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The Conserved Scavenger Receptor Cysteine-Rich Superfamily in Therapy and Diagnosis

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Abstract—The scavenger receptor cysteine-rich (SRCR) superfamily of soluble or membrane-bound protein receptors is characterized by the presence of one or several repeats of an ancient and highly conserved protein module, the SRCR domain. This superfamily (SRCR-SF) has been in constant and progressive expansion, now up to more than 30 members. The study of these members is attracting growing interest, which parallels that in innate immunity. No unifying function has been described to date for the SRCR domains, this being the result of the limited knowledge still available on the physiology of most members of the SRCR-SF, but also of the sequence versatility of the SRCR domains. Indeed, involvement of SRCR-SF members in quite different functions, such as pathogen recognition, modulation of the immune response,

epithelial homeostasis, stem cell biology, and tumor development, have all been described. This has brought to us new information, unveiling the possibility that targeting or supplementing SRCR-SF proteins could result in diagnostic and/or therapeutic benefit for a number of physiologic and pathologic states. Recent research has provided structural and functional insight into these proteins, facilitating the development of means to modulate the activity of SRCR-SF members. Indeed, some of these approaches are already in use, paving the way for a more comprehensive use of SRCR-SF members in the clinic. The present review will illustrate some available evidence on the potential of well known and new members of the SRCR-SF in this regard.

I. Introduction

Innate immunity is an ancient and universal form of host defense against invading pathogens but also an integral part of a broader system responsible for the homeostasis of the internal environment in multicellular organisms. It is usually regarded as the first line of defense for such organisms, both plants and animals, implicating that it first arose before these two kingdoms diverged. Its main function is to detect nonself molecules and eliminate them, whether directly or through the stimulation of an adaptive immune response. To do this, receptors have evolved that recognize pathogen-associated molecular patterns (PAMPs¹), which are conserved, essential for the pathogen survival, and not shared by the host. Examples of those PAMPs recognized by innate

immune receptors are lipopolysaccharide (LPS) from Gram-negative bacteria, lipoteichoic acid (LTA), peptidoglycan from Gram-positive bacteria, or β -glucans and mannans from yeast. The innate immune receptors recognizing PAMPs are termed pattern-recognition receptors (PRRs). Only a limited number of PRRs are present in the genome that are germline-encoded and have been acquired by natural selection (Janeway and Medzhitov, 2002). Aside from PAMPs, PRRs are able to bind and establish a response to a number of other ligands, including modified self-ligands, and thus play a role in the modulation of autoimmunity (Palm and Medzhitov, 2009).

The C-type lectin domain, the leucine-rich repeat, and the scavenger receptor cysteine-rich (SRCR) domain are prominent protein domains associated with pattern recognition (Gordon, 2002). The SRCR domain is the common feature in a group of proteins termed the SRCR superfamily (SRCR-SF). Although key residues in the SRCR domain have been conserved with relatively little change throughout evolution, other amino acids surrounding them have evolved freely, thus generating a myriad of proteins with vast functional diversity. The variability of the SRCR domain is not limited to its structure but is also defined by numerical variations of the domain, ranging from single copy to up to 14 repeated domains. Furthermore, many SRCR-SF members are mosaic or multidomain proteins, adding to the multifaceted nature of these proteins. Proteins containing SRCR domains have been proposed to function in the homeostasis of epithelia and the immune system, and some have been associated with a number of diseases and pathogenic states, such as atherosclerosis, Alzheimer's disease, autoimmune diseases and cancer, thus exhibiting

¹Abbreviations: AIM, apoptosis inhibitory molecule; ALCAM, activated leukocyte cell adhesion molecule; BTB/POZ, broad complex, tramtrack and bric-a-brac/poxvirus and zinc finger; CRP-ductin, C-reactive protein-ductin; CUB, complement C1r/C1s, Uegf, Bmp1; DMBT1, deleted in malignant brain tumors 1; ECM, extracellular matrix; Hb, hemoglobin; HCC, hepatocellular carcinoma; HO, heme oxygenase; Hp, haptoglobin; IL, interleukin; IVR, intervening region; kb, kilobase(s); LDL, low-density-lipoprotein; LPS, lipopolysaccharide; LTA, lipoteichoic acid; Mac-2BP, Mac-2-binding protein; MARCO, macrophage receptor with collagenous structure; NK, natural killer; PAMP, pathogen-associated molecular pattern; PBMC, peripheral blood mononuclear cell; PKC, protein kinase C; PMA, phorbol 12-myristate 13-acetate; PRR, pattern-recognition receptor; PRRSV, porcine reproductive and respiratory syndrome virus; PST, proline-serine-threonine; rshCD5, recombinant soluble human CD5; rshCD6, recombinant soluble human CD6; SAG, salivary agglutinin; sCD163, soluble CD163; SID, SRCR interspersed domain; SLE, systemic lupus erythematosus; Sp α , secreted protein α ; SP, surfactant protein; SR, scavenger receptor; SR-AI, scavenger receptor type I A; SRCR, scavenger receptor cysteine-rich; SRCR-SF, scavenger receptor cysteine-rich superfamily; TCR, T-cell receptor; TLR, Toll-like receptor; TNF, tumor necrosis factor; Treg, T-regulatory cells; ZP, zona pellucida.

promising potential as targets for diagnostic and/or therapeutic intervention.

II. The Scavenger Receptor Cysteine-Rich Superfamily

A. History and Definition. Scavengers versus Scavenger Receptor Cysteine-Rich Proteins

The superfamily of receptors with SRCR domains was described at the beginning of the nineties upon the identification of a series of receptors containing one or several extracellular domains homologous to the cysteine-rich C-terminal domain of the type I class A scavenger receptor expressed in macrophages (SR-AI) (Freeman et al., 1990). Certain features common to both the SRCR and the immunoglobulin domain suggested at first that these proteins could be related to the Ig superfamily: indeed, all its members were either cell-surface or secreted proteins, presenting cysteine-containing tandem-repeated domains and expressed in cells of the immune system (Huang et al., 1987; Resnick et al., 1994). However, this theory was not supported by detailed alignment analysis. It was then speculated that these proteins could be related to the bacterial chaperone PapD, which mediates the assembly of pili in *Escherichia coli* (Holmgren and Bränden, 1989). This protein possesses two Ig-like domains that share a certain homology with the SRCR-SF member CD5; again, further alignment analysis did not support the idea that these proteins belonged to the same family. It then became clear that these proteins form a separate superfamily, termed SRCR.

Scavenger receptors (SRs) were initially defined by their ability to uptake modified lipoproteins (Brown and Goldstein, 1983). It is now known that these receptors have a much broader ligand-binding capacity, including also polyribonucleotides, proteins, polysaccharides, and lipids. Some of these are host molecules (such as oxidized or acetylated LDL, haptoglobin-hemoglobin complexes, or polysulfated structures) and others are of pathogenic origin (such as LPS or LTA). The factor common to these ligands is their polyanionic nature, so the term SR now defines an extracellular glycoprotein (either soluble or membrane-bound) involved in the recognition and/or endocytosis of negatively charged molecules (Sarrias et al., 2004a). It is noteworthy that not all polyanionic molecules are SR ligands, indicating that there are structural as well as charge requirements for binding. Most SRs are multidomained proteins; however, no common domain has been identified that confers scavenger activity to an extracellular protein (Gough and Gordon, 2000). Thus, SRs constitute a functional family of structurally unrelated receptors. The opposite situation is true for the SRCR-SF, whose members are closely related from the structural point of view but share few common functions. The fact that some SRCR-SF members behave functionally as SRs has in-

troduced a certain degree of confusion between these two families of innate receptors. Indeed, even when an SRCR domain is present, it is not necessarily involved in ligand binding, as seems to be the case for SR-AI (Rohrer et al., 1990).

B. Structure of the Scavenger Receptor Cysteine-Rich Domains: Group A and B Members

SRCR domains are approximately 90 to 110 amino acids long and are characterized by their high and well defined cysteine content (Resnick et al., 1994; Sarrias et al., 2004a). Depending on the characteristics of their SRCR domains, two types of SRCR-SF members are reported: those with type A domains, which are encoded by at least two exons and contain six cysteine residues, and those with type B domains, encoded by a single exon and containing eight cysteine residues. There are, however, some exceptions: for instance, some group A members, such as SR-AIII, present truncated SRCR domains containing four cysteines (Rohrer et al., 1990). Likewise, isolated domains containing six cysteines are found among group B members, as is the case with CD5, CD163, WC1, and MC16 (Sarrias et al., 2004a). Moreover, SpA/AIM, WC1/T19 and CRP-ductin (mouse DMBT1) possess individual domains containing seven cysteines. However, the simultaneous presence of type A and B domains on the same SRCR-SF receptor has never been reported. Sequence analysis revealed that although SRCR domains share different levels of homology, the relative position of cysteines is well conserved within the domain, as is the pattern of disulfide bonds. Thus, sequence analysis revealed that cysteines C1 and C4 form a disulfide bond, because they are always present in group B but not group A. Proteolytic analysis showed that the other cysteine pairs forming disulfide bonds are C2-C7, C3-C8, and C5-C6 (Resnick et al., 1996). These results have been confirmed by structural analysis of crystallized individual protein domains. The first SRCR domain crystallized was the type A domain of Mac-2BP, which revealed a compact fold organized around a curved six-stranded β -sheet cradling an α -helix (Hohenester et al., 1999), as well as the replacement of C4 present in group B members by an aromatic amino acid. A similar compact globular fold was found for the group A SRCR domain of MARCO (Ojala et al., 2007). In this case, however, the fold was composed of a twisted five-stranded antiparallel β -sheet and a long loop covering a single α -helix. Analysis of the dimerized protein revealed that it contains a large eight-stranded β -sheet formed by β -sheet swapping between the two monomers. This different conformation might explain why certain ligands can only be bound by SRCR-SF members in multimeric form. The β -sheet was found to contain a series of basic residues, among them a cluster of arginines, which were essential for ligand binding; the fact that all of them seemed to be needed for binding suggests the existence of a cooperative effect. Binding was

also shown to be dependent on Ca^{2+} ions, presumably because these ions modulate electrostatic charges and might help accommodate the ligand in the binding site. An acidic cluster on the long loop region was also revealed that seems to be involved in metal ion binding.

