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Standardizing Scavenger Receptor Nomenclature

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Disclosures

M.K. has patents covering SR-AI/II; one SR-BI patent is used as a license to the Massachusetts Institute of Technology. There are several SR-BI patents pending. S.K.M. is a minority shareholder of a biotechnology company, Affinicon, which exploits CD163 for drug targeting. The remaining authors have no financial conflicts of interest.

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Abstract

Scavenger receptors constitute a large family of proteins that are structurally diverse and participate in a wide range of biological functions. These receptors are expressed predominantly by myeloid cells and recognize a variety of ligands, including endogenous and modified host-derived molecules and microbial pathogens. There are currently eight classes of scavenger receptors, many of which have multiple names, leading to inconsistencies and confusion in the literature. To address this problem, a workshop was organized by the U.S. National Institute of Allergy and Infectious Diseases, National Institutes of Health to help develop a clear definition of scavenger receptors and a standardized nomenclature based on that definition. Fifteen experts in the scavenger receptor field attended the workshop and, after extensive discussion, reached a consensus regarding the definition of scavenger receptors and a proposed scavenger receptor nomenclature. Scavenger receptors were defined as cell surface receptors that typically bind multiple ligands and promote the removal of non-self or altered-self targets. They often function by mechanisms that include endocytosis, phagocytosis, adhesion, and signaling that ultimately lead to the elimination of degraded or harmful substances. Based on this definition, nomenclature and classification of these receptors into 10 classes were proposed. The discussion and nomenclature recommendations described in this report only refer to mammalian scavenger receptors. The purpose of this article is to describe the proposed mammalian nomenclature and classification developed at the workshop and to solicit additional feedback from the broader research community.

Scavenger receptor activity was first described by Drs. Michael Brown and Joseph Goldstein when they identified receptors in macrophages that endocytosed and degraded modified (acetylated), but not native, low-density lipoprotein (LDL) (1). Drs. Brown and Goldstein showed that these acetylated LDL receptors (LDLRs) recognized a wide variety of polyanionic ligands (2). Purification and cloning of the corresponding receptor protein and cDNA (3, 4) was soon followed by the identification of other modified LDLRs with broad binding specificity. In an initial attempt to systematically categorize these receptors, Dr. Monty Krieger proposed to subdivide them into “classes” (A, B, and so forth) based on their sequences, and each class was subdivided further into “types” based on additional variations in their sequences due to alternative splicing (5).

There are currently eight classes of scavenger receptors (classes A–H). In some cases multiple names have been assigned to the same receptor (e.g., MSR1, SR-AI, CD204, SCARA1). Additionally, there are proteins exhibiting scavenger receptor activity that have been named based on other criteria and have not been included in a general scavenger receptor nomenclature. Some examples include receptor for advanced glycation end products (RAGE), LRP1, LRP2, ASGP, CD163, scavenger receptor that binds phosphatidylserine and oxidized lipids (SR-PSOX), and CXCL16. New scavenger receptors

also continue to be discovered and identified (6, 7). Therefore, it is important to convey consistent understanding and minimize redundancy and miscommunication in the scavenger receptor field. Developing a standardized nomenclature has the benefit of decreasing redundancy and facilitating communication and collaboration among investigators within a field, as well as in different fields, by building on a common understanding. Efforts to standardize other scientific nomenclatures have occurred in areas such as chemokines and their receptors (8), the TNF family of receptors involved in bone metabolism (9), complement peptide receptors (10), and glutamate receptors (11). Committees formed specifically for these processes by scientific societies or investigators in the field have developed systematic nomenclatures within each field for adoption by the broader scientific community.

To address the lack of a unified nomenclature system for scavenger receptors and better organize the field, the U.S. National Institute of Allergy and Infectious Diseases, National Institutes of Health, represented by Dr. Mercy PrabhuDas, initiated discussions with Dr. Joseph El Khoury and Prof. Siamon Gordon, which led to organizing and convening a workshop in which 15 investigators from five countries proposed a consensus definition of scavenger receptors and a systematic, standard nomenclature. We regret that Prof. Gordon was unable to participate in the workshop due to prior commitments. The workshop participants and their areas of expertise are listed in Table I.

The objectives of this workshop were to: 1) establish guidelines and recommendations for standardizing the nomenclature for scavenger receptors; 2) consider strategies for dealing with future discoveries of scavenger receptors; and 3) communicate the recommendations to the wider scientific community as a point of reference and for further discussion and final scavenger receptor nomenclature standardization. The discussion and nomenclature recommendations described in this report only refer to mammalian scavenger receptors.

Scavenger receptor background and history

The original description of scavenger receptors was in the context of studies of lipoproteins, atherosclerosis, and familial hypercholesterolemia (1, 12). Drs. Michael Brown and Joseph Goldstein had previously identified LDLRs and LDLR-mediated endocytosis and established that familial hypercholesterolemia was caused by loss of function mutations in the LDLR, which led to increased plasma LDL, premature atherosclerosis, and heart disease. Analysis of familial hypercholesterolemia patients showed that plasma LDL could also be partially cleared by an LDLR-independent pathway called the “scavenger pathway.” The earliest use of the term “scavenger receptor” to refer to the broad specificity receptor identified by Drs. Brown and Goldstein was in 1981 by Dr. Alan Fogelman and colleagues (13).

