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Scavenger receptors for oxidized and glycated proteins

Review Article

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Summary. Our present knowledge on chemically modified proteins and their receptor systems is originated from a proposal by Goldstein and Brown in 1979 for the receptor for acetylated LDL which is involved in foam cell formation, one of critical steps in atherogenesis. Subsequent extensive studies using oxidized LDL (OxLDL) as a representative ligand disclosed at least 11 different scavenger receptors which are collectively categorized as ''scavenger receptor family''. Advanced glycation endproducts (AGE) and their receptor systems have been studied independently until recent findings that AGE-proteins are also recognized as active ligands by scavenger receptors including class A scavenger receptor (SR-A), class B scavenger receptors such as CD36 and SR-BI, type D scavenger receptor (LOX-1) and FEEL-1/FEEL-2. Three messages can be summarized from these experiments; (i) endocytic uptake of OxLDL and AGE-proteins by macrophages or macrophage-derived cells is mainly mediated by SR-A and CD36, which is an important step for foam cell formation in the early stage of atherosclerosis, (ii) selective uptake of cholesteryl esters of high density lipoprotein (HDL) mediated by SR-BI is inhibited by AGE-proteins, suggesting a potential pathological role of AGE in a HDL-mediated reverse cholesterol transport system, (iii) a novel scavenger receptor is involved in hepatic clearance of plasma OxLDL and AGE-proteins.

Keywords: Scarenger receptors – Modified LDL – Advanced glycation endproducts (AGE) – Macrophage – Foam cell – Cholesterol transport – Atherosclerosis

1. Introduction

In 1967, Mego et al. first studied the *in vivo* behavior of *in vitro*-prepared chemically modified proteins; formalin-treated bovine serum albumin upon intravenous injection exhibited a rapid plasma clearance which was explained by effective uptake by sinusoidal liver cells such as Kupffer cells and endothelial cells (Mego et al., 1967). The pathophysiological meaning of this phenomena remains unsolved except that formalin-treated albumin has been used as a marker to distinguish sinusoidal liver cells from hepatocytes. A major breakthrough in the biological significance of chemically modified proteins was made in 1979 by Goldstein and Brown and their associates who reported that incubation of cultured macrophages with acetylated low density lipoprotein (AcLDL) resulted in intracellular accumulation of cholesteryl esters (CE), foam cell formation characteristically found in an atheroma lesion in atherosclerosis (Goldstein et al., 1979). This study implicated the presence of a receptor(s) for AcLDL or chemically modified LDL in macrophages which might play an important role in foam cell formation in atherosclerotic processes and initiated a subsequent molecular level approach to ''the scavenger function of macrophages or macrophage-derived cells''. The initial definition of the term ''scavenger receptor'' is the receptor(s) that mediates endocytic uptake of modified proteins. Since AcLDL, an initial ligand proposed for the scavenger receptor, is unlikely to occur *in vivo*, oxidized LDL (OxLDL) has then been replaced as a naturally-occurring ligand and atherogenic LDL *in vivo* (Palinski et al., 1989; Yla-Herttuala et al., 1989). A number of different scavenger receptors for modified LDL (SR-A, SR-B, SR-C SR-D, SR-E, SR-F, SR-PSOX, FEEL-1 and FEEL-2) have now been identified not only in macrophages but also non-macrophage cells and the growing scavenger receptor family also currently includes cell surface receptor (SR-BI) whose main ligand is high density lipoprotein (HDL). Currently identified scavenger receptors and their lipoprotein ligands are summarized in Table 1 according to a modification of the classification proposed by Krieger (Krieger, 1997).

Table 1. Ligand-binding profiles of members of the scavenger receptor family and AGE receptors