It should be noted that group B SRCR domains of only one protein have been crystallized to date, corresponding to the most membrane-proximal (D3) (Rodamilans et al., 2007) and distal (D1) SRCR domains (Garza-Garcia et al., 2008) of CD5. It is noteworthy that, on the basis of the available data, the basic three-dimensional structure characteristics of group A and B SRCR domains seem to be superimposable and therefore indistinguishable, which makes it questionable to maintain the existence of two different types of SRCR domains from the structural point of view.

C. Phylogeny and Ontogeny

Currently, the SRCR-SF contains more than 30 members, but this number is in constant and progressive expansion (Sarrias et al., 2004a) (see Tables 1 and 2; Figs. 1 and 2). Although the great majority of SRCR-SF members have been described in mammals (man, mouse, rat, pig, cow, rabbit, sheep), these proteins have also been detected in other species of vertebrates, whether highly developed (birds, amphibians) or primitive (fish), in invertebrates (sponges, echinoderms, insects), and even in algae (Wheeler et al., 2008). Sponges constitute the oldest and lowest metazoan phylum; within them, *Geodia cydonium*, from the family Geodiidae, represents the oldest living group (Müller et al., 1999). Several alternatively spliced forms of an SRCR group A protein and a group B protein have been identified in *G. cydonium* (Pancer et al., 1997; Blumbach et al., 1998; Pahler et al., 1998). The group A protein has both membrane-bound and soluble forms, whereas the SRCR domain of MAP_GEOCY, the group B protein, displays high homology with those of CD5 and CD6. These facts indicate that this superfamily is indeed very ancient and conserved throughout the phylogenetic scale. These receptors may act as pattern recognition receptors in the traditional sense in these organisms but are believed to be more important for protein-protein interaction (Bowdish and Gordon, 2009).

All eutherian (placental) mammals express a form of SR-A, suggesting that this gene was present in the ancestral stage, before the separation of this family from the common tree that would give rise to birds and amphibians (Bowdish and Gordon, 2009). This is further reinforced by the presence of SR-A homologs outside eutherian mammals, such as Eater in *Drosophila melanogaster* (Kocks et al., 2005). This could change in the future when more complete genome analysis data for lower phyla are available. MARCO homologs, on the other hand, have been found in chicken, zebrafish, and sea urchin, suggesting that it is closer to the ancestral gene from which SR-A evolved. However, more evidence

is needed before this can be asserted. A notable difference between these two receptors is that the SRCR domain of SR-A is poorly conserved between species, whereas there is high sequence identity among SRCRs from MARCO homologs. This could be explained by the fact that the SRCR domain of MARCO acts as a pattern recognition receptor, whereas this domain does not seem to be required for bacterial binding by SR-A.

D. General Function(s)

Members of the SRCR-SF may display type A or B SRCR domains, single or tandem-repeated, embedded or not in mosaic or multidomain proteins [with domains such as EGF, collagen, SCR, complement C1r/C1s, Uegf, Bmp1 (CUB), zona pellucida (ZP), protease domains, etc.]. Such variability is in part responsible for the fact that functional activities attributed to the members of the SRCR-SF have rarely been unequivocally assigned to their SRCR domains. Even though the precise, characteristic biological function of the SRCR domain remains to be determined, the current paradigm states that these domains may mediate protein-protein interactions, whether homo- or heterotypic, such as the one described for CD6 and ALCAM (Bowen et al., 1996) or CD163 and the hemoglobin-haptoglobin complex (Kristiansen et al., 2001). However, some data would indicate that some members of the SRCR-SF are indeed able to recognize PAMPs (Bikker et al., 2002, 2004a; Brännström et al., 2002; Sarrias et al., 2005, 2007; Fabrick et al., 2009; Vera et al., 2009).

The SRCR-SF includes secreted as well as membrane-bound proteins, some of which have been implicated in the development of the immune system and in the regulation of immune responses, both innate and adaptive (Aruffo et al., 1997). In mammals, members of the SRCR-SF can be found in lymphocytes, but most of them are expressed in epithelia and in the mononuclear-phagocytic system, displaying multiadhesive and/or enzymatic properties (e.g., protease or oxidase activities), which could suggest an important role for them in mucosal defense.

III. Class A Macrophage Scavenger Receptor Type I: the Prototypical Scavenger Receptor

SR-AI is a ~220-kDa trimeric type II surface glycoprotein initially identified as an acetylated LDL binding receptor in bovine lung (Kodama et al., 1988). The protein consists of three identical subunits of ~77 kDa; each subunit contains an intracellular N-terminal domain, a transmembrane region, a spacer domain, an α -helical coiled-coil domain followed by a collagenous domain and an isoform-specific domain at the C terminus, which for SR-AI is a type A SRCR domain. The α -helical coiled-coil domain is composed of seven-amino acid repeats and seems to be important for SR-AI trimerization, which occurs through

the collagenous region; thus, both regions seem to be needed (Ashkenas et al., 1993). Homologs to SR-AI have been identified in cow, mouse, and *D. melanogaster* (Freeman et al., 1990; Kodama et al., 1990; Rohrer et al., 1990; Gough and Gordon, 2000), suggesting that this receptor is conserved across different species, including nonmammalian ones.

Three different forms of SR-A exist: SR-AI, SR-AII, and SR-AIII. These are generated by alternative splicing from the same gene (Emi et al., 1993; Gough et al., 1998). SR-AII differs from SR-AI in that the C-terminal SRCR domain is replaced by a six-residue sequence (Rohrer et al., 1990); SR-AII is still able to bind acetylated LDL with high affinity, indicating that the SRCR is not implicated in the binding. SR-AIII is a truncated form of SR-A lacking the amino acids coded by exons 9 and 10 and two of the six cysteines from the SRCR C-terminal region; this deletion results in altered intracellular processing of this receptor, so that it is not inserted in the cell membrane but instead is retained in the endoplasmic reticulum. It is noteworthy that this form acts as a dominant-negative receptor, decreasing acetylated LDL uptake by SR-AI and SR-AII (Gough et al., 1998). It has been speculated that this could be a post-translational mechanism of SR-AI/II activity regulation.

SR-AI and II are mainly expressed by macrophages, including Kupffer cells in the liver, alveolar macrophages, and foam cells in atherosclerotic regions. Perivascular macrophages surrounding arterioles in normal brain, termed MATO cells, also express SR-AI/II (Matsumoto et al., 1990; Naito et al., 1992; Honda et al., 1998; Gough et al., 1999). Expression of SR-AI/II is not exclusive of macrophages: this receptor has been detected in dendritic cells and endothelial as well as in smooth muscle cells (Pitas, 1990; Bickel and Freeman, 1992; Harshyne et al., 2003). SR-AI expression seems to correlate with macrophage differentiation, whereas SR-AII can be readily detected in monocytes, and its levels do not appear to increase significantly with macrophage differentiation (Geng et al., 1994). It is noteworthy that increased SR-AI/II expression in mature macrophages seems to protect these cells from a number of different apoptotic stimuli, including oxidized LDL (Liao et al., 1999; Liao et al., 2000). Transfection with SR-AI/II also protected Jurkat and Chinese hamster ovary cells from apoptosis. This could explain why macrophages expressing SR-AI/II can interact with cytotoxic compounds such as oxidized LDL without undergoing apoptosis.

A. Role in Scavenging and Other Macrophage Homeostatic Functions

Although SR-AI was initially described as an acetylated LDL-binding receptor (Kodama et al., 1988), it was later found that its binding specificity is much broader, including modified—but not unaltered—lipoproteins, advanced glycation end products, bacterial surface lipids, and certain nucleotide aggregates (Krieger et al.,

1993; Araki et al., 1995; Suzuki et al., 1999). These ligands seem to bind equally to SR-AI and -II, although some differences in affinity have been observed for acetylated LDL and *Escherichia coli* (Ashkenas et al., 1993; Peiser et al., 2000). All the ligands identified so far are polyanionic, suggesting that the SR-A–ligand interaction is electrostatic. Indeed, a charged structure formed by a cluster of basic amino acids highly conserved among different species and located in the collagenous region of SR-AI/II seems to mediate binding in the multimeric form (Doi et al., 1993), whereas the monomers are unable to bind acetylated LDL (Tanaka et al., 1993, 1996). Thus, so far, the SRCR domain seems to play a small, if any, role in ligand binding in this receptor.

