction of NMs with scavenger receptors may allow therapeutic targeting in some instances, it also presents a challenge for the stealth delivery of NMs and avoidance of the scavenging capability of this class of receptors. Due to their role in facilitating immune responses, scavenger receptor-mediated inflammation is also of concern following NM delivery. The research highlighted in this brief review intends to summarize our current understanding regarding the consequences of NM-scavenger receptor interactions.**

***Keywords:*** SR-A; SR-B1; MARCO; CD36; Mast Cell; Macrophage; Nanotoxicology; Nanomedicine; Nanoparticle

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## Introduction

Nanomaterials (NMs) possess an impressive array of unique physicochemical properties allowing for their use in numerous applications. NMs are uniformly synthesized particles with one dimension less than 100 nm that can be designed to have diverse shape, chemical composition, size, electrothermal conductance, and solubility. They can also be modified through the addition of various surface groups further altering their characteristics. These modifiable properties allow for a broad range of applications including their incorporation into medical devices, consumer products, manufacturing processes, and their use as nanomedicines. Within the field of nanomedicine, NMs are useful for drug delivery, protein and peptide delivery, therapeutic targeting, and imaging [1]. In general, the NMs presently being used can be classified as carbon-based, metal/metal oxides, dendrimers, or composites.

Due to the rapid development of NMs with many diverse characteristics as well as their increased usage in medical applications, the screening of NM-induced toxicity is necessary for safe clinical use. To understand how to appropriately design and engineer NMs it is necessary to understand how they interact biologically on a cellular level. The interactions with cells are primarily mediated by

cell-surface receptors and the interactive interface of the NM, which is determined by its physicochemical properties. Recently, the scavenger class of receptors has gained attention as a group of receptors, which may be targeted for the application of NMs. Further, scavenger receptors may also mediate possible NM toxicity and adverse health effects. Elucidating interactions between NMs and scavenger receptors is necessary for the safe development of NMs for widespread clinical applications.

**Scavenger Receptors**

Scavenger receptors are expressed by a variety of cell types including macrophages, dendritic cells, endothelial cells, and epithelial cells. These pattern recognition receptors recognize a number of ligands including oxidized-lipoproteins, pathogens, and negatively charged foreign particles. Binding of these ligands facilitates cellular uptake and ligand removal. Association of scavenger receptors with their ligands has also been shown to induce pro-inflammatory immune responses. Scavenger receptors are well known for their role in lipid metabolism and atherosclerosis development. Recently, they have been shown to be involved in the recognition, uptake and cellular responses to NM exposure. Scavenger receptors are classified based on structure into three types Class A, Class B, and Class C. To date research has identified roles for Class A and Class B scavenger receptors in the removal and cellular responses to NMs. Currently most investigation has focused on Class A scavenger receptors however our research has recently examined the role of Class B scavenger receptors.

**Scavenger Receptor Class B**

Class B scavenger receptors (SR-B) include SR-B1 and CD36 which have two hydrophobic transmembrane domains [2]. They express a heavily N-glycosylated extracellular domain and an intracellular C-terminal domain that interacts with PDZK1, a multisubunit adaptor protein. PDZK1 is important for SR-B mediated cell signaling. Typically SR-B type receptors are located in lipid rich regions of the cell's plasma membrane such as the caveolae. SR-B type receptors have affinity for a number of ligands including unmodified low-density lipoproteins, oxidized low-density lipoproteins, high-density lipoproteins, and apoptotic cells. The high affinity of SR-B class of receptors for lipoproteins suggests a critical role in lipoprotein metabolism. Mice deficient in the SR-B1 receptor have demonstrated increase plasma levels of cholesterol compared to wild-type mice supporting the role of SR-B1 in cholesterol metabolism [3]. SR-B receptors are expressed in a number of cell types including platelets, macrophages, hepatocytes, endothelial cells and epithelial cells. Endothelial and epithelial cells however express SR-B1 on their surface as their primary scavenger receptor [4-6]. Specifically, SR-B1 expression levels have been shown to be regulated by cholesterol metabolism and trophic hormones [7].