Class	Member(s)	Lipoprotein ligands				AGE	References
		AcLDL	OxLDL	LDL	HDL		
SR-A	I	+	+	−		+	(Kodama et'al., 1990; Araki et'al., 1995)
	II	+	+	−		+	(Rohrer et'al., 1990; Suzuki et'al., 1997)
	III	+	+	−			(Gough et'al., 1998)
	MARCO	+					(Elomaa et'al., 1995)
SR-B	CD36	+/−	+	−	+	+	(Endemann et'al., 1993; Ohgami et'al., 2001a)
	SR-BI	+	+	+	+	+	(Acton et'al., 1996; Ohgami et'al., 2001b)
SR-C	dSR-C1	+		−			(Pearson et'al., 1995)
SR-D	Macrosialin/CD68	+	+	−			(Yoshida et'al., 1998)
SR-E	LOX-1	+/−	+	−		+	(Sawamura et'al., 1997; Jono et'al., 2002)
SR-F	SREC-I	+	+			−	(Adachi et'al., 1997)
Others	SR-PSOX	−	+	−			(Shimaoka et'al., 2000)
Others	FEEL-1, FEEL-2	+	−	−	−	+	(Adachi et'al., 2002; Tamura et'al., 2003)
	RAGE					+	(Neeper et'al., 1992)
	80K-H/OST48/Galectin-3 complexes					+	(Vlassara et'al., 1995)

+ indicates that the molecule is demonstrated to serve a ligand for the receptor, whereas − indicates that the molecule is demonstrated to not to be a ligand for the receptor. A space indicates no reported data

A primary driving force of research on these scavenger receptors has been their potential links to atherosclerotic processes. In contrast, glycated proteins and their receptor systems have been studied from the potential link to diabetes or diabetic complications. The nonenzymatic reaction of proteins with glucose is known as the Maillard reaction, in which proteins react with glucose or reduced sugars to form Schiff bases and Amadori products. These early products are converted to advanced glycation end products (AGE) which are characterized physicochemically by fluorescence, brown color, and intra- or intermolecular cross-linking (Baynes and Thorpe, 1999; Horiuchi, 1996; Vlassara, 1997). The term ''glycated proteins'' include these early products such as Schiff bases and Amadori products and AGE-structures. There are two major breakthroughs in this field; first is the discovery of hemoglobin AIc, Amadori adducts to amino group of N-terminal valine of hemoglobin β chain (Bookchin and Gallop, 1968; Rahbar, 1968), which is used as a clinical marker for treatment of diabetic patients, and the second is the proposal of the receptor for AGE-proteins (the AGE-receptors) (Vlassara et al., 1985). Immunohistochemical studies have revealed the presence of AGE-modified proteins in human and animal tissues under various pathological conditions related to aging and age-related disorders such as diabetic macro- and microangiopathy (Mitsuhashi et al., 1993; Nakamura et al., 1993), atherosclerosis (Kume et al., 1995), Alzheimer's disease (Smith et al., 1994; Vitek et al., 1994), and various types of amyloidosis characterized by deposition of abnormal amyloid fibril proteins (Miyata et al., 1993). AGE proteins are known to induce a variety of cellular events in vascular wall cells and other cells, possibly through the functions of AGE-receptors, thereby playing an active role in pathogenesis of several diseases. The AGE-receptors so far known are RAGE (receptor for AGE), 80K-H/OST48/galectin-3 complexes and several members of the scavenger receptor family which are also included in Table 1.

The studies on OxLDL receptors and AGE-receptors have developed independently. However, our recent discovery that several scavenger receptors including SR-A, CD36, SR-BI and LOX-1 are able to recognize AGE-proteins as efficient ligands strongly suggests that other AGE-receptors such as 80K-H/OST48/galectin-3 complexes and RAGE could be categorized as the same members

of the scavenger receptor family. Based on this point, the receptors we focus in this article are members of scavenger receptors which have been characterized as AGE-receptors, such as SR-A type I and type II, CD36, SR-BI, LOX-1, and FEEL-1/FEEL-2. The review articles which cover the present status of the scavenger receptor family (de Villiers and Smart, 1999; Krieger, 1997; Krieger, 2001; Platt et al., 2001) and AGE-receptors (Vlassara et al., 2002; Miyazaki et al., 2002) are available.