Ligand binding by SR-AI/II triggers endocytosis and activates signaling pathways, including Mer receptor tyrosine kinase (Mertk), protein kinase C and the mitogen-activated protein kinase pathway, phosphatidylinositol bisphosphate hydrolysis, changes in intracellular Ca^{2+} levels, and nuclear factor κ B-mediated transcription (Misra et al., 1996; Hsu et al., 1998, 2001; Collier and Paulnock 2001; Todt et al., 2008). It has been shown that different ligands elicit activation of different pathways. It is noteworthy that acetylated and oxidized LDL appear to bind to different, albeit interacting sites on SR-AI/II (Freeman et al., 1991). The existence of different binding sites could explain the existence of ligand-specific responses.

Uptake of modified LDL into macrophages leads to the formation of foam cells, which are found in atherosclerotic lesions. This has prompted authors to propose a proatherogenic role for SR-AI/II (Febbraio et al., 2000; Kamada et al., 2001). Indeed, macrophages from mice deficient in SR-A show severely impaired ability to take up modified LDL (Lougheed et al., 1997). Furthermore, in hyperlipidemic mouse models [apoE(−/−) and LDLR(−/−)], SR-AI/II deficiency decreases the size of atherosclerotic lesions (Suzuki et al., 1997; Sakaguchi et al., 1998). However, foam cells were still present in the double knockout mice, suggesting that another receptor for modified LDL can induce their formation; candidates for this role are MARCO, CD36, and macrosialin (Sakaguchi et al., 1998). Overexpression of SR-AI/II, on the other hand, does not seem to be sufficient on its own to promote atherogenesis, although it seems to increase serum cholesterol levels (Herijgers et al., 2000; Van Eck et al., 2000).

The role of SR-AI/II-expressing macrophages in atherogenesis was demonstrated with a series of experiments carried out on both wild-type and LDLR(−/−) mice. In these experiments, mice were irradiated to abolish bone marrow function and subsequently reconstituted with either SR-A(−/−) or SR-A(+ +) cells (Babaev et al., 2000). In both wild-type and LDLR(−/−) mice, reconstitution with SR-A(−/−) cells resulted in a significant reduction in atherosclerotic lesions compared with mice that had been reconstituted with SR-A(+ +) cells. It has been shown that uptake of oxidized LDL mediated

TABLE 1
Group A SRCR proteins

Proteins described in mammals, unless indicated otherwise.

Name	No. SRCR	Other Domains	Expression	Function	Form	References
SR-AI/III/III	1/0/1TRUN	Coiled-coil, collagen	Macrophages	Binding to bacteria, modified LDL and other ligands, endocytosis	M, RE	Freeman et al., 1990; Kodama et al., 1990; Gough et al., 1998
MARCO	1	Collagen	Macrophages	Binding to bacteria and modified LDL; binding to UGRP1	M	Elomaa et al., 1995
SCARA5	1	Collagen	Testis, bladder, trachea, lung, adrenal gland, skin, ovary, kidney, aorta and muscle	Binding to bacteria; ferritin receptor; tumor suppressor	M	Jiang et al., 2006
Speract receptor	4		<i>Strongylocentrotus purpuratus</i> (marine sea urchin) sperm	Sperm activator peptide	M	Dangott et al., 1989
M2BP/gp90/ CyCAP	1	BTB/POZ, IVR	Intestinal duct, lung, human fluids and carcinoma	Binding to cyclophilin C, galectin-3, collagen, β_1 -integrins and fibronectin	S	Friedman et al., 1993; Kohts et al., 1993
LOXL2/WS9-14/LOR	3-4	LOX	Fibroblasts, adherent tumor cell lines and reproductive tissues; described in mammals, <i>Perca flavescens</i> and <i>D. melanogaster</i>	Role in cell adhesion and senescence	S	Saito et al., 1997; Jourdan-Le Saux et al., 2000; Kocks et al., 2005
LOXL3	4	LOX	Heart, CNS, reproductive tissues, colon, spleen and leukocytes	Unknown	S	Jourdan-Le Saux et al., 2001
LOXL4	4	LOX	Pancreas, testicles and fibroblasts	Unknown	S	Asuncion et al., 2001
AR/SRCR-SCR	14	SCR	Spherulous cells of <i>G. cydonium</i> (marine sponge)	Aggregation factor receptor	M, S	Pancer et al., 1997; Blumbach et al., 1998
SpSRCR1	4	vWF, ECM	<i>S. purpuratus</i> coelomocytes	Unknown	S	Pancer et al., 1999
SpSRCR5	2		<i>S. purpuratus</i> coelomocytes	Unknown	S	Pancer et al., 1999
SpSRCR6	3	vWF	<i>S. purpuratus</i> coelomocytes	Unknown	S	Pancer, 2000
SpSRCR7	7	SCR, EGF	<i>S. purpuratus</i> coelomocytes	Unknown	M	Pancer, 2000
SpSRCR12	20		<i>S. purpuratus</i> coelomocytes	Unknown	S	Pancer, 2000
SpSRCR20	7		<i>S. purpuratus</i> coelomocytes	Unknown	S	Pancer, 2000
CFI	1	Protease, LDL-R, FIMAC	Secreted to plasma by monocytes, described in mammals and <i>X. laevis</i>	Serine protease, regulates the complement cascade	S	Goldberger et al., 1987
TRAMP	2	Protease, LDL-R, apple	Mesenchymal cells during <i>Polyandrocarpa misakiensis</i> (tunicate) gemmation	Serine protease	S	Ohashi et al., 1999
Sp22D/GRAAL-Tequila	2	Protease, LDL-R, mucin, CBD	Hemocytes and intestine of <i>Anopheles gambiae</i> (mosquito) and <i>D. melanogaster</i>	Serine protease	S	Gorman et al., 2000
Neurotrypsin/Leydin/BSSP3/259PRSS12/Motopsin	3-4	Protease, kringle	Brain, lung, kidney, and testicular cells of Leydig	Serine protease	S	Yamamura et al., 1997; Proba et al., 1998
Xesp-2	1 TRUN	Protease, LDL-R	Embryos and adult tissues of <i>X. laevis</i>	Serine protease; blastula/gastrula formation	M	Yamada et al., 2000
Enterokinase/Enteropeptidase	1 TRUN	Protease, LDL-R, meprin, CUB, SEA	Intestine	Serine protease; digests trypsinogen; main activator of digestive hydrolases	M, S	Kitamoto et al., 1994
Corin	1 TRUN	Protease, LDL-R, Frizzled	Heart	Serine protease; digests atrial natriuretic propeptide	M	Yan et al., 1999, 2000
Epitheliasin/TMPRSS2	1 TRUN	Protease, LDL-R	Intestine, liver, heart, lung, kidney, and fetal brain	Serine protease	M	Paoloni-Giacobino et al., 1997; Jacquinet et al., 2000

TABLE 1
Continued

Name	No. SRCR	Other Domains	Expression	Function	Form	References
TMPRSS3	1 TRUN	Protease, LDL-R	Pancreatic tumors, urogenital and gastrointestinal tracts	Serine protease	M	Wallrapp et al., 2000
Spinesin/TMPRSS5	1 TRUN	Protease	Spinal medulla	Serine protease	M	Yamaguchi et al., 2002
Hepsin	1	Protease	Various human, rat, and baboon tissues, especially liver. Also renal cell carcinoma, ovarian cancer, prostate cancer, and hepatoma cells	Serine protease	M	Leytus et al., 1988; Somoza et al., 2003

Abbreviations: CBD, chitin binding domain; CNS, central nervous system; EGF, epidermal growth factor; FIMAC, factor I membrane attack complex; LDL-R, low density lipoprotein receptor; LOX, lysil oxidase; M, membrane; S, secreted; SCR, short consensus repeat; SEA, domain found in sea urchin sperm protein, enterokinase. and agrin; RE, retained in the endoplasmic reticulum; TRUN, truncated group A SRCR domain; UGRP1, uteroglobin-related protein1; vWF, von Willebrand factor.

by SR-AI/II induces macrophage proliferation (Sakai et al., 1996); this could create a positive loop that progressively worsens atherosclerotic lesions. Overall, these results suggest that SR-AI/II expression induces the loading of macrophages with modified lipoproteins to generate foam cells; accumulation of foam cells then results in atherosclerotic lesions. Furthermore, considering that SR-A expression has an antiapoptotic effect in macrophages (Liao et al., 1999, 2000), this receptor could also promote atherogenesis by enhancing macrophage survival within lesions, allowing them to take up more lipids and causing further endothelial damage. This theory, however, was challenged by studies with transgenic mouse models overexpressing SR-A, which showed decreased size of atherosclerotic lesions in two different atherosusceptible models (De Winther et al., 2000). These differences could be ascribed to the different constructs used for the generation of transgenic mice but also to the different susceptibility of mouse strains to atherosclerosis. The controversy, however, warrants further investigation.