The first scavenger receptors were purified in 1988 (14) and cloned in 1990 (15, 16) by Dr. Monty Krieger’s group. These receptors initially were named type I and type II macrophage scavenger receptors and were found to be alternatively spliced products of a single gene. When additional scavenger receptors were identified, the type I and II macrophage receptors were renamed scavenger receptor, class A, type I and type II (SR-AI and SR-AII) by Dr.

Krieger's group. One distinct feature of the broad binding specificity of scavenger receptors was that they could recognize a large repertoire of ligands, ranging from bacteria and yeast to self (native proteins) and modified-self targets (2, 17–21). Besides playing a role in host defense, class A scavenger receptors were shown to be involved in functions such as homeostasis, Ag presentation, and pathogenesis of neurodegenerative disorders (22, 23).

Based on their broad ligand-binding specificities and expression in macrophages, Dr. Krieger and colleagues proposed that scavenger receptors could serve as pattern recognition receptors for innate immunity (5). Work done by groups led by Drs. Siamon Gordon, Tatsuhiko Kodama, and Joseph El Khoury provided direct evidence that the class A receptors are adhesion receptors, and that they recognize Gram-positive bacteria and β-amyloid, confirming the broad ligand specificity for these receptors (24, 25). Additional members of the class A scavenger receptors such as macrophage receptor with collagenous structure (MARCO) (26) and SCARA5 (27) were subsequently identified and shown to be involved in host defense.

Since the first discovery of the class A scavenger receptors, other multiligand pattern recognition receptors were independently identified, including CD14 (28), mannose receptors (29), and CD36 (30). There are currently eight classes of scavenger receptors, and summaries of each class of scavenger receptors are included under the proposed nomenclature recommendations below.

Scavenger receptor nomenclature recommendations

Prior to initiating a discussion about nomenclature, the workshop participants developed a definition of scavenger receptors, incorporating the various facets and characteristics of these receptors. This definition was used as the benchmark against which proposed nomenclatures were considered. As mentioned above, scavenger receptors were originally defined as cell surface proteins that bound chemically modified lipoproteins with high affinity. Additional characteristics included the ability to bind multiple ligands (broad-binding specificity), mediate endocytosis, in some cases mediate signaling, and act as innate immune pattern recognition receptors. Based on the discussion, the group agreed on the following working definition: *Scavenger receptors are cell surface receptors that typically bind multiple ligands and promote the removal of non-self or altered self targets. They often function by mechanisms that include endocytosis, phagocytosis, adhesion, and signaling that ultimately lead to the elimination of degraded or harmful substances.*

Fig. 1 illustrates the consensus nomenclature formula agreed on at the meeting. As an example, a scavenger receptor belonging to class A would be designated as SR-A1, where SR stands for scavenger receptor and is followed by a hyphen, then a capital letter representing the class of SR, and then an Arabic numeral representing the type of molecule within the class. Alternate splice variants are designated by a dot and an Arabic numeral following the type of molecule within the class (e.g., SR-A1.1). The numbering is based on the order in which the molecules were identified. Tables II and III provide the current and proposed nomenclature for human and mouse scavenger receptors. The following sections

provide a brief overview of the currently known scavenger receptor classes and the proposed nomenclature for each class and member, as recommended by the workshop participants.

Class A scavenger receptors: SR-A

Class A scavenger receptors are expressed primarily on tissue macrophages and macrophage subtypes such as Kupffer cells and cortical and medullary thymic macrophages (31). They have also been observed on high endothelial venules (31) and on subpopulations of dendritic cells (32), binding to a variety of foreign and self ligands. Members in this class have a similar structure, comprised of a cytoplasmic tail, transmembrane domain, spacer region, α helical coiled coil domain, collagenous domain, and a C-terminal cysteine-rich domain. SCARA1/MSR1, the prototypical SR-A molecule, was the first scavenger receptor to be cloned and was initially isolated from bovine lung mRNA. It has subsequently been identified in other species, including mice and humans. There are three isoforms, identified as alternative splice variants encoded by the same gene, namely, SR-AI, SR-AII, and SR-AIII (33, 34). Other members of this class of scavenger receptors include MARCO, SCARA5, and scavenger receptor with C-type lectin domain (SRCL)-I/II, also designated collectin from placenta receptor-I (35).

The scavenger receptor currently designated as SCARA1 or MSR1 would now be referred to as SR-A1. SR-A1 is predominantly found in macrophages, monocytes, mast cells, and dendritic cells in both mice and humans (36). A diverse array of ligands is recognized by members of this class. SR-A1 binds to β-amyloid, heat shock proteins, surface molecules of Gram-positive and Gram-negative bacteria, hepatitis C virus (34), and modified LDL such as acetylated LDL and oxidized LDL (oxLDL), but not native LDL.

SR-A1.1, an alternatively spliced form of SR-A1 (currently referred to as SR-AII), is characterized by a shortened C terminus. SR-A1.2, another alternatively spliced form of SR-A1 (currently referred to as SR-AIII), is characterized by a truncated C terminus and remains trapped in the endoplasmic reticulum. The collagenous region of SR-A1 and SR-A1.1 has been identified as a ligand-binding domain (37). There would be no receptor designated as SR-A2 to avoid confusion with the current SR-AII (new designation of SR-A1.1)

Whereas SR-A1 and SR-A6 (currently known as MARCO) are primarily expressed in macrophages, SR-A3 (also referred to as SCARA3, cellular stress response [CSR]), SR-A4 (SCARA4, SRCL, collectin placenta 1 [CL-P1]), and SR-A5 (SCARA5) are expressed in a variety of other tissues and cell types, including the lung, placenta, intestine, heart, and epithelial cells (38). SR-A3 has been associated with protecting cells from the detrimental effects of reactive oxygen species (21). SR-A4 functions as an endocytic receptor for lipoproteins and mediates the recognition, internalization, and degradation of oxidatively modified LDL by vascular endothelial cells (39). SR-A5 (currently known as SCARA5) expression is restricted to epithelial cells within the testis, airway, thymus, and the adrenal gland. SR-A5 has the capacity to bind bacteria and may play an important role in host defense (27). Under normal conditions, in the absence of inflammation, the expression of SR-A6 is restricted to macrophages in the lymph nodes and marginal zone of the spleen.