2. Scavenger receptors that recognize AGE-proteins as ligands

2.1. SR-A, type I and type II

SR-A type I and type II are the first identified members of the scavenger receptor family (Kodama et al., 1990; Rohrer et al., 1990). Several studies reveal important roles of this receptor in atherogenesis. SR-A gene knockout mice bred either on atherosclerosis-susceptible apolipoprotein E (apoE)-knockout mice (Suzuki et al., 1997) or LDL-receptor knockout mice (Sakaguchi et al., 1998) show a marked reduction in the size of atherosclerotic lesions ($\sim$50% reduced relative to apoE-/- and $\sim$20% reduced relative to LDLR-/-, respectively), suggesting SR-A as an important pro-atherogenic molecule *in vivo*. The degradation capacity by peritoneal macrophages obtained from SR-A-knockout mice was reduced significantly for AcLDL ($<$30%) but partially for OxLDL ($\sim$50%) when compared with wild type macrophages (Suzuki et al., 1997). However, a recent experiment using peritoneal macrophages obtained from double knockout mice of SR-A and CD36 clearly showed that SR-A and CD36 account for 75–90% of degradation of AcLDL or OxLDL, providing a solid evidence that SR-A and CD36 are responsible for endocytic uptake of modified LDL by macrophages or macrophage-derived cells (Kunjathoor et al., 2002).

SR-A as one of AGE-receptors has come from studies with CHO cells overexpressing SR-A; degradation capacity for AGE-BSA by transfected cells increases almost in an all-or-none fashion, which is parallel with the degradation capacity for AcLDL (Araki et al., 1995). Furthermore, peritoneal macrophages from SR-A gene knockout mice reduce their capacity to degrade AGE-BSA to 33% when compared with wild type macrophages (Suzuki et al., 1997). Combined with a recent result that degradation of AGE-BSA by human monocyte macrophages was significantly inhibited by anti-SR-A antibody (Takaki, personal communication), these results strongly indicate that SR-A is a major player in endocytic uptake of AGE-ligands (Sano et al., 1999). Regarding the ligand specificity of SR-A for AGE-ligands, among BSA preparations modified with several aldehydes such as glycolaldehyde, methyglyoxal, and glyoxal, which are known to be important intermediates for formation of AGE structures, glycolaldehyde-modified BSA was a most active ligand for SR-A (Nagai et al., 2000). LDL modified with glycolaldehyde also serves as a ligand for SR-A and induces CE accumulation in macrophages (Jinnouchi et al., 1998). Glycolaldehyde-modified proteins are demonstrated immunohistochemically to occur in human atherosclerotic lesions (Nagai et al., 2002). Taken together, it seems likely that AGE-proteins produced by modification with glycolaldehyde might play a crucial role in the atherogenesis *in vivo*.

2.2. CD 36

CD36 is a highly glycosylated 88 kDa protein that binds to various ligands such as fatty acids, collagen, thrombospondin, anionic phospholipids, and OxLDL (Febbraio et al., 2001). Its two major pathophysiological functions are an OxLDL receptor in macrophages (Endemann et al., 1993) and a fatty acid transporter in adipocytes (Abumrad et al., 1993). Monocyte-derived macrophages obtained from CD36-deficient patients reduced $\sim$50% of their endocytic capacity for OxLDL compared with those from normal subjects (Nozaki et al., 1995). CD36 is highly expressed in macrophage-derived foam cells in the core of atherosclerotic plaques, whereas SR-A-positive macrophage-derived foam cells tend to localize in the periphery of atherosclerotic lesions (Nakata et al., 1999), suggesting that CD36 is a major OxLDL receptor as SR-A but plays a different role from SR-A in the formation of atherosclerotic plaques. This notion is supported by the report that targeted disruption of CD36 in apoE null mice resulted in reduced atherosclerotic lesions (Febbraio et al., 2000).

Recent experiments using CHO cells overexpressing CD36 demonstrated that AGE-BSA possesses high affinity for and saturable binding to CD36 and thereby induces receptor-mediated endocytosis (Ohgami et al., 2001a), indicating that CD36 is one of AGE receptors. Since AGE-modified proteins are accumulated intracellularly in foam cells as well as extracellularly in atheroscleoric lesions (Kume et al., 1995; Meng et al., 1996), interaction of these AGE-ligands with CD36 may accelerate atherosclerosis and diabetic vascular complications. The contention of CD36 as one of AGE-receptors is also supported by the recent result that a significant increase in

CD36 expression during cell differentiation from preadipocytes into adipocytes is accompanied with an increase in the endocytic uptake of AGE-ligand by these adipocytes (Kuniyasu et al., 2003).