Uptake of ligands by SR-AI/II is related not only to atherosclerosis but also to Alzheimer's disease and other degenerative brain conditions. Indeed, aggregated and/or glycated β -amyloid protein can be endocytosed by SR-AI/II-expressing microglial cells located in the vicinity of senile plaques from patients with Alzheimer's disease (Christie et al., 1996; Yan et al., 1996). Binding and uptake of modified β -amyloid protein results in cell activation and generation of reactive oxygen species, which can cause neuronal damage (Christie et al., 1996; El Khoury et al., 1996; Paresce et al., 1996). This could be important in the pathogenesis of senile dementia.

Apart from its potential role in pathologic conditions, SR-AI/II has also been implicated in homeostatic macrophage functions, such as adhesion to extracellular matrix (ECM). Indeed, blocking SR-AI/II with a monoclonal antibody results in decreased adhesion of macrophages to plastic (Fraser et al., 1993) and smooth muscle extracellular matrix (Santiago-García et al., 2003). Conversely, macrophages from patients suffering from a familial disorder causing overexpression of SR-AI/II dis-

play increased adhesion and overaccumulation of lipids (Giry et al., 1996). Adhesion to ECM components mediated by SR-AI/II seems to take place only when these components have been degraded, heat-denatured, glycosylated, or enzymatically modified (el Khoury et al., 1994; Gowen et al., 2001). Glycation of ECM components occurs in the basal membrane of arterial walls during aging and diabetes, creating potential binding sites for SR-AI/II-expressing macrophages and increasing the risk of atherosclerotic lesion development.

Removal of apoptotic cells by phagocytic macrophages also seems to be mediated by SR-AI/II, although results with knockout mice suggest the presence of a redundant receptor that exerts this function in the absence of SR-A (Platt et al., 1996, 2000; Getchell et al., 2006). Removal of inhaled particles also seems to be mediated, at least in part, by SR-AI/II: alveolar macrophages can bind and phagocytize crocidolite asbestos, the causative agent of asbestosis, via SR-AI/II, suggesting that this receptor could be involved in the pathogenesis of asbestosis and mesothelioma (Resnick et al., 1993).

B. Role in Innate Immune Defense against Microorganisms

Involvement of SR-A in the phagocytic activity of macrophages has been discussed in the previous section with regard to the removal of apoptotic cells and inhaled particles. However, other targets can be phagocytized by macrophages and elicit an immune response. Indeed, SR-AI/II has been shown to efficiently bind to and phagocytize a number of bacterial species, including *E. coli*, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Enterococcus hirae*, *Neisseria meningitidis*, and *Listeria monocytogenes* (Dunne et al., 1994; Peiser et al., 2000; Plüddemann et al., 2009b). Interaction with SR-AI/II seems to be mediated by lipopolysaccharides from the bacterial surface: LPS- and LTA-coated latex beads were also bound and internalized by SR-AI/II-expressing cells. Further evidence for the importance of SR-AI/II expression in phagocytosis of pathogens is provided by macrophages from SR-A(-/-)

TABLE 2
Group B SRCR proteins

Proteins described in mammals, unless indicated otherwise.

Name	No. SRCR	Other Domains	Expression	Function	Form	References
CD5	3		Thymocytes, T and B1a lymphocytes; mammals and <i>Gallus gallus</i> (chicken)	Modulation of TCR and BCR signaling	M, S	Jones et al., 1986
CD6	3		Thymocytes, T and B1a lymphocytes, neurons; mammals and <i>G. gallus</i> (chicken)	Modulation of TCR signaling; binding to ALCAM/CD166	M, S	Aruffo et al., 1997
T19/WC1	11		T $\gamma\delta$ lymphocytes	Reversible G $_0$ /G $_1$ cell cycle arrest	M	Wijngaard et al., 1992
M130/CD163	9		Macrophages	Haptoglobin-hemoglobin receptor; role in inflammation; binding to bacteria	M, S	Law et al., 1993
M160 DMBT1/gp340/ SAG/Hensin/ Ebnerin/ CRP-ductin/ BGM/H3	12 4–14	CUB, ZP	Macrophages Intestinal epithelium, kidney, lung, liver, stomach, pancreas, prostate, von Ebner's gland, brain, heart	Role in inflammation Epithelial differentiation and polarization; binding to galectin-3; binding to SP-D and SP-A; binding to bilirubin and cholesterol; binding to bacteria, fungi, and gp120 from HIV-1; suppression of infection and inflammation	M M, S	Gronlund et al., 2000 Li and Snyder, 1995; Nunes et al., 1995; Cheng et al., 1996; Takito et al., 1996; Mollenhauer et al., 1997
Pema-SREG	2		<i>Petromyzon marinus</i> (sea lamprey) intestine	Unknown	M	Mayer and Tichy, 1995
Sp α /AIM	3		Tissue macrophages	Apoptosis inhibitory factor; binding to PAMPs from bacteria and fungi; adipocyte lipolysis	S	Gebe et al., 1997; Miyazaki et al., 1999
18-B	4		Unknown; described in <i>G. gallus</i>	APR	S	Iwasaki et al., 2001
SCART1/2	8		T $\gamma\delta$ lymphocytes, lymph node, trachea, lung, and low expression in thymus, spleen, skin, and tissues throughout the gastrointestinal tract.	Role in inflammation and T cell development	M, S	Kisielow et al., 2008; Holm et al., 2009
S4D-SRCRB	4		Heart, liver, brain, PBL, spleen, intestine, kidney, and placenta	Unknown	S	Padilla et al., 2000
S5D-SRCRB/SSc5D	5	Syndecan domain	Genitourinary and digestive tracts	Binding to PAMPs from bacteria and fungi, and to ECM and Galectin-3	S	Gonçalves et al., 2009; Miró-Julià et al., 2011
MAP_GEOCY	1	Fibronectin, SCR	Extracellular matrix of <i>G. cydonium</i> (marine sponge)	Multiadhesive protein	S	Pahler et al., 1998
PSLAP	2	LCCL, PLAT	<i>Plasmodium falciparum</i> (parasite) gametocytes	Mosquito and/or vertebrate immune response evasion	S	Delrieu et al., 2002

APR, acute phase reactant; BCR, B-cell receptor; EGF, epidermal growth factor; LCCL, *Limulus* factor C, Coch-5b2, and Lgl1 domain; M, membrane; PBL, peripheral blood leukocytes; PLAT, polycystin-1, lipoxygenase, and α -toxin domain; S, secreted; SCR, short consensus repeat.

mice, because these cells show impaired bacterial uptake (Platt et al., 1999). SR-A-deficient mice were also found to be more susceptible to in vivo infection by *L. monocytogenes* and the herpes simplex virus type 1 (Suzuki et al., 1997). These mice also show reduced formation of granulomas after challenge with *Corynebacterium parvum* (Hagiwara et al., 1999). This provides proof of the protective role of SR-A in vivo, as well as evidence of interaction between SR-A and viruses. Indeed, a recent study has proposed SR-AI/II as a receptor for double-stranded RNA of viral origin, working in cooperation with other established double-stranded RNA receptors such as Toll-like receptor (TLR) 3 (DeWitte-Orr et al., 2010).

It is generally believed that the SRCR domain of SR-AI is not involved in bacteria binding; this belief arises from the observation that SR-AII, which lacks the SRCR domain, is still able to bind modified LDL and other such ligands (Rohrer et al., 1990). However, the fact that the collagen-like domain of this protein is essential for bacteria binding does not mean that the SRCR domain of SR-AI is not able to bind bacteria as well; the SRCR domain could thus represent a redundant binding site for bacteria, a possibility yet to be explored.

Resistance to infection promoted by SR-AI/II appears to be mediated by enhanced bacterial ingestion or killing, which result in clearance from the circulation