SR-B receptors are a potential target for a variety of nanotherapeutics and diagnostic applications. For example Gadolinium-containing NMs with anti-CD36 antibodies have been produced for early magnetic resonance imaging of atherosclerosis [8]. These NMs are taken up more efficiently by macrophages *in vitro* and within human aortic specimens as compared to non-targeted NMs lacking the CD36 antibodies. The SR-B1 receptor is also highly expressed in human nasopharyngeal carcinoma. This increased expression of SR-B1 in nasopharyngeal carcinoma makes it a likely biomarker of disease as well as a therapeutic target. Synthesized HDL-mimetic nanoparticles were found to have a high affinity for SR-B1 rich cancer cells likely allowing for the development of theranostic approaches [9]. Further, HDL nanoparticles have been utilized for the delivery of siRNA therapeutics to malignant tumors expressing high levels of SR-B1 in mouse models [10]. These HDL nanoparticles also have been shown to deliver paclitaxel to prostate cancer cells through SR-B1 mediated uptake[11]. These studies demonstrate the potential for targeting of nanoparticles via the SR-B1 receptor in several disease states. However, nanotherapeutics designed for other applications may have to evade SR-B1 receptor-mediated clearance by macrophages and other cells to avoid reduction in retention times, due to their high levels of SR-B1 expression.

Silver nanoparticles (AgNPs) are being utilized for a variety of consumer products and biomedical applications due to their antimicrobial properties [12, 13]. These antimicrobial effects occur following uptake of AgNPs into cells and subsequent ionic dissolution resulting in cytotoxicity. Macrophage uptake of AgNPs has been shown to be scavenger receptor-mediated through the use of a general pharmacologic inhibitor of scavenger receptors, dextran sulfate [14]. Interestingly, dextran sulfate has been proposed as a possible surface coating to avoid immune cell uptake and increase delivery of nanoparticles to target tissues. Uptake of AgNPs through scavenger receptors resulted in their accumulation in the cytoplasm of macrophages and the induction of apoptosis [14]. Recently, our group and others have identified a specific role for the SR-B receptor class in mediating cellular uptake and toxicity following AgNP exposure. Specifically, we have demonstrated that through pharmacological inhibition of SR-B1 with 2-(2-butoxyethyl)-1-cyclopentanone thosemicarbazone (Blt-2), uptake of AgNPs was reduced in endothelial and epithelial cells [15]. Further by coating AgNPs

with various individual proteins (human and bovine serum albumin and mouse HDL) uptake was reduced. Coating of nanoparticles with these proteins reduced the zeta potential of the AgNPs suggesting that these reductions in uptake were in part driven by surface charge. Interestingly however, coating of AgNPs with HDL resulted in increased mRNA expression of IL-6 by endothelial cells as compared to non-coated AgNPs. This increased expression was reduced following inhibition of SR-B1 with Blt-2. Although coating AgNPs with HDL reduced SR-B1-mediated uptake, endothelial cellular inflammatory responses were exacerbated. This finding suggests multiple roles for the SR-B1 receptor including inflammatory signaling that is not solely uptake dependent.