2.3. SR-BI

SR-BI was originally identified as a scavenger receptor that mediates endocytosis of AcLDL by expression cloning using cDNA libraries from CHO cells with a mutated LDL receptor gene (Acton et al., 1994). SR-BI has two transmembrane domains similar to CD36 (Fig. 1), but its function is quite different from CD36. SR-BI recognizes HDL and mediates ''selective uptake'' of HDL-CE without endocytic uptake of HDL apolipoproteins (Acton et al., 1996), indicating that SR-BI is a HDL receptor. This idea is strongly supported by animal studies; (i) adenovirus-mediated overexpression of SR-BI in the liver leads to a marked reduction in plasma HDL levels and increased cholesterol secretion into bile acids (Kozarsky et al., 1997) and (ii) SR-BI-knockout mice exhibits an increase in abnomally large apoE-enriched HDL-like particles in the plasma (Rigotti et al., 1997). In addition to hepatic selective uptake, SR-BI also mediates cholesterol efflux from peripheral cells to HDL particles (Ji et al., 1997; Chinetti et al., 2000). Therefore, it is evident that SR-BI plays crucial roles in reverse cholesterol transport and atheroprotective functions of HDL (Krieger, 2001).

Experiments using CHO cells overexpressing hamster SR-BI showed that AGE-BSA undergoes active endocytosis and subsequent lysosomal degradation by these cells (Ohgami et al., 2001b). Thus, SR-BI is identified as a novel AGE-receptor. Intriguingly, however, cross-competition assay showed that AGE-BSA and HDL did not compete for binding to SR-BI, suggesting that AGE-BSA and HDL bind to independent sites on SR-BI. This notion is also supported from a difference in their post-binding behavior; AGE-BSA undergoes endocytic degradation, whereas HDL does not.

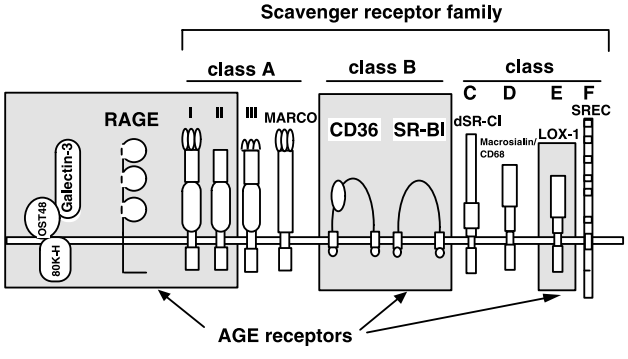

Fig. 1. Schematic representation of scavenger receptor family and AGE-receptors. The scavenger receptor family consists of class A, class B, class C, class D, class E, class F and other not yet-classified receptors. Six receptors out of them have been shown to recognize AGE as ligands which include SR-A type I and type II, CD6, SR-BI, LOX-1 and FEEL-1/FEEL-2. Independent of these studies, RAGE and 80K-H/OST48/galectin-3 complex have been identified and characterized as AGE receptors. See Table 1 for details

Effects of AGE on SR-BI functions such as selective uptake of HDL-CE and cholesterol efflux from cells to HDL were also determined by experiments using CHO cells overexpressing hamster SR-BI (Ohgami et al., 2001b). As a result, AGE-BSA efficiently inhibited selective uptake of HDL-CE (Ohgami et al., 2001b). The precise mechanism for SR-BI-mediated CE transfer from HDL to plasma membrane remains unsolved. A hydrophobic channel between HDL particles and cell membrane was proposed in which HDL-CE moves through the channel in a CE gradient dependent manner (Rodrigueza et al., 1999). AGE-BSA binding to SR-BI could somehow interfere with the formation of this channel. A more recent model was proposed for selective uptake of HDL-CE. After binding to SR-BI, HDL particles undergo endocytosis followed by resecretion without lysosomal degradation during which HDL-CE is selectively transferred to cells (Silver et al., 2001). AGE-ligand could affect on the intracellular processing of HDL. Experiments using the same cells overexpressing SR-BI showed that the cholesterol efflux from these cells to HDL as a cholesterol acceptor was significantly inhibited by AGE-BSA, indicating that AGE-ligands might inhibit SR-BI-dependent cholesterol efflux, but not SR-BI-independent cholesterol efflux. Taken together, these *in vitro* observations using CHO cells overexpressing SR-BI suggest that AGE-proteins inhibit reverse cholesterol transport by suppressing SR-BI-mediated selective uptake of HDL-CE by liver and SR-BI-mediated cholesterol efflux from peripheral cells to HDL.