Studies have shown that SR-A6 mediates the clearance of bacteria from the lungs (40) and bloodstream (41).

Proposed member nomenclature

SR-A1: the protein currently known as MSR1, SCARA1 [prototype].

SR-A1.1: the protein currently known as SR-AII. This is an alternatively spliced form of SR-A1.

SR-A1.2: the protein currently known as SR-AIII. This is also an alternatively spliced form of SR-A1.

There would be no receptor designated as SR-A2. This exception was agreed on during the meeting to avoid confusion with the current SR-AII, which would now be designated as SR-A1.1.

SR-A3: the protein currently known as MSRL1 or APC7; the current gene name is SCARA3.

SR-A4: the protein currently referred to as scavenger receptor C-type lectin; the current gene name is SCARA4.

SR-A5: the protein currently known as TESR; the current gene name is SCARA5.

SR-A6: currently named MARCO; the gene name is SCARA2. The workshop participants recommended that the gene name be changed to SCARA6 for consistency.

Class B scavenger receptors: SR-B

Class B scavenger receptors include receptors currently known as SR-BI, SR-BII, CD36, and LIMP2. Receptors belonging to this class are characterized by two transmembrane domains flanking an extracellular loop, with both the amino and carboxyl termini located within the cytoplasm. The extracellular domain of these receptors is extensively N-linked glycosylated, and this modification provides protection against proteases often found in inflammatory sites. CD36 is the prototype class B type I scavenger receptor and was initially identified as a receptor for thrombospondin (42), and in this capacity it modulates angiogenesis and cell-to-cell interactions. It is one of the most widely studied scavenger receptors and is involved in multiple aspects of macrophage biology, including migration and signaling and inflammatory processes such as foam cell formation. CD36 also plays an important role in the host immune response to fungi and bacteria and binds erythrocytes infected with the malaria parasite *Plasmodium falciparum* (43), as well as functions as a facilitator of long chain fatty acid uptake (44). It is expressed in many cell types, including insulin-responsive cells; hematopoietic cells such as platelets, monocytes, and macrophages; and endothelial cells and specialized epithelial cells in the breast and eye. Dr. Gerda Endemann and colleagues were the first to characterize CD36 as a receptor for oxLDL, thereby cementing its role as a scavenger receptor (30). CD36 also binds polyanionic ligands of both host (e.g., high-density lipoprotein [HDL]) (45) and pathogen (examples are *Staphylococcus aureus* and *Candida albicans*) (20, 46) origin, and it plays an important role

in the recognition and endocytic uptake of oxidized phospholipids, apoptotic cells, and amyloid proteins (47). Dr. Cameron Stewart and colleagues have shown that CD36 (SR-B2) cooperates with TLR family members (TLR4 and TLR6) to activate the innate immune response to ligands that accumulate in Alzheimer's disease and atherosclerosis, inducing proinflammatory mediators such as IL-1β and RANTES.

SR-B1 (also known as SCARB1 or SR-BI) was the first HDL receptor to be identified and mediates the selective transport of lipids, such as cholesteryl esters from HDL, from lipoproteins to cells (48, 49). SR-B1 is most highly expressed by hepatocytes and steroidogenic cells and is also found in cells within the arterial wall and macrophages in human and murine atherosclerotic lesions (50). SR-B1 has been shown to have a protective effect on atherosclerosis development; total body ablation of SR-B1 in apolipoprotein E knockout mice fed a normal chow diet led to severe coronary arterial atherosclerosis, myocardial infarction, and death (51). Ablation of SR-B1 in bone marrow cells of LDL receptor knockout mice also resulted in increased atherosclerosis, but not death, indicative of partial protection against atherosclerosis (52).

SR-BII, an alternatively spliced form of SR-BI, contains a distinctly different cytoplasmic tail than SR-BI. SR-BII is expressed in adrenal glands, testes, and liver, and it has been shown to mediate selective uptake of cholesteryl ester from HDL, with ~4-fold lower efficiency than SR-BI (53).

One other member of the CD36 family of membrane proteins, LIMP2 (SR-B3), functions primarily in delivering β-glucocerebrosidase from the endoplasmic reticulum to lysosomes. SR-B3 has been identified as a cellular receptor for enterovirus 71 (EV71), coxsackievirus 7 (CVA7), CVA14, and CVA16 entry into host cells. SR-B3 also serves a role in viral uncoating, thereby increasing infection efficiency (21). Expression of SR-B3 on the cell membrane has not been confirmed.

Proposed member nomenclature

SR-B1: originally cloned as the HDL receptor, the gene name is SCARB1; protein is currently also known as SR-BI.

SR-B1.1: an alternatively spliced form of SR-B1, currently known as SR-BII.