To increase the retention time of nanotherapeutics it is necessary to evade clearance mechanisms such as the innate immune system. Further NMs, which interact with cells of the innate immune system, can trigger immune responses resulting in unintended toxicity. Macrophages are the primary innate immune cell responsible for the recognition of foreign pathogens and substances, and their subsequent clearance. We have demonstrated *in vitro* that macrophage uptake of AgNPs is also mediated through SR-B1 receptor recognition [16]. Specifically, we demonstrated that SR-B1 inhibition by use of the pharmacological inhibitor Blt-2 resulted in decreased macrophage uptake of AgNPs. Further, inhibition of SR-B1 resulted in reduced AgNP-induced macrophage protein expression of the inflammatory cytokine oncostatin M as well as inhibition of cell surface expression of CD86, which is responsible for macrophage mediated T cell activation. These *in vitro* findings demonstrate that SR-B1 is involved not only in the uptake of AgNPs but also the stimulation of the immune system through the release of pro-inflammatory cytokines and up-regulation of co-stimulatory molecules. In a mouse model utilizing the pharmacological inhibitor Blt-2 and also in a SR-B1 deficient mouse model we verified the role of SR-B1 in macrophage uptake and response to AgNPs. Following inhibitor treatment, macrophages were found to have reduced uptake of AgNPs as well as reduced inflammatory responses as measured by neutrophilic influx and IL-6 mRNA expression. Macrophages from SR-B1 deficient mice were found to internalize fewer AgNPs and had a blunted inflammatory response as measured by neutrophilic influx and IL-6 mRNA expression. Bone marrow-derived macrophages that do not express the SR-B1 receptor demonstrate reduced uptake of AgNPs as well as inflammatory responses. These blunted responses are not to the same degree as treatment with the pharmacological inhibitor of SR-B1, Blt-2. These exacerbated reductions in responses with the pharmacological inhibitor compared to knockout are likely due to an up-regulation of other scavenger receptors on their surfaces such as CD36 and class A scavenger receptors when SR-B1 is absent. In this evaluation of macrophage responses mediated via SR-B1 we also coated AgNPs with HDL a natural ligand for SR-B1. It was demonstrated that by coating the surface of AgNPs with HDL, macrophage uptake and inflammatory responses were increased *in vitro*. This enhancement of macrophage responses could be nullified through inhibition of SR-B1 with Blt-2. Overall these findings demonstrated a role for SR-B1 in the macrophage response to NMs, which will likely influence nanotherapeutic clearance, activity, and immune responses.

Recently, our laboratory has demonstrated a significant role for mast cells in mediating immune responses to NMs[17]. While mast cells are an important component of the innate immune system and found in most tissue types they are currently understudied in terms of NM toxicity. Mast cells have been primarily evaluated for their role in allergic disease and activation through IgE stimulation of the FceRI receptor leading to the release of a variety of mediators including histamine, eicosinoids and inflammatory cytokines. Mast cells however also express toll-like receptors and scavenger receptors on their surface for the recognition of pathogens and foreign particles [18-20].

Our laboratory has recently investigated how different NM physicochemical properties including size, shape, and surface coating could influence interactions with SR-B1 on mast cells and lead to degranulation *in vitro* [21]. To date, there are no reports of mast cell degranulation mediated through SR-B1. Interestingly, PVP-coated and citrate-coated 20 nm spherical AgNPs, PVP-coated silver plates with an optical resonance peak at a wavelength of 550, and PVP-coated silver nanowires were found to induce degranulation of mast cells through a non-IgE mediated mechanism. We determined that inhibition of SR-B1 with Blt-2 inhibited mast cell degranulation. Interestingly, all AgNPs evaluated induced increased protein levels of the inflammatory cytokine osteopontin, which could be reduced following inhibition of SR-B1. Further this evaluation determined that inhibition of SR-B1 by Blt-2 reduced the uptake of PVP-coated 20 nm and 110 nm spherical AgNPs, citrate-coated 110 nm spherical AgNPs, and PVP-coated silver plates with an optical resonance peak at a wavelength of 850 nm. This suggests differential uptake of AgNPs by mast cells based on physicochemical properties, some of which are mediated via SR-B1. These findings point to a complex process by which mast cells respond to NMs through the SR-B1 receptor, that appears to be related to variations in physicochemical properties. Ultimately, for the safe development of nanotherapeutics mast cell responses mediated through the SR-B1 receptor need to be understood and evaluated to mitigate possible allergic responses [22].