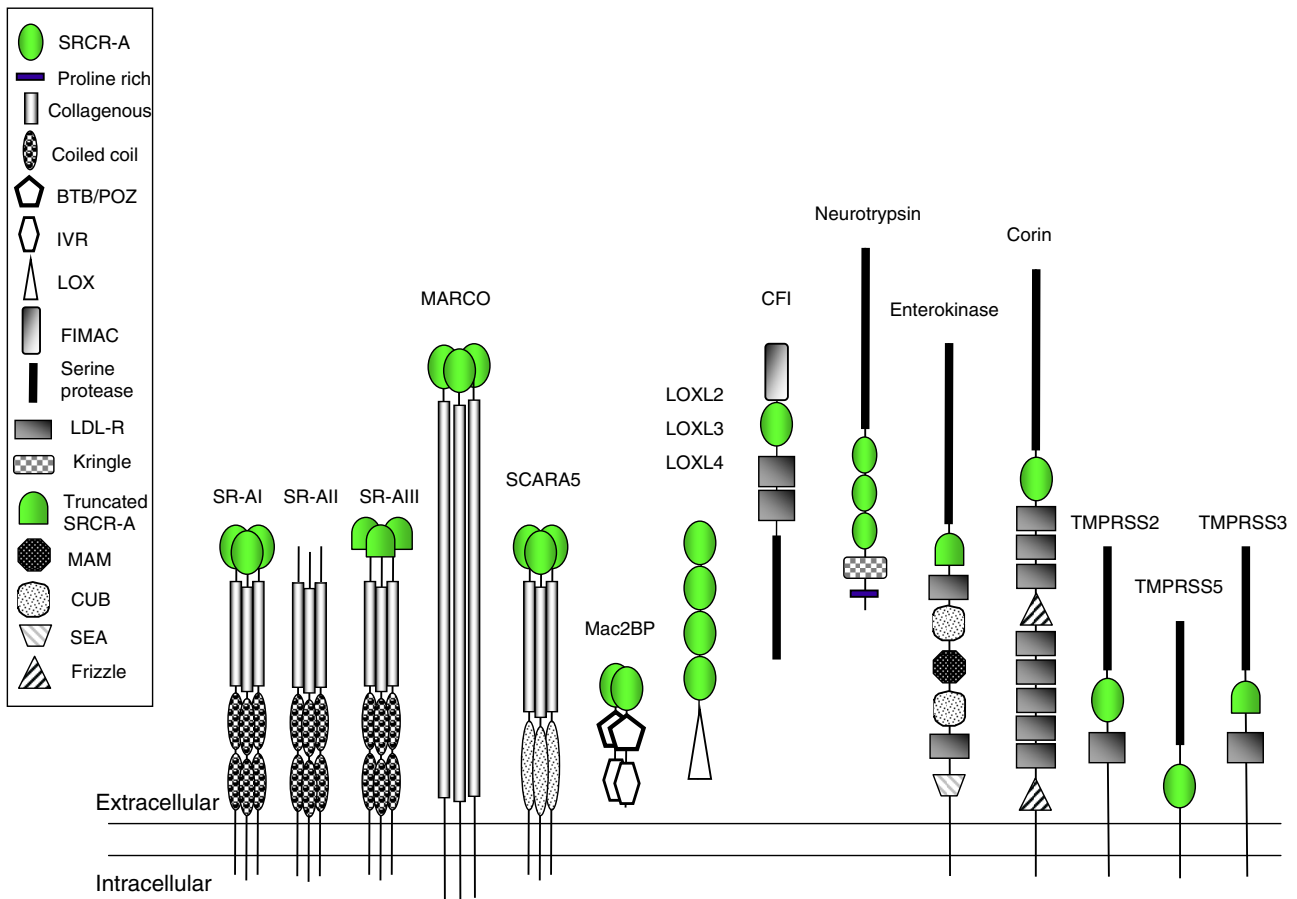


FIG. 1. Human group A SRCR members. BTB/POZ, *D. melanogaster* kelch protein dimerization domain; CUB, C1r/C1s Uegf Bmp1 domain; FIMAC, factor I membrane attack complex; IVR, intervening region from *D. melanogaster* kelch protein; LDL-R, low density lipoprotein receptor; LOX, lysyl oxidase; MAM, domain homologous to members of a family defined by motifs in the mammalian metalloprotease meprin, the *X. laevis* neuronal protein A5, and the protein tyrosine phosphatase μ ; SEA, domain found in sea urchin sperm protein, enterokinase, and agrin.

(Thomas et al., 2000; Arredouani et al., 2006; Plüddemann et al., 2009a). SR-AI/II can also be protective in mice suffering from bacterial endotoxin-mediated septic shock. Indeed, SR-A(+/+) mice were more likely to survive LPS-induced shock after infection with bacillus Calmette-Guerin, and showed decreased production of proinflammatory cytokines such as IL-1 β , TNF α , and IL-6 compared with SR-A(-/-) (Haworth et al., 1997). In this case, protection from LPS-induced shock is probably a result of endotoxin sequestration and removal from circulation by SR-AI/II. However, opposite results were found when using another model of LPS-mediated septic shock, SR-A(-/-) mice showing higher resistance to LPS treatment (Kobayashi et al., 2000). Although the different models of endotoxic shock used could explain the discrepancy in the results, more research is needed to clarify the role of SR-A in bacterial endotoxin-mediated septic shock.

The presence of T cells—mostly CD4+—in atherosclerotic lesions has been reported. Moreover, some of these T cells proliferate and secrete cytokines in the presence of oxidized LDL, which might indicate recognition of this molecule (Palinski et al., 1995, 1996; Stemme et al., 1995; Daugherty and Rateri 2002). Alternatively, these

results might suggest that macrophages present in the lesions are able to initiate an immune response against the modified lipoproteins they phagocytize (for instance, by releasing proinflammatory mediators). Indeed, SR-A deletion has been reported to increase alveolar macrophage expression of inducible nitric-oxide synthase and oxidative stress of lung cells in hyperoxia-induced lung injury (Kobayashi et al., 2007). It has also been shown that spleen cells from SR-A(-/-) mice immunized with a modified protein are unable to proliferate in response to antigen, in contrast with wild-type mice treated in the same way (Nicoletti et al., 1999). Furthermore, modification of proteins by maleylation or glycation to make them SR ligands enhanced their immunogenicity in vitro and in vivo, increasing T-cell activation and proliferation and also generating an antibody response (Abraham et al., 1995; Ilchmann et al., 2010). This effect could be explained by SR-AI/II-enhanced antigen presentation. Indeed, dendritic cells, which also express SR-AI/II, can take up membrane antigens directly from either dying or healthy cells by a process called nibbling and present them to cytotoxic T lymphocytes via major histocompatibility complex class I (Harshyne et al., 2001). A later study showed that capture of membrane antigen

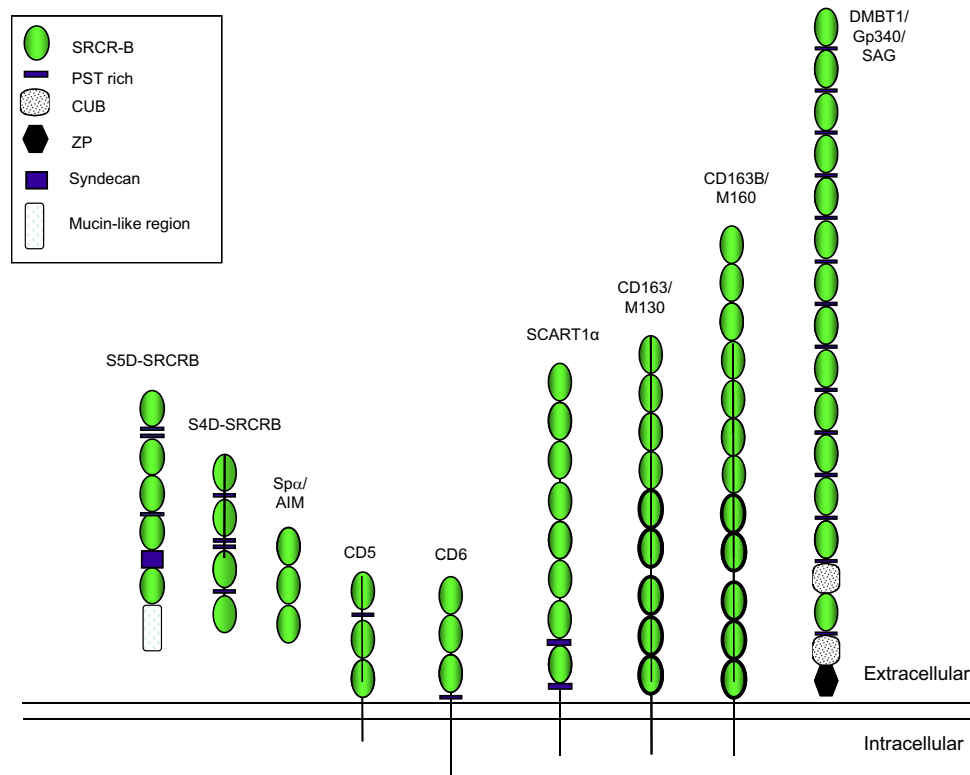


FIG. 2. Human group B SRCR members. CUB, C1r/C1s Uegf Bmp1 domain; PST, proline-, serine-, and threonine-rich sequence; ZP, zona pellucida domain.

by dendritic cells was blocked by an anti-SR-AI/II antibody (Harshyne et al., 2003). SR-A was also shown to participate in the binding, internalization, and presentation of antigen to cytotoxic T lymphocytes. All together, these results implicate SR-AI/II in the modulation of the immune response. Moreover, they imply that SR-AI/II could be involved in the development of autoimmunity. Indeed, it has been shown that induction of arthritis in SR-A-deficient mice resulted in decreased severity of disease compared with wild-type mice (van Lent et al., 2009).

Despite all these data, an anti-inflammatory role has also been proposed for SR-AI/II. Mice deficient in SR-AI/II exhibited increased morbidity and mortality after experimental myocardial infarction, showing impaired remodelling of infarcted tissue and deregulated cytokine production (Tsujita et al., 2007). Moreover, mice deficient in SR-AI/II were resistant to diabetic nephropathy as a result of reduced inflammation of renal tissue (Usui et al., 2007). However, SR-AI/II-deficient mice also exhibited slower tumor growth, presumably as a consequence of enhanced antitumor activity of macrophages as a result of increased NO synthase and IFN γ expression (Komohara et al., 2009). This suggests that modulation of the immune response by SR-AI/II is complex and can vary in different pathogenic situations.