2.4. LOX-1

LOX-1 (lectin-like OxLDL receptor-1) is a C-type lectin identified as a novel scavenger receptor for OxLDL which is highly expressed on endothelial cells (Sawamura et al., 1997), and mediates endocytic uptake and subsequent lysosomal degradation of OxLDL. Binding of OxLDL to this receptor induces several cellular events such as activation of NF-kB (Cominacini et al., 2000), up-regulation of monocyte chemoattractant protein-1 (Li D et al., 2000), and reduction in intracellular nitric oxide (Cominacini et al., 2001). LOX-1 is expressed in endothelial cells covering early

atherosclerotic lesions and macrophages and smooth muscle cells accumulated in the intima of advanced atherosclerotic plaques (Kume and Kita, 2001), indicating its crucial role as an initiator as well as accelerator for formation of atherosclerotic lesions. In addition to OxLDL, ligands for LOX-1 include polyanionic compounds, aged/apoptotic cells (Oka et al., 1998), activated platelets (Kakutani et al., 2000) and bacteria (Shimaoka et al., 2001). A recent cellular experiment revealed that AGE-proteins showed the specific binding to CHO cells overexpressing bovine LOX-1, which was effectively suppressed by an anti-LOX-1 antibody (Jono et al., 2002). Cultured bovine aortic endothelial cells also showed the specific binding for AGE-proteins, which was also inhibited significantly by the anti-receptor antibody, indicating LOX-1 might be an endothelial AGE-receptor like RAGE. Further studies using LOX-1 knockout mice will be needed to test this contention. A soluble form of LOX-1 in human plasma is being analyzed as a potential clinical marker for atherosclerosis (Kume and Kita, 2001).

2.5. FEEL-1/FEEL-2

Fasciclin, EGF-like, laminin-type EGF-like and link domain-containing scavenger receptor-1 (FEEL-1) and its paralogous gene, FEEL-2, were recently cloned by expression cloning of human umbilical vein endothelial cells. These receptors are structurally unrelated to other scavenger receptors. FEEL-1 is a protein of 2570 amino acids, including 7 fasciclin, 16 EGF-like, 2 laminin-type EGF-like and 1 link domain near the transmembrane region. FEEL-2 is similar to FEEL-1 whose amino acid sequence is about 40% identical to FEEL-1. Both FEEL-1 and FEEL-2 are expressed at mRNA levels in the spleen and lymph node, while only FEEL-1 is expressed in CD14-positive mononuclear cells and vascular endothelial cell lines. Recent studies using CHO cells overexpressing FEEL-1 or FEEL-2 showed the specific binding of these cells for AGE-ligands, suggesting that both receptors belonging to scavenger receptor family are the AGE-receptors (Tamura et al., 2003).

2.6. Other scavenger receptors recognizing AGE-ligands

It remains unsolved whether other members belonging to the scavenger receptor family such as SR-A, type III (Gough et al., 1998), MARCO (Elomaa et al., 1995), dSR-C1 (Abrams et al., 1992; Ramet et al., 2001), macrosialin (Rabinowitz et al., 1991; Ramprasad et al., 1995; Yoshida et al., 1998), SREC-I (Adachi et al., 1997) and SR-PSOX (Shimaoka et al., 2000) (Table 1) are able to recognize AGE-proteins as their ligands. Experiments using cells overexpressing these receptors or cells obtained from mice in which one of these receptors is knockout are to be designed to clarify this issue. A recent study showed that CHO cells overexpressing SREC-I did not show any specific binding to AGE-ligands (Tamura et al., 2003), indicating that all the members of the scavenger receptor family does not necessarily serve as AGE-receptors.

A novel receptor for HDL with 228 amino acids was recently cloned which resembles GPI-anchored proteins and designated as GPI-anchored HDL binding protein 1 (GPI-HBP1). Like SR-BI, this receptor mediates selective CE uptake but not HDL-dependent cholesterol efflux. The binding of HDL to this receptor was inhibited partially by OxLDL and AcLDL. It remains unknown whether AGE-ligands are recognized by this receptor.