SR-B2: the protein currently known as CD36 [prototype].

SR-B3: the protein currently known as LIMP2.

Class C scavenger receptors

Class C scavenger receptors have been described in *Drosophila* (5), but there are currently no known mammalian class C scavenger receptors. This scavenger receptor class was not discussed because the workshop participants focused on mammalian scavenger receptors.

Class D scavenger receptors: SR-D

CD68 is the only known member of the class D scavenger receptors. CD68, also known as macrosialin in mice, is a type I transmembrane glycoprotein that belongs to the lysosome-

associated membrane protein family of molecules (54). There is a 300-aa extracellular region that is rich in threonine and serine, which may serve as an attachment site for carbohydrates, and a short cytoplasmic tail. Human CD68 shares 75% amino acid sequence identity to mouse CD68 in the extracellular region. CD68 is found on monocytes and tissue-specific macrophages in the peritoneum, lungs, liver, spleen, Langerhans cells, and microglia, and it serves as a scavenger receptor for oxLDL. CD68 is a differentiation marker of hematopoietic cells of the monocyte/macrophage lineage. It is mostly found in the late endosomal compartment in macrophages and dendritic cells, with limited expression on resting cells. CD68 plays a minor role in the binding and uptake of oxidized lipoproteins and apoptotic cells by macrophages (23). The proposed new nomenclature for this molecule is: **SR-D1**: currently known as CD68 [prototype].

Class E scavenger receptors: SR-E

Class E scavenger receptors are type 2 transmembrane proteins with C-type lectin-like domains and demonstrated scavenger receptor activity; sequence homology alone is not sufficient to include a protein in this class of receptors. These proteins structurally belong to a subfamily of the C-type lectin (CLEC)–like NK cell receptor family. The NK receptor gene complex encodes a large number of CLEC-like receptors that are expressed on NK cells and other leukocytes. Analysis of the NK receptor gene complex in five species revealed variations in the sizes of gene clusters in each species that ranged from 22 to 75 clusters and are noted in these species: human (29 clusters), dog (22 clusters), cattle (32 clusters), rat (75 clusters), and mouse (57 clusters) (55). Among these gene clusters, the first two members of the CLEC family, lectin-like oxLDL receptor (LOX-1) and Dectin-1, have been well characterized and shown to have scavenger activity.

LOX-1 is expressed on macrophages and dendritic cells and binds oxidized LDL and the acute phase protein C-reactive protein (56). It was originally cloned from a bovine aortic endothelial cDNA expression library screened for receptors for oxidized LDL (57). LOX-1 is expressed on vascular endothelial cells, platelets, smooth muscle cells, adipocytes, and macrophages. In addition to binding oxidized LDL, LOX-1 has been implicated in recognizing other ligands, including apoptotic cells, Gram-positive bacteria, and Gram-negative bacteria (23, 56). A splicing variant of human LOX-1 lacking a lectin-like domain, called LOXIN, works as a dominant-negative isoform, forming a heterodimeric complex with LOX-1 (58).

Dectin-1 is expressed predominantly on myeloid cells (macrophages, dendritic cells, and neutrophils) and can be regulated by cytokines and microbial stimuli. Human Dectin-1 is alternatively spliced, resulting in two functional forms. This receptor recognizes various bacterial, fungal, and plant carbohydrates (β-1,3- and/or β-1→6-glucans) in addition to intact fungi and parasites (59). Dectin-1 mediates proinflammatory cytokine production in response to β-glucan particles, in conjunction with TLR2. It can also function as a phagocytic receptor through a novel Syk-independent pathway. Dectin-1 has been reported to act as a costimulatory molecule to activate both CD4 and CD8 T cells. Moreover, Dectin-1 is expressed on macrophages and dendritic cells in the medullary regions of the thymus, suggesting a role in thymocyte development (60).

Some CLEC family members are known to recognize pathogen-associated molecules. However, most of the members of the CLEC family have not been shown to have scavenger receptor activity. At this time, only LOX-1 and Dectin-1 would be classified as scavenger receptors using the definition proposed by the workshop participants.

Proposed member nomenclature

SR-E1: the protein currently known as LOX1. Gene name OLR1 [prototype].

SR-E1.1: alternatively spliced form of SR-E1 also known as LOXIN (no known scavenger receptor activity but works as a dominant-negative form).

SR-E2: the protein currently known as Dectin-1.

Class F scavenger receptors: SR-F

There are currently three members belonging to the class F scavenger receptors. The first class F scavenger receptor (SCARF1) was identified as an endothelial receptor for modified LDL and is characterized by the presence of an extracellular ligand-binding domain, with multiple extracellular epidermal growth factor–like repeats, a transmembrane domain, and a long cytoplasmic tail that includes a serine/proline-rich region followed by a glycine-rich region. It was named scavenger receptor expressed by endothelial cells (SREC)-I (61) and later was also named SCARF1. SCARF1/SREC-I is also expressed in macrophages and functions to bind calreticulin and associated peptides, which are transported into the MHC class I pathway in macrophages and dendritic cells (23). SCARF1 also was shown to be a receptor for fungal pathogens and heat shock proteins (20, 34). Interestingly, a *Caenorhabditis elegans* ortholog of SCARF1, CED-1, plays a role in engulfing apoptotic cells and has been implicated in host defense (23). A recent report indicates that SCARF1, similar to CED-1, is also involved in the clearance of apoptotic cells (62).