C. Diagnostic and Therapeutic Potential

Although the exact contribution of SR-AI/II to the pathogenesis of atherosclerosis needs further study, ac-

cumulating evidence indicates that this receptor facilitates the formation of atherosclerotic lesions by macrophages. Indeed, measuring RNA and/or protein levels of SR-AI/II in macrophages is of diagnostic utility in patients suffering of normolipidemic planar xanthomatosis (Giry et al., 1996). From the therapeutic point of view, blocking SR-AI/II function would be expected to decrease the size and number of these lesions. Indeed, treatment of mice with a soluble decoy form of SR-AI/II delivered by adenoviral transduction resulted in decreased degradation of modified lipoproteins and reduced formation of foam cells in vitro (Laukkanen et al., 2000; Jalkanen et al., 2003b). Moreover, treatment of atherosusceptible LDLR(-/-) mice with a soluble decoy form of SR-AI/II significantly reduced the atheroma area in the aorta (Jalkanen et al., 2003a,b). These preliminary studies suggest that soluble SR-AI/II could be used in the prevention and treatment of atherosclerosis.

Further perspectives are that preventive treatment with SR-AI/II soluble forms could also reduce the development of autoimmune responses and excessive inflammation. As shown by preliminary studies in mice, administration of a soluble form of SR-AI/II could improve recovery after infarction and other tissue injuries (Jalkanen et al., 2003a; Jalkanen et al., 2003b). On the basis of the role of SR-AI/II in particulate removal, it can be envisioned that a soluble form of this protein that could be administered to the lungs may reduce pulmonary inflammation, thus preventing later events such as the development of fibrosis or malignancies. This would be

important in the prevention of pathologic lung conditions in persons exposed to silica or asbestos, whether by occupational hazard or otherwise. However, it should be noted that in some cases, this might be detrimental, in that the impaired clearance of inhaled particles by SR-A-mediate phagocytosis might have the opposite effect, increasing pulmonary inflammation. Evidence seems to suggest that the pro- or anti-inflammatory effect of SR-A depends on the type of particle involved (Arredouani et al., 2007; Thakur et al., 2008), which should be taken into account when developing this strategy.

More recently, SR-AI/II expression has been detected in vascular leukocytes, a type of leukocyte that promotes immunosuppression and angiogenesis and facilitates metastasis, and thus seems critical for tumor progression (Bak et al., 2007). It is noteworthy that treatment of ovarian tumors with a toxin-conjugated anti SR-A antibody resulted in reduced tumor burden, suggesting that SR-AI/II is a novel and useful target for the immunotherapeutic treatment of cancer.

IV. MARCO: A Macrophage Surface Receptor with Collagenous Structure

MARCO (from Macrophage Receptor with Collagenous structure) is a membrane-bound type II glycoprotein that exists as a trimer in its native form (Elomaa et al., 1995). This protein consists of five regions, an N-terminal short cytoplasmic tail, a transmembrane region, a spacer domain, a type XIII collagen-like region involved in protein trimerization (Kraal et al., 2000), and a C-terminal group A-type SRCR domain that displays high similarity with that of SR-AI/II (Elomaa et al., 1995). Indeed, these proteins share a high level of homology in their structure, expression pattern and binding properties. However, the extracellular region of MARCO is longer and its collagenous domain uninterrupted by long noncollagenous structures (Kraal et al., 2000).

Expression of MARCO in murine tissue is localized to macrophages from the interface between the red and the white pulp of the spleen, known as marginal zone macrophages, and also from the medullary region of the lymph nodes (Elomaa et al., 1995). It is noteworthy that macrophage-rich tissues such as lung and liver showed no staining for MARCO, although a later study did find expression of this protein in alveolar macrophages (Palcanda et al., 1999). However, exposure of mice to bacillus Calmette-Guerin, LPS, or bacterial sepsis rapidly up-regulated expression of MARCO in tissue macrophages, including dendritic cells (Granucci et al., 2003) and Kupffer cells of the liver (van der Laan et al., 1999). It is noteworthy that studies on MARCO expression in human tissue showed distribution of this receptor in macrophages from several types of tissues (Elomaa et al., 1998). It should be noted, however, that experiments were carried out on tissue from septic patients; given the fact that murine MARCO expression extends to tissue

macrophages outside spleen and lymph nodes after infection or inflammatory stimuli, further studies on samples from healthy patients are needed.

MARCO-transfected Chinese hamster ovary cells were found to bind modified LDL but not Ficoll, a polysaccharide taken up by most marginal zone macrophages (Elomaa et al., 1995). Binding of MARCO to modified LDL was shown to be mediated by the SRCR domain (Chen et al., 2006). MARCO was also found to bind directly to *E. coli* and *S. aureus*, but not to yeast: all these interactions were inhibited by poly-G, a polyanionic inhibitor of scavenger receptor binding (Elomaa et al., 1995). Experiments with a recombinant form of MARCO consisting solely of the extracellular region showed that this receptor also binds to LPS (Sankala et al., 2002). MARCO also seems to mediate the scavenging of unopsonized particles, such as TiO₂, Fe₂O₃, and latex beads, by alveolar macrophages (Palcanda et al., 1999; Arredouani et al., 2005); this receptor was later shown to bind crystalline silica (CSiO₂), which is responsible for silicosis (Thakur et al., 2009a,b). Binding was mapped to an acidic cluster at the long loop region covering the α -helix of the SRCR domain, in contrast with the site responsible for pathogen binding, which resides in a basic amino acid cluster on the β -sheet region of the SRCR domain (Ojala et al., 2007). All together, these data point to a role for MARCO in the clearance of inhaled particles in the lung. It could be speculated that exposure to noxious particles such as CSiO₂ in the air would up-regulate the expression of MARCO in line with what happens in response to pathogens, but this remains to be proven.

Circulating apoptotic cells are trapped in vivo in the marginal zone of the spleen, where they bind to macrophages present in that region (Wermeling et al., 2007); these macrophages express high levels of SR-AI/II and MARCO. MARCO was shown to actively bind apoptotic cells and thus participate in their clearance. Removal of apoptotic cells from this area is of prime importance because they are a source of autoantigens that can activate marginal zone B cells and thus induce autoantibody production (Enzler et al., 2006; Mandik-Nayak et al., 2006). Indeed, defective removal of apoptotic cells has been associated with increased susceptibility to autoimmune disorders such as systemic lupus erythematosus (SLE) (Casciola-Rosen et al., 1994; Kim et al., 2003), which is characterized by the presence of anti-DNA antibodies. It is remarkable that MARCO-deficient mice were found to have increased levels of anti-DNA antibodies in response to in vivo injection of apoptotic cells (Wermeling et al., 2007). In SR-AI/II and MARCO double knockout mice, this increase was independent of apoptotic cell injection, suggesting the development of spontaneous autoimmunity. It is noteworthy that anti-MARCO antibodies were detected in a transgenic mouse model of SLE; these antibodies were present at very early stages, before the onset of the disease. Moreover,

MARCO expression was shown to be down-regulated in spleen macrophages in a transgenic mouse model of SLE (Rogers et al., 2009). Macrophages derived from these mice also showed impaired ability to take up apoptotic cells, a consequence of an overall decrease in their phagocytic activity. It is noteworthy that MARCO readily binds LDL, and impairment of this activity could explain the increased risk of cardiovascular disease in SLE patients.

Activated macrophages undergo changes in their cytoskeleton that are probably related to the acquisition of phagocytic properties. It is noteworthy that transfection of MARCO in resting dendritic cells was sufficient to induce rearrangements of the cytoskeleton similar to those seen in mature, activated cells (Granucci et al., 2003). Conversely, depletion of MARCO from dendritic cells prevented the acquisition of maturation-related changes by these cells. This suggests that MARCO is more than a pattern recognition receptor and is indeed able to modulate maturation of macrophages and dendritic cells.

A. Role in Pathogen Recognition and Phagocytosis

The presence of MARCO in the marginal zone of the spleen and in the cortical region of lymph nodes means that this receptor is in a key position to interact with blood-borne pathogens. Moreover, MARCO expression is up-regulated after inflammatory stimuli and extends to tissue macrophages. All together, these data suggest that MARCO is involved in the response to pathogens. Indeed, *in vitro* experiments showed the ability of MARCO to bind directly to bacteria (Elomaa et al., 1995) and to LPS (Sankala et al., 2002). In contrast with SR-AI/II, bacteria-binding has been mapped to an arginine-based motif (R-X-R) within the SRCR domain (Elomaa et al., 1998; Brännström et al., 2002). Furthermore, a form lacking most of the collagenous domain but containing enough of it to be able to trimerize was still able to bind efficiently to bacteria. However, another study showed that a recombinant form of MARCO consisting only of the SRCR domain had very low, barely detectable bacteria-binding activity (Sankala et al., 2002). Considering that previous work has shown that the collagenous structure of MARCO has no direct binding activity and does not seem to promote or enhance binding, it is very likely that the SRCR domain needs to be in trimeric form to interact correctly with bacteria. This would provide an excellent means to create selectivity for patterns with a specific spatial organization.