3. AGE-receptors

3.1. RAGE

Receptor for AGE (RAGE), which was originally purified from bovine lung endothelial cells (Neeper et al., 1992) as a 35-kDa protein that belongs to the immunoglobulin superfamily (Schmidt et al., 2001), is now regarded as a representative AGE receptor on endothelial cells. Binding of AGE to RAGE is not accompanied by endocytosis of the ligand, which is a sharp contrast to the scavenger receptors, but generates intracellular signals, including activation of a transcription factor NF-κB (Kislinger et al., 1999). N^{ε}-(carboxymethyl) lysine (CML) was identified as an AGE-structure responsible for recognition by RAGE (Kislinger et al., 1999). AGE-proteins interaction with RAGE increases expression of vascular cell adhesion molecule-1 and tissue factor in endothelial cells, which play essential roles in the development of atherosclerosis. Atherosclerotic lesions in apoE-knockout mice that were accelerated under streptozotocin-induced diabetic conditions were significantly suppressed by intraperitoneal administration of a soluble form of RAGE (Park et al., 1998), indicating that the AGE-RAGE system is involved in accelerated atherosclerosis in diabetes. The supporting data came recently; type I diabetic mice were prepared by transgenic expression of iNOS with insulin promoter. Upon these animals were double transgenic with RAGE, the renal sclerotic lesions became worsen (Yamamoto et al., 2001). Compared to these animal studies (Park et al., 1998; Yamamoto et al., 2001) which strongly support the active involvement of RAGE in diabetes-enhanced atherosclerosis, a further

information of its ligand specificity at a molecular level is needed to understand an underlying mechanism for a RAGE-induced pathology.

3.2. 80K-H/OST48/Galectin-3 complexes

Two AGE-binding proteins of 60 kDa and 90 kDa (P60 and P90) are identified from rat liver (Yang et al., 1991). Subequently, P60 is shown to be homologueous to a 50 kDa component of the oligosaccharyltransferase complex (OST 48), whereas P90 is identical to an 80-kDa phospho-tyrosine containing proteins (80K-H). Galectin-3, a lectin like protein with a high affinity for galactose-containing glycoproteins, is identified as a component of p90 (Vlassara et al., 1995). Galectin-3 exerts multiple functions, such as modulation of cell adhesion, cell cycle control, and mRNA splicing (Pricci et al., 2000). Compared with wild-type mice, galectin-3-knockout mice show increased AGE accumulation in kidney and accelerated glomerulopathy under diabetic conditions, suggesting a protective role of galectin-3 against diabetic glomerulopathy (Pugliese et al., 2001).

3.3. Other AGE-receptors or AGE-binding proteins

One of important and controversial issues with respect to receptors for glycated proteins is whether or not a novel receptor is present *in vivo* which specifically recognizes Amadori products as a ligand. Cohen and her associates have proposed the presence of the receptor system for Amadori-modified proteins and their recent study has identified calnexin as the receptor or binding protein for Amadori products (Wu et al., 2001). Further studies at a molecular level are needed to characterize calnexin by using calnexin-inactivated cells or calnexin knockout mice.

4. Scavenger receptors involving in plasma clearance of oxidized proteins and glycated proteins

The presence of chemically modified proteins in plasma such as OxLDL and AGE-proteins has been under an active investigation not only from diagnostic interest but also from the metabolism of modified proteins *in vivo*. Intravenously injected AGE-BSA, AcLDL and OxLDL are rapidly cleared from the circulation, which is explained by receptor-mediated endocytosis by sinusoidal liver endothelial cells to a major extent and by Kupffer cells to a lesser extent (Smedsrod et al., 1997; Nagelkerke et al., 1983). In contrast to the major role in SR-A in endocytic uptake of modified proteins by macrophages, interesting observations were that plasma clearance rates of intravenously injected AcLDL (Suzuki et al., 1997), OxLDL (Ling et al., 1997; Van Berkel et al., 1998), or AGE-ligands (Matsumoto et al., 2000) in SR-A-knockout mice are indistinguishable from those of wild type mice, although the immunohistochemical analysis confirms the total disappearance of SR-A from liver of SR-A-null mice. In addition, studies using cultured sinusoidal liver endothelial cells obtained from SR-A-knockout mice clearly show that endocytic uptake of AcLDL and AGE-BSA by these cells does not significantly differ from those of wild type mice (Matsumoto et al., 2000). From these *in vivo* and *in vitro* experiments, it is likely that the hepatic clearance of plasma OxLDL and AGE-proteins from the circulation is mediated by the scavenger receptor(s) distinct from SR-A. Identification of such a receptor responsible for plasma clearance of chemically modified proteins could provide an important clue to clinical significance of plasma OxLDL and AGE-proteins. The phenotypic changes expected for mice laking such a receptor would be a high plasma level of OxLDL and AGE-proteins as well as a marked retardation in their plasma clearance rates.