A second isoform of SREC-I, SREC-II, was cloned by Dr. Hiroyuki Arai's group (63) and was shown to be predominantly expressed in heart, placenta, lung, kidney, spleen, small intestine, and ovary. SREC-II is a type I transmembrane receptor containing N-terminal epidermal growth factor–like domains, a transmembrane domain, and a long cytoplasmic tail, and it engages in heterophilic interactions with SREC-I. In contrast to SREC-I that binds and internalizes modified LDL, SREC-II is unable to internalize modified LDL. The cytoplasmic domain of SREC-II is rich in arginine and lysine, whereas SREC-I is rich in serine and proline. The significance of these residues is not known at this time.

Another member of the SCARF family, multiple epidermal growth factor (EGF)–like domains (MEGF)10, recently has been shown to be a receptor for the protein amyloid-β in the brain, and it is thought to be involved in the pathogenesis of Alzheimer's disease (23). It is not clear yet whether other MEGF family members, such as MEGF8, 9, and 11, also have scavenger receptor function because no functional studies have been published to date on these molecules.

Proposed member nomenclature

SR-F1: the protein currently known as SREC-I/SCARF1 [prototype].

SR-F2: the protein currently known as SREC-II/SCARF2.

SR-F3: the protein currently known as MEGF10.

Class G scavenger receptors: SR-G

Currently, one receptor belongs to scavenger receptor class G, SR-PSOX/CXCL16. Dr. Takeshi Shimaoka and colleagues used expression cloning of a cDNA library from PMA-treated human monocytic THP-1 cells to identify scavenger receptors that bound oxLDL, and they discovered this receptor, which they called SR-PSOX (64). At about the same time, Drs. Jason Cyster and Michael Briskin discovered a new chemokine that was capable of activating the receptor, CXCR6 (also known as BONZO, STRL33 or TYMSTR), resulting in migration of T cells in vitro (65–67). This chemokine was named CXCL16 and was found to be identical to SR-PSOX in its amino acid sequence.

Studies show that the SR-PSOX/CXCL16 gene is located on chromosome 17p13, and its protein exists in both membrane and soluble forms (65). It is a type I transmembrane glycoprotein with a CXC chemokine motif, mucin stalk, and transmembrane and soluble domains. SR-PSOX/CXCL16 does not share structural homology with other scavenger receptors. SR-PSOX/CXCL16 has the capacity to mediate adhesion and phagocytosis of bacteria by APCs (66). The membrane-bound form can function as an adhesion molecule for CXCR6-expressing T cells without requiring CXCR6- induced signal transduction and integrin activation.

This multifunctional transmembrane protein has a chemokine- like CXC motif and appears to be involved in several phases of an immune response, from Ag recognition to migration of immune cells to formation of inflammatory foci (68). The soluble form of SR-PSOX/CXCL16, produced from cleavage of the membrane-bound form, functions as a chemo-attractant for activated T cells and bone marrow plasma cells via its receptor CXCR6 (69). The membrane-bound form acts as a scavenger receptor for oxLDL and facilitates phagocytosis of bacteria by APCs (69).

Proposed member nomenclature

SR-G1: the protein currently known as SR-PSOX/CXCL16 [prototype].

Class H scavenger receptors: SR-H

Receptors in this class are transmembrane proteins that consist of Fasciclin, EGF-like and lamin type EGF-like (FEEL) domains. The currently known SR-H members are FEEL-1/Stabilin-1/CLEVER-1 and FEEL-2/stabilin-2/HARE. FEEL-1 is predominantly expressed in macrophages, mononuclear cells, hematopoietic stem cells, and endothelial cells, whereas FEEL-2 is found mainly in sinusoidal endothelial cells. FEEL-1 and FEEL-2 have been shown to be involved in lymphocyte adhesion, transmigration, angiogenesis, apoptotic cell clearance, and intracellular trafficking. FEEL-1 and FEEL- 2 also have been implicated in the clearance of aged RBCs by macrophages (70, 71) in a phosphatidylserine-dependent manner. FEEL-1 has been shown to directly interact with and is sufficient for phagocytosis of phosphatidylserine-coated beads. These results have yet to be confirmed in vivo.

However, FEEL-1 and FEEL-2 double knockout mice have been shown to be impaired in the clearance of noxious blood factors (72).

Proposed member nomenclature

SR-H1: the protein currently known as FEEL-1, Stabilin-1 and CLEVER -1 [prototype].

SR-H2: the protein currently known as FEEL-2/Stabilin-2.

Class I scavenger receptors: SR-I

Members of the class I scavenger receptors are primarily restricted to the monocytic lineage, of which CD163, the prototypic class I scavenger receptor, is expressed exclusively in monocytes and macrophages and binds to haptoglobin/hemoglobin (Hgb) complexes to promote the clearance of plasma Hgb via endocytosis during intravascular hemolysis. CD163 is a type I transmembrane protein that consists of an extracellular region composed of nine scavenger receptor cysteine-rich (SRCR) domains and a short cytoplasmic tail. CD163 was originally cloned from the spleen of a patient afflicted with hairy cell leukemia, characterized by a large number of tissue macrophages. It is a 130-kDa membrane glycoprotein, and was known as M130 prior to being given a CD designation. CD163 was also given the functional name “hemoglobin scavenger receptor” to describe its primary role in tissue macrophages (73). Its role as an Hgb receptor may contribute to enhancement of an anti-inflammatory response because the proinflammatory heme is converted to anti-inflammatory metabolites (74).