The importance of MARCO activity was shown when the uptake of bacteria by the spleen was found to be decreased in mice treated *in vivo* with anti-MARCO antibodies shown to block ligand binding (van der Laan et al., 1999). Bacterial clearance from the circulation was not impaired in these mice, suggesting that other receptors carry out this function. This confirms the role

of MARCO as a bacterial receptor *in vivo*, involved in the binding and phagocytosis of pathogens.

Confirming its role in the defense against pathogens and environmental particles, MARCO-deficient mice show increased mortality in response to pneumococcal pneumonia as a result of decreased bacteria clearance from lungs and excessive pulmonary inflammation and cytokine release (Arredouani et al., 2004). Similar effects were observed in response to inert particle inhalation. This suggests that MARCO is able to prevent lung inflammation by pathogens and inhaled particles by enhancing their clearance. However, the role of MARCO is not limited to pathogen uptake. A recent report shows that MARCO-deficient mice exhibit comparable uptake of inhaled antigen but have increased numbers of dendritic cells migrating from the lung into the lymph nodes (Arredouani et al., 2007). This suggests that MARCO has a broader anti-inflammatory effect in the lungs that is not limited to the removal of inhaled particles.

The binding of MARCO to pathogens is not exclusive of bacteria: infection of macrophages with intracellular parasite *Leishmania major* was shown to depend on MARCO expression (Gomes et al., 2009), whereas treatment with anti-MARCO antibodies reduced infection with *L. major* both *in vitro* and *in vivo*. This suggests that MARCO may facilitate infection by serving as a receptor for parasites.

B. Diagnostic and Therapeutic Potential

As previously explained, anti-MARCO antibodies can be detected in the early stages of a murine model of SLE, before the full onset of the disease (Wermeling et al., 2007). Patients with SLE were also found to have elevated titers of anti-MARCO antibodies compared with healthy control subjects in the same study. However, it remains to be determined whether these antibodies can be detected before the onset of the disease, in which case they would constitute a valuable marker for diagnosis to potentially initiate early treatment. MARCO gene expression in lymphoma tissue was also found to correlate with better prognosis and response to rituximab plus CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisone) in follicular lymphoma (Harjunpää et al., 2006), thus acting as a prognostic and therapy-response marker.

A subpopulation of immunosuppressive macrophages that express MARCO, as well as immunosuppressive genes such as arginase and IL-10, has been identified (Qian and Pollard, 2010). Although the precise role of MARCO in this subpopulation is still unknown, antibodies against this receptor could be used to target immunosuppressive macrophages and improve immune response against tumors.

In addition, soluble forms of MARCO could be used in a way similar to those of SR-AI/II, to prevent excessive inflammatory response and to enhance pathogen and/or particle clearing, for example, from the

lung. In this case, it should be noted that the soluble form should contain enough of the collagenous region to be able to oligomerize and therefore display its full binding ability. In fact, the same approach—in addition to inhibiting MARCO via antibodies—can be imagined to find application for suppression of *L. major* infection.

V. Mac-2 Binding Protein: a Tumor-Associated Antigen

Mac-2-binding protein (Mac-2BP) is a large secreted oligomeric protein that binds to galectin-3 (also named Mac-2) and that was originally described as a tumor-associated antigen (Natali et al., 1982; Iacobelli et al., 1986; Linsley et al., 1986). Each subunit of approximately 90 kDa possesses four distinct domains: an N-terminal group A SRCR domain; a putative member of the BTB/POZ (broad complex, tramtrack and bric-a-brac/poxvirus and zinc finger) dimerization domains; an IVR (intervening region) related to the kelch protein from *D. melanogaster* (Robinson and Cooley 1997; Müller et al., 1999); and a C-terminal region with no similarity to any other known protein (Müller et al., 1999). The BTB/POZ and IVR domains are responsible for protein oligomerization, as determined by studies with recombinant truncated protein forms (Hellstern et al., 2002). The protein can be found only in monomeric form under strongly denaturing conditions. In physiological conditions, the protein forms ring-shaped oligomers visible by electron microscopy (Sasaki et al., 1998); linear aggregates and ring-ring association are also observed. These multivalent forms of the protein could enhance interaction with multiple targets.

Mac-2BP was soon reported as a protein associated with cyclophilin C, a member of the family of cyclophilins, which bind to the immunosuppressive drug cyclosporin A (Friedman et al., 1993). The two proteins are found associated in the surface of viable cells in the absence of CsA, suggesting that cyclophilin C could be important for proper folding/processing of Mac-2BP. Mac-2BP was also found to bind to extracellular matrix proteins such as laminin; collagens IV, V, and VI; fibronectin; and nidogen, as well as to integrin $\beta 1$ subunits (Sasaki et al., 1998). The presence of this protein can indeed be detected bound to the extracellular matrix of a number of different types of tissue, such as testis, thymus, lung, gastrointestinal tract, spleen, and skeletal muscle. Mac-2BP is also present in serum as well as in other secretions such as breast milk and saliva (Ullrich et al., 1994; D'Ostilio et al., 1996; Sasaki et al., 1998), although the cell type(s) responsible for secretion has not yet been identified. The high levels of glycosylation found in Mac-2BP make this protein a possible ligand for lectins. Indeed, carbohydrate-mediated interactions with galectin-3 (also termed Mac-2) (Rosenberg et al., 1991; Koths et al., 1993; Inohara and Raz, 1994)

and galectin-1 (Tinari et al., 2001) have been reported. Mac-2BP is also able to induce homotypic cell aggregation in a melanoma cell line expressing galectin-3 (Inohara et al., 1996). Supporting this notion, galectin-1 was shown to induce Mac-2BP-mediated aggregation of a melanoma cell line. These results implicate Mac-2BP in homotypic cell adhesion, suggesting that it could play a role in tumor embolization during metastasis. Overexpression of Mac-2BP in vitro led to increased adhesiveness of lung cancer cell lines to extracellular matrix proteins (Ozaki et al., 2004a), consistent with previous in vitro binding results, prompting the authors to speculate a possible role for Mac-2BP in metastasis. Increased levels of Mac-2BP were also found in cells after exposure to proinflammatory cytokines involved in the protective immune response against tumors.

A possible modulating role for Mac-2BP in the innate and adaptive immune responses is supported by the expression of this protein in lymphoid organs such as thymus and spleen, together with its reported involvement in homotypic cell-cell interactions and the implication of the SRCR domain in innate and adaptive immune response modulation; it should be noted, however, that the contribution of the SRCR domain to the function of this protein remains unknown. Exposure of peripheral blood mononuclear cells (PBMCs) to Mac-2BP in vitro was shown to generate cytotoxic effector NK and lymphokine-activated killer cells (Ullrich et al., 1994); PBMCs also increased their secretion of IL-1, IL-2, IL-6, granulocyte macrophage–colony-stimulating factor, and TNF α after incubation with Mac-2BP in combination with suboptimal doses of concanavalin A (Powell et al., 1995). Increased levels of Mac-2BP were also able to induce cytokine production in accessory cells, particularly monocytes (Powell et al., 1995; Lee et al., 2005), and to generally enhance immune response mediated by cytotoxic CD8⁺ T cells or NK/NK T cells to tumor challenge. Potential for modulating the immune response was also demonstrated for Mac-2BP when it was shown that exposure to this protein altered T-cell proliferation after stimulation with nonspecific mitogens such as phytohemagglutinin and concanavalin A as well as TCR agonists such as superantigens and allogeneic cells (Silvestri et al., 1998). Finally, exposure to Mac-2BP caused breast cancer cells to directly increase their expression of class I major histocompatibility complex (Natali et al., 1996), thereby augmenting their immunogenicity; similar results were obtained by transfection of thyrocytes (Grassadonia et al., 2004).

A. Therapeutic and Diagnostic Potential

Mac-2BP was originally discovered as a tumor-associated antigen, so it is not surprising that its major clinical use is as a tumor biomarker. As early as the mid 80s, the levels of this protein were found to be increased in patients with cancer, especially in those suffering from breast cancer, compared with healthy subjects (Iacobelli

et al., 1986). Elevated levels of Mac-2BP were found in all histological types of breast cancer and titers were significantly higher in sera from advanced-stage patients than in those with limited disease (Iacobelli et al., 1988). In the case of ovarian cancer, however, the percentage of Mac-2BP positivity did not correlate with histological type or disease stage (Scambia et al., 1988). It is noteworthy that increased levels of Mac-2BP preceded clinical symptoms and signals of recurrence. These results were also shown for breast cancer, where Mac-2BP levels were associated with poor prognosis, presence of metastasis in liver, and shorter disease-free interval (Iacobelli et al., 1994). Elevated levels of this protein have also been shown in lung carcinoma (Ozaki et al., 2002), correlating strongly with clinical staging (Ozaki et al., 2004a).