**Table 1. Scavenger Receptor**

| Class | Type | Nanomaterial (NMs) | Scavenger Receptor Role in Biological Response | References |
|---|---|---|---|---|
| **SR-A** | SR-A1 | Silica Nanoparticles | Uptake of NMs by human embryonic kidney 293 (HEK293) cells with overexpression of SR-A, as well as the uptake by macrophages | Orr *et al.*, 2011 |
| | MARCO | Silver Nanoparticles | Decreased uptake in MARCO-deficient alveolar macrophages | Hamilton *et al.*, 2014 |
| | | Multiwalled Carbon Nanotubes | MWCNTs bind MARCO in macrophages | Hirano *et al.*, 2008 |
| | | Dextran-coated Superparamagnetic Iron Oxide Nanoparticles (SPIO) | Promotes SPIO uptake by embryonic kidney cells (HEK293T) engineered with increased expression of SR-AI and MARCO | Chao *et al.*, 2012 |
| | | Fluorescent-tagged Polystyrene Particles (20 nm in diameter) | Macrophages associate with nanoparticles through MARCO | Kanno *et al.*, 2007 |
| **SR-B** | SR-B1 | Biocompatible HDL-Mimicking Peptide-Phospholipid Scaffold (HPPS) Nanocarrier | 1. Improved uptake by nasopharyngeal carcinoma 2. Inhibition of the motility and colony formation of 5-8F cells, and suppression of NPC cell growth in nude mice without tumor cell necrosis or apoptosis | Zheng *et al.*, 2013 |
| | | HDL-Coated Nanoparticles | Facilitate highly efficient systemic delivery of siRNA *in vivo* | Shahzad *et al.*, 2011 |
| | | Silver Nanoparticles | Reduced uptake of AgNPs in endothelial and epithelial cells through inhibition of SR-B1 inhibitor | Shannahan *et al.*, 2015 |
| | | Silver Nanoparticles | Reduced uptake of AgNPs in macrophages through inhibition of SR-B1 with inhibitor | Aldossari *et al*. in press |
| | | Silver Nanoparticles, Plates and Wires | Inhibition of SR-B1 prevents NM-induced mast cell degranulation | Aldossari *et al*., 2015 |
| | CD36 | Gadolinium (Gd)-Containing Lipid-Based Nanoparticles | Uptake of nanoparticles by macrophages | Lipinski *et al.*, 2009 |

Taken together these studies demonstrate that SR-B receptors could be used to target nanotherapeutics to specific cell types and certain disease states, which express high levels of SR-B1 such as tumor cells and macrophages (Table 1). However, nanotherapeutics, which are being targeted to other cell types or disease states, likely will need to avoid SR-B mediated uptake to ensure delivery to the target tissues. This SR-B mediated uptake will result in reduced retention time and biodistribution to cells, which highly express SR-B. Further, activation of SR-B receptors may lead to activation of the immune system stimulating inflammatory responses and allergic reactions.

## Scavenger Receptor Class A

Class A scavenger receptors (SR-A) include SR-A1 and MARCO which have collagenous and cysteine-rich domains in their extracellular regions allowing for the association of a variety of ligands including oxidized lipoproteins and beta-amyloid fibrils [23-25]. Specifically, computer modeling has suggested that the collagenous domain is responsible for mediating the uptake of negatively charged NMs [26]. Interestingly, SR-A receptors function by interacting with other membrane bound signaling and transport proteins to induce intracellular signaling pathways [27]. Signaling through SR-A can result in either pro-survival or pro-death pathways. SR-A type receptors are primarily expressed on innate immune cells such as macrophages and dendritic cells where they facilitate endocytosis of ligands and cellular adhesion. SR-A type receptors are also expressed on the surface of fibroblasts, microglia, astrocytes, and endothelial, and epithelial cells [27]. Involvement of SR-A has been evaluated in a variety of diseases including atherosclerosis, sepsis, and bacterial and viral infections [27]. The role of SR-A type receptors in these diseases is directly related to the induction of immune cell-mediated inflammatory responses.