In addition to functioning as an Hgb receptor, CD163 appears to be involved in intracellular signaling, resulting in a protein-kinase–dependent signal and secretion of cytokines such as IL-6 and IL-10 (75). Several CD163 mRNAs arising from an alternatively spliced CD163 gene have been reported (73, 75). Confocal microscopy studies revealed that the shortest tail variant is predominantly present in the cell membrane, whereas the longer variants are located in the endosomal/Golgi cellular compartment (75). One short tail variant and two long tail variants have been shown to bind and internalize haptoglobin/Hgb complexes leading to lysosomal degradation of the complex. The short tail variant is the predominant isoform found in human blood, liver, and spleen, and most of the long tail variants appear in endosomal compartments (75).

CD163-L1 (M160), a long tail variant of CD163, is a type I transmembrane molecule structurally composed of scavenger receptor cysteine-rich domains, expressed by cells of the myeloid lineage, and may be involved in the differentiation of monocytes to macrophages. Two cytoplasmic splice variants of CD163-L1 have been identified thus far; these include the full-length variant (CD163L1α) with a cytoplasmic tail of 71 residues and the short tail variant (CD163-L1β) with 39 residues. CD163-L1α is the predominant membrane-associated form in several human tissues such as spleen, placental, and small intestine, whereas CD163-Lβ is mainly found in intracellular compartments (76). Studies to identify endogenous and microbial ligands of CD163-L1β are currently in progress.

Proposed member nomenclature

SR-I1: the protein currently known as CD163, M130 [prototype].

SR-I1.1: the CD163 long tail variant 1.

SR-I1.2: the CD163 long tail variant 2.

SR-I2: currently known as CD163B, M160.

Class J scavenger receptors: SR-J

RAGE is currently the only member of the class J scavenger receptor group, and it is a member of the Ig superfamily of cell surface molecules capable of interacting with a broad spectrum of ligands, including advanced glycation end products, high mobility group protein box 1, and the S-100 protein. RAGE is composed of a single transmembrane domain that connects the ectodomain with a short cytoplasmic domain and an extracellular domain required for ligand recognition and binding. The extracellular domain comprises an N-terminal sequence and three Ig-like regions. RAGE is a pattern recognition receptor predominantly involved in the recognition of endogenous molecules released in the context of infection, physiological stress, or chronic inflammation (77). Signaling through RAGE mediates processes such as inflammation, oxidative stress, and apoptosis, which can lead to pathologies including atherosclerosis, diabetes, cancer, neurodegenerative disease, and stroke. RAGE signaling also mediates normal neuronal processes such as cell migration and neuronal differentiation. Studies assessing brain pathology in Alzheimer's disease revealed that diseased brains expressed higher levels of RAGE in the vasculature and on neurons compared with normal brains (23). In addition to a membrane-bound form, a circulating portion of the protein known as "soluble" RAGE also has biological properties.

Proposed member nomenclature

SR-J1: the protein currently known as the membrane-bound form of RAGE/AGER [prototype].

SR-J1.1: the soluble form of RAGE.

Other potential scavenger receptors: SR-Others

The SR-Others group refers to molecules with scavenger activity that do not belong to the current SR classes, but belong to other receptor families. These receptors include LDL receptor family proteins such as LRP1, LRP2/megalin, cubam (the cubilin/amnionless complex), ASGP, MR, and CD11b/CD18α. Classifying these receptors as scavenger receptors will require the input of the wider scientific community.

Conclusions

In addition to their functions as phagocytic receptors and innate immune recognition receptors, scavenger receptors also play an important role as regulators of inflammatory signaling. These receptors have been implicated in a number of physiological and pathological processes, including interactions with other innate immune receptors, delivery of ligands to different cellular compartments, and Ag presentation. Furthermore, the roles of these receptors in neurodegenerative diseases, diabetes, and other metabolic disorders, as

well as their potential as targets for therapeutic interventions to treat various disorders, warrant further study. Having a standardized nomenclature as described in this report would help to overcome current ambiguities in communication about specific scavenger receptors and, perhaps, remove a major barrier for researchers in other fields to enter the scavenger receptor field.

This report serves as an initial step in presenting the proposed nomenclature to the research community. A Web site has been established to invite comments from fellow investigators in response to the proposed nomenclature. The Web site is https://respond.niaid.nih.gov/ScavengerReceptors/, which will be open for public comment from March 1 through July 31, 2014. Additionally, the National Institute of Allergy and Infectious Diseases is organizing several discussion sessions at the following upcoming national meetings: Experimental Biology 2014 (April 29, 2014; http://experimentalbiology.org/2014/Home.aspx) in San Diego, CA; IMMUNOLOGY 2014 in Pittsburgh, PA (May 4, 2014; http://www.immunology2014.org/); and FOCIS 2014 (June 25, 2014; http://www.focisnet.org/focis-2014) in Chicago, IL. These sessions will be open to the meeting attendees to provide the broader scientific community with the opportunity to offer their comments and recommendations on the proposed scavenger receptor nomenclature. The National Institute of Allergy and Infectious Diseases plans to publish the final nomenclature recommendations in a subsequent publication in *The Journal of Immunology*, based on the comments received at these meetings and at the scavenger receptor nomenclature Web site. The final nomenclature will also be communicated to the International Union of Pharmacology to facilitate distribution to scientists working in areas related to pharmacology and biological target research.