5. Ligand stucture(s) responsible for receptor recognition

All the receptors for oxidized and glycated proteins described in this review belong to the scavenger receptor family except for RAGE and 80K-H/OST48/galectin-3 complexes. A big and critical difference between receptors of scavenger receptor family and conventional receptors such as insulin receptor and cytokine receptors is the ligand specificity. Whereas the ligand specificity of the latter is narrow and ligand specific, the ligand specificity of the former is not only broad but also overlapped to some extent. For instances, in addition to receptor-specific ligands (like HDL for SR-BI), the receptors of the scavenger receptor family are able to recognize a remarkably wide variety of ligands, ranging from polyanionic compounds such as modified proteins (AcLDL, OxLDL and AGE-proteins), sulfated polysaccharides and certain polynucleotides to apoptotic cells, bacteria and LPS. Recently, its analogy to hepatic cytochrome P450s is emphasized. (Krieger, 2001).

Our final goal is to elucidate the *in vivo* function of individual receptors for oxidized proteins and AGE-proteins. One way to achieve this is to determine ‘‘a receptor-specific ligand structure’’ or ‘‘a receptor-common ligand

structure'' so that we might develop an agonist/antagonist for one or some receptors of the scavenger receptor family. Small-molecule inhibitors for the SR-BI-mediated selective CE-transfer were recently discovered; HDL binding to SR-BI was not inhibited but enhanced by these inhibitors (Nieland et al., 2002). Moreover, oxidized choline glycerophospholipids ($oxPC_{CD36}$), components of OxLDL, was recently identified as crucial ligand structures for CD36 (Podrez et al., 2002a) and these structures were demonstrated not only to be enriched in atherosclerotic lesions, but also to promote macrophage foam cell formation via CD36 (Podrez et al., 2002b). These approaches are highly promising because such structural insights into CD36- or SR-BI-mediated ligand recognition could provide a platform for the development of potential therapeutic agents.

Proteins modified with glycolaldehyde or glyceraldehyde are known to serve as effective ligands for SR-A (Nagai et al., 2000). A pyridine derivative purified from glyceraldehyde-modified N^{α}-acetyl-L-lysine was shown to stimulate the superoxide production from human HL-60 cells (Hayase, personal communications). A similar fluorescent pyridine compound (3-hydroxy-4-hydroxymethyl-1-(5-amino-5-carboxypentyl) pyridinium cation) was purified from glycolaldehyde-treated Na-Cbz-lysine (Nagai et al., 2002). This compound was shown to enhance the chemotactic migration of human monocytes (Araki et al., unpublished observations). From these observation together with a recent report that pyrrole or pyridinium adducts of LDL is recognized as effectively as OxLDL by macrophages (Podrez et al., 2000), it is possible that these pyridinium structures could mimic, in part, a receptor-specific ligand structure, or a receptor-common ligand structure for scavenger receptor family. Further insight into structural basis of receptor-ligand interaction in scavenger receptor family is necessary for another breakthrough in this field of research.

6. Conclusions

RAGE and 80K-H/OST48/galectin-3 complexes have been identified and characterized as AGE-receptors independently of receptors of scavenger receptor family. However, the physicochemical property of AGE-proteins such as an increase in net negative charge which makes modified proteins being polyanionic is closely similar to that of oxidized proteins. Furthermore, some of the members of scavenger receptor family such as SR-A type I and type II, CD36, SR-BI, LOX-1, and FEEL-1/FEEL-2 were shown to serve as AGE-receptors. Therefore, it probably is reasonable at present to propose here that RAGE and 80K-H/OST48/galectin-3 complexes are to be categorized as the members of the scavenger receptor family until their definite biological function(s) is clarified. Further studies in this direction will be important for understanding their pathophysiological functions particularly in life-style-related vascular disease which is enhanced by dyslipidemia, diabetes and hypertension.

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