To date a significant amount of *in vitro* research has investigated possible AgNP-induced toxicity while few studies have examined the role of SR-A receptors in response to AgNP exposure. Specifically, alveolar macrophages that did not express the SR-A receptor MARCO were found to internalize fewer AgNPs compared to wild-type alveolar macrophages [28]. This diminished uptake was determined to result in less cytotoxicity in MARCO deficient macrophages as compared to wild-type macrophages. MARCO receptors have also been shown to interact with multiwalled carbon nanotubes, superparamagnetic iron oxide nanoparticles, and are also responsible for the uptake and intracellular accumulation of negatively charged 20 nm polystyrene nanoparticles [25, 29, 30]. Further, through silencing of SR-A receptors on macrophages, the uptake and inflammatory responses to amorphous silica nanoparticles has been inhibited [31]. The role of SR-A in silica nanoparticle uptake and responses was also demonstrated by overexpressing SR-A in non-phagocytic human embryonic kidney 293 (HEK293) cells, which do not normally express SR-A. This resulted in increased silica nanoparticle uptake in HEK293 cells demonstrating a role for SR-A in NM uptake. To further confirm SR-A mediated silica nanoparticle uptake by macrophages, fluorescence confocal microscopy revealed intracellular colocalization of extracellular SR-A components

and silica nanoparticles [31]. These studies taken together illustrate how the SR-A class of receptors can influence cellular uptake and specifically macrophage uptake of NMs (Table 1).

Nanoparticles may not only induce responses and toxicity through direct scavenger receptor interaction but may alter scavenger receptor density on cells. Alterations in scavenger receptor density on the surface of cells could result in altered responses to their endogenous ligands (e.g. lipoproteins) thus accelerating disease progression. Research has demonstrated that exposure to ZnO nanoparticles but not $TiO_2$ nanoparticles induced increased expression of SR-A in macrophages as well as the SR-B type scavenger receptor CD36 [32]. This increased expression could enhance lipid uptake influencing atherosclerotic disease progression. Scavenger receptors are also known to be involved in the transformation of macrophages to foam cells, which populate atherosclerotic plaques [33]. Increased levels of SR-A type receptor expression on the surface of macrophages could possibly drive increased foam cell differentiation and acceleration of atherosclerosis. These findings imply that NMs, which influence cell-surface receptor density, may result in modified and exacerbated atherosclerotic disease progression.

Immune responses that are normally mediated through scavenger receptors may also be modified following exposure to NMs. Specifically, SR-A is known to participate in the uptake of NMs as well as bacteria. Exposure to superparamagnetic iron oxide nanoparticles, at a concentration that did not cause cytotoxicity or an inflammatory response, has been found to reduce the phagocytic activity of macrophages following challenge with *Streptococcus pneumonia* [34]. This exposure to iron oxide nanoparticles was also found to result in suppressed induction of the IL-10 pathway, enhanced TNF-α production, and an inhibition of the transition from an M1 to M2-like activation state in macrophages. Lastly, challenge with lipopolysaccharide following iron oxide exposure resulted in enhanced activation of oxidative stress response pathways and impaired activation of pro- and anti-inflammatory pathways [34]. Many of these responses are known to be dependent on macrophage SR-A activation suggesting receptor involvement. These findings demonstrate that although not toxic by themselves NMs may alter receptor function and impair anti-microbial responses.

## Conclusions

NMs are rapidly being developed and will influence most existing and emerging technologies. They have potential to advance many clinical applications including both therapeutic and diagnostic techniques. In order for NMs to be developed, which are safe and effective we must understand interactions between NMs and cell-surface receptors. To date, research has demonstrated that scavenger receptors are a class of receptors that will likely interact with NMs. These interactions make scavenger receptors both a novel NM target for certain theranostic applications and also a likely mediator of NM toxicity.

## Conflicting interests

The authors have declared that no competing interests exist.

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