Acknowledgments

We are grateful to Prof. Siamon Gordon for his invaluable input and suggestions for the scavenger receptor nomenclature workshop and proposed recommendations.

Abbreviations used in this article

CLEC	C-type lectin
CL-P1	collectin placenta 1
EGF	epidermal growth factor
FEEL	Fasciclin, epidermal growth factor–like and lamin type epidermal growth factor–like
HDL	high-density lipoprotein
Hgb	hemoglobin
LDL	low-density lipoprotein
LDLR	low-density lipoprotein receptor
LOX-1	lectin-like oxidized low-density lipoprotein receptor 1
MARCO	macrophage receptor with collagenous structure

MEGF	multiple epidermal growth factor–like domains
RAGE	receptor for advanced glycation end products
SRCL	scavenger receptor with C-type lectin domain
SRCR	scavenger receptor cysteine-rich
SREC	scavenger receptor expressed by endothelial cells
SR-PSOX	scavenger receptor that binds phosphatidylserine and oxidized lipids

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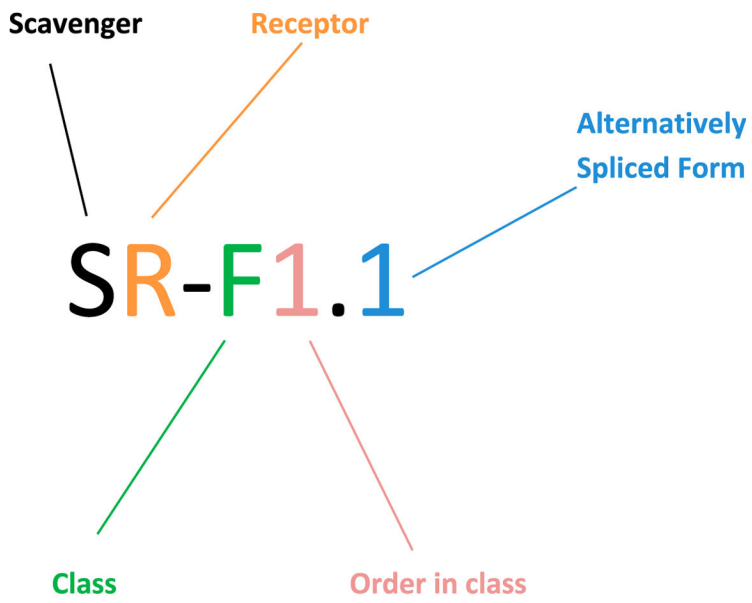

FIGURE 1.

Proposed scavenger receptor nomenclature formula. Proposed nomenclature formula: SR stands for scavenger receptor. SR is followed by a hyphen, then a capital letter representing the class of SR (A–J) followed by an Arabic numeral representing the type of molecule within the class (the numbering is based on the order in which the molecules were identified). Alternatively spliced forms of a molecule will be designated as 1.1, 1.2, and so forth. For existing spliced variants, the longest variant in terms of amino acid sequence will be given the first number.

Table I

Workshop participants and their areas of expertise

Participant	Affiliation	Area of Expertise
Dawn Bowdish	McMaster University, Hamilton, ON, Canada	Macrophage scavenger receptors in host defense
Kurt Drickamer	Imperial College, London, U.K.	C-type lectin and glycan recognition
Joseph El Khoury	Massachusetts General Hospital, Harvard Medical School, Boston, MA	Macrophage and microglial scavenger receptors in inflammation
Maria Febbraio	University of Alberta, Edmonton, AB, Canada	CD36 signaling
Joachim Herz	University of Texas Southwestern Medical Center, Dallas, TX	Functions of LDL receptor-related proteins
Lester Kobzik	Harvard School of Public Health, Boston, MA	MARCO and lung inflammation
Monty Krieger	Massachusetts Institute of Technology, Cambridge, MA	Scavenger receptors in host defense and lipoprotein and lipid metabolism
John Loike	Columbia University, New York, NY	Scavenger receptors in neuropathology
Terry Means	Massachusetts General Hospital, Harvard Medical School, Boston, MA	Scavenger receptors and antifungal immune mechanisms
Soren Moestrup	Aarhus University, Aarhus, Denmark	Hemoglobin scavenger receptor
Philip Murphy	National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD	G protein–coupled receptors in leukocyte trafficking
Steven Post	University of Arkansas for Medical Sciences, Little Rock, AR	Scavenger receptor A and atherosclerosis
Tatsuya Sawamura	National Cerebral and Cardiovascular Center, Osaka, Japan	Oxidized LDL receptor (LOX-1) and vascular inflammation
Samuel Silverstein	Columbia University, New York, NY	Roles of scavenger receptors on mononuclear phagocytes in chronic inflammatory diseases
Xiang-Yang Wang	Virginia Commonwealth University, Richmond, VA	Scavenger receptors in immune modulation and host response

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Table II

Summary of current mouse scavenger receptor nomenclature and proposed changes

Current NCBI Gene Name	Alternative Names	Proposed Nomenclature[a]	Accession No.	NCBI Gene ID	Chromosome
MSR1	SR-A1, SCARA1	SR-A1	NM_031195	20288	8
Alternatively spliced form of SR-A1	SR-AII	SR-A1.1	—[b]	—[b]	8
MARCO	SCARA2, Ly112	SR-A6	NM_010766	17167	1
SCARA3	MSRL1, APC7	SR-A3	NM_172604	219151	14
COLEC12	SCARA4, SRCL, CL-P1	SR-A4	NM_130449	140792	18
SCARA5	TESR	SR-A5	NM_028903	71145	14
CD36	SCARB3, PAS4	SR-B2	NM_001159558	12491	5
SCARB1	SR-B1, CD36L1	SR-B1	NM_016741	20778	5
Alternatively spliced form of SR-B1	SR-BII	SR-B1.1	—[b]	—[b]	5
SCARB2	LIMP2, CD26L2, LGP85	SR-B3	NM_007644	12492	5
CD68	gp110, SCARD1, Macrosialin	SR-D1	NM_009853	12514	11
OLR1	LOX-1, SCARE1	SR-EI	NM_138648	108078	6
Alternatively spliced form of SR-E1	LOXIN	SR-E1.1	—[b]	—[b]	6
CLEC7A	DECTIN-1	SR-E2	NM_020008	56644	6
SCARF1	SREC-1	SR-F1	NM_001004157	380713	11
SCARF2	SREC-II	SR-F2	NM_153790	224024	16
MEGF10	GM331	SR-F3	NM_1001979	70417	18
CXCL16	SR-PSOX	SR-G	NM_023158	66102	11
STAB1	FEEL-1	SR-H1	NM_138672	192187	14
STAB2	FEEL-2	SR-H2	NM_138673	192188	10
CD163	(*M130*)	SR-I1	NM_053094	93671	6
CD163L1	SCART1	SR-I2	NM_172909	244233	7
SRCRB4D	S4D-SRCRB	To be named	NM_001160366	109267	5
SSC5D	S5D-SRCRB	To be named	NM_173008	269855	7
Fcrls	IgSR, MSR	To be named	NM_030707	80891	3
CD14	None known	To be named	NM_009841	12475	18
Ly75	CD205, DEC-205	To be named	NM_013825	17076	2
MRC1	CD206, MR	To be named	NM_008625	17533	2

Current NCBI Gene Name	Alternative Names	Proposed Nomenclature[a]	Accession No.	NCBI Gene ID	Chromosome
CD207	Langerin	To be named	NM_144943	246278	6
CD209a	DC-SIGN, CLEC4L	To be named	NM_133238	170786	8
LRP1	CD91, ASGPR	To be named	NM_008512	16971	10
RAGE (membrane form)	AGER	SR-J1	NM_007425	11596	17
RAGE (soluble form)	AGER (soluble)	SR-J1.1	AB207883	11596	17

[a] Scavenger receptors that are designated “To be named” were not discussed at the workshop and will require additional input from the scientific community.

[b] National Center for Biotechnology Information reference sequence numbers are not available for the alternatively spliced forms of these receptors at this time.

NCBI, National Center for Biotechnology Information.

Table III

Summary of current human scavenger receptor nomenclature and proposed changes

Current NCBI Gene Name	Alternative Names	Proposed Nomenclature[a]	Accession No.	NCBI Gene ID	Chromosome
MSR1	SR-A1, CD204, SCARA1	SR-A1	NM_138715	4481	8
Alternatively spliced form of SR-A1	SR-AIII	SR-A1.2	NM_138716	4481	8
MARCO	SCARA2	SR-A6	NM_006770	8685	2
SCARA3	MSRL1	SR-A3	NM_016240	51435	8
COLEC12	SCARA4, SRCL, CL-P1	SR-A4	NM_130386	81035	18
SCARA5	TESR, NET33	SR-A5	NM_173833	286133	8
CD36	SCARB3, FAT, GPIV, PAS4	SR-B2	NM_001001548	948	7
SCARB1	SR-BI, CD36L1	SR-B1	NM_005505	949	12
SCARB2	LIMP2, CD36L2, LGP85	SR-B1.1	NM_005506	950	4
CD68	gp110, SCARD1, LAMP4	SR-D1	NM_001251	968	17
OLR1	LOX-1, SCARE1, CLEC8A	SR-E1	NM_002543	4973	12
Dectin 1	CLEC7A	SR-E2	NM_197947	64581	12
SCARF1	SREC-1	SR-F1	NM_003693	8578	17
SCARF2	SREC-II	SR-F2	NM_153334	91179	22
MEGF10	EMARDD	SR-F3	NM_032446	84466	5
CXCL16	SR-PSOX	SR-G	NM_001100812	58191	17
STAB1	FEEL-1	SR-H1	NM_015136	608560	3
STAB2	FEEL-2	SR-H2	NM_017564	55576	12
CD163	M130	SR-I1	NM_004244	9332	12
CD163L1	M160, CD163B	SR-I2	NM_174941	283316	12
SRCRB4D	S4D-SRCRB	To be named	NM_080744	136853	7
SSC5D	None known	To be named	NM_001144950	284297	19
CD14	None known	To be named	NM_000591	929	5
CD205	Ly75	To be named	NM_002349	4065	2
CD206	MRC1	To be named	NM_002438	4360	10
CD207	Langerin	To be named	NM_015717	50489	2
CD209\DC-SIGN	CLEC4L	To be named	NM_021155	30835	19
RAGE (membrane form)	AGER	SR-J1	NM_001136	177	6

Current NCBI Gene Name	Alternative Names	Proposed Nomenclature[a]	Accession No.	NCBI Gene ID	Chromosome
RAGE (soluble form)	AGER	SR-J1.1	AB061668	177	6

[a] Scavenger receptors that are designated “To be named” were not discussed at the workshop and will require additional input from the scientific community.

NCBI, National Center for Biotechnology Information.