Progression from chronic hepatitis to cirrhosis to hepatocellular carcinoma (HCC) can also be monitored by measuring serum Mac-2BP levels (Correale et al., 1999); moreover, negative staining for Mac-2BP in liver tissue was associated with poor prognosis (Valentini et al., 2005). These results were confirmed by later work showing that Mac-2BP serum levels significantly correlated with overall survival of HCC patients under 70 years of age (Iacovazzi et al., 2001). In this case, determination of Mac-2BP and α -fetoprotein—the reference marker for HCC—together was better correlated to prognosis than AFP determination alone. The combined determination of both markers has been proposed as a standard diagnosis tool for HCC (Iacovazzi et al., 2003). A similar picture has been described for biliary tract carcinoma, where determination of biliary levels of the reference marker, CA19-9, and Mac-2BP improved the diagnostic efficiency, providing a useful tool for differential diagnosis from non-neoplastic biliary diseases such as benign biliary conditions and primary sclerosing cholangitis (Koopmann et al., 2004).

Further uses of Mac-2BP in the diagnosis, prognosis, and prediction of response to treatment have been found for non-Hodgkin's lymphoma (Zhang et al., 2003), gastric cancer (Park et al., 2007), prostate cancer (Sardana et al., 2007), pancreatic cancer (Xue et al., 2008), colorectal cancer (Iacovazzi et al., 2010), and neuroendocrine tumors (Srirajaskanthan et al., 2010).

Serum levels of Mac-2BP not only allow for the follow-up of cancer patients but have also been shown to be a predictor of disease severity in patients infected with hepatitis C (Kittl et al., 2000). Mac-2BP can also be used as a predictor of the response of the hepatitis C virus to interferon alone and in combined therapy (Iacovazzi et al., 2008). This protein therefore displays multiple advantages for its use not only in diagnosis but also in viral disease patient follow-up.

The presence of Mac-2BP in cancer cells could allow for this protein to be used as a target in immunotherapy. Indeed, cytotoxic T lymphocytes can be activated by pulsing with peptides derived from Mac-2BP loaded onto

antigen-presenting cells (Ozaki et al., 2004b). Thus, immunotherapy with Mac-2BP peptide-pulsed cytotoxic T lymphocytes could become an attractive alternative in the treatment of certain cancers. Alternatively, ex vivo treatment of either PBMC or tumor cells with Mac-2BP seems to potentiate antitumoral immune responses, by increasing both innate (Ullrich et al., 1994; Powell et al., 1995; Lee et al., 2005) and adaptive (Silvestri et al., 1998) cytotoxic activity and tumor immunogenicity (Natoli et al., 1996).

It is noteworthy that the levels of Mac-2BP in milk were revealed to correlate inversely with acute respiratory infections in children under 12 months fed with human milk (Fornarini et al., 1999). Authors speculate that this could be a result of direct neutralizing interaction of milk Mac-2BP with microorganisms or could occur through stimulation of the infant immune system mediated by this protein. Whichever the mechanism is, these data suggest that supplementation of milk or feeding with Mac-2BP could protect children from infection in a similar way to that proposed for lactoferrin (Sherman, 2010); however, no evidence currently supports this contention, and more research is needed before such an approach might be considered.

VI. SCARA5: A Newcomer into the Family

A recently discovered member of the SRCR superfamily is SCARA5, a type II transmembrane glycoprotein with high homology to SR-AI/II (Jiang et al., 2006). Similar to SR-AI/II and MARCO, this protein contains a short N-terminal domain, a transmembrane domain, a spacer region, a collagenous domain, and a type A SRCR domain at the C terminus. The collagenous region seems to be determinant in the formation of protein trimers, much as it is in SR-AI/II and MARCO. Analysis of the protein sequence identified seven putative N-glycosylation sites, suggesting that this protein is heavily glycosylated. The cytoplasmic domain contains Ser and Thr residues that are potential phosphorylation sites for casein kinase II and protein kinase C (PKC). This protein is expressed at the cytoplasmic membrane, although immunofluorescence studies have suggested that this protein may be present in the endoplasmic reticulum and Golgi, which is to be expected for a membrane-bound protein.

In stark contrast with other group A SRCR members, expression of SCARA5 was not detected in macrophage cell lines; real-time PCR analysis, however, did detect expression of SCARA5 mRNA in testis, bladder, trachea, adrenal gland, skin, lung, and ovary. These results were confirmed by in situ hybridization, which showed that the highest levels of SCARA5 were present in the testis, particularly in Sertoli cells. These results were confirmed by a later study that also showed expression of SCARA5 in gonadal epithelia, the airway, kidney cells, developing aorta, and muscle bundles (Li et al., 2009).

SCARA5 expression has also been found at alveolar epithelial cells and in the lung cell line A549, although not at bronchial epithelial cells or lung macrophages (Leino et al., 2010). The expression pattern of SCARA5, not in macrophages but pre-eminently epithelial, has prompted researchers to postulate a role for this receptor in epithelial homeostasis. It is noteworthy that the authors also reported that SCARA5 expression was increased in peripheral lung extracts after a 24-h incubation with LPS.

A significant difference with SR-AI/II is that SCARA5 does not seem to bind or take up acetylated or oxidized LDL (Jiang et al., 2006). This protein does, however, bind to *E. coli* and *S. aureus*, although not to zymosan, in a polyanionic-inhibitable manner (Jiang et al., 2006).

A. Role as a Nontransferrin Iron Delivery Receptor

A recently defined role for SCARA5 was discovered in renal cells from transferrin receptor-1 knockout mice: these cells were not deficient in iron; indeed, they showed high levels of iron in their cytoplasm, stored as ferritin deposits. The cells did not take up transferrin, discarding the existence of an alternative transferrin receptor, but were shown to take up ferritin through SCARA5, thus revealing a new role for this protein as a ferritin receptor in both embryonic and adult renal cells (Li et al., 2009). SCARA5 bound preferentially to L-ferritin and also to apo-ferritin, but not to H-ferritin, demonstrating specificity for the ferritin chain. It is noteworthy that SCARA5 also bound hemoglobin-haptoglobin (Hb-Hp) complexes, albeit with less avidity. There is no evidence that the SRCR complex mediates the binding of Hb-Hp complexes, something that has been shown for CD163 (see section VIII). Binding of ferritin seems to be followed by endocytosis into an acidic compartment and incorporation of iron into the cell, supporting cell survival. Polyanionic compounds inhibited the interaction between SCARA5 and ferritin, suggesting that the binding is dependent on electrostatic forces; indeed, ferritin contains repeating chains of polyanionic monomers. Whether ferritin binds to other scavenger receptors or is uniquely bound by SCARA5 is a pending issue.

B. Role in Tumor Suppression

Intriguingly, SCARA5 has also recently been reported to act as a tumor suppressor in HCC (Huang et al., 2010). SCARA5 seems to be silenced in HCC by promoter hypermethylation; moreover, down-regulation of SCARA5 expression correlates with cellular invasion, venous permeation, and overall progression of HCC. Suppression of SCARA5 expression was also found in other cancers as well, such as gastric cancer, suggesting that the protective effect of SCARA5 is not exclusive of HCC. The mechanisms through which SCARA5 prevents tumor development are multiple and involve decreases in cell proliferation, colony formation, cell migration, and invasion, as shown for tumor cell lines; these results were confirmed with in vivo

experiments demonstrating that SCARA5 overexpression impairs tumorigenicity, decreases tumor growth, and inhibits metastasis. Knockdown of SCARA5 consistently caused hepatic tumor cells to increase their anchorage-independent growth, colony formation ability, and tumorigenesis in vivo. Overexpression of SCARA5 was found to inhibit phosphorylation of focal adhesion kinase, whereas SCARA5 knockdown readily activated the focal adhesion kinase signaling cascade, including the downstream induction of matrix metalloproteinase-9, involved in tumor invasion and metastasis. All together, SCARA5 seems to be a multifaceted protein worthy of further investigation.

C. Therapeutic and Diagnostic Potential

Although SCARA5 was discovered very recently, it is already possible to suggest a clinical application for this protein as a biomarker of certain malignancies and also as a prognosis-associated protein because of the apparent correlation of SCARA5 expression levels with HCC progression (Huang et al., 2010). Likewise, the ability of SCARA5 to bind both bacteria and Hp-Hb complexes paves the way for its putative use in post-transfusional reactions and also in sepsis (see section VIII.C).

VII. CD5 and CD6: Innate and Adaptive Lymphocyte Surface Receptors

CD5 and CD6 are type I lymphocyte membrane glycoproteins of 67 kDa and 105 to 130 kDa, respectively. Their homology is important not only from a structural point of view but also at the level of their expression pattern and their functional properties. These proteins are in fact encoded by contiguous genes located in the same chromosomal region (chr11q22 in humans and chr9 in mice), which probably derive from the duplication of a common ancestral gene (Lecomte et al., 1996; Padilla et al., 2000). Both proteins possess an extracellular region composed exclusively of three SRCR domains in tandem, a transmembrane region, as well as an intracytoplasmic region well adapted for intracellular signal transduction (Sarrias et al., 2004a). Both CD5 and CD6 are expressed on thymocytes from early maturation states, on mature T lymphocytes, and on the B1a subpopulation (Kamoun et al., 1981). CD6 (but not CD5) expression has also been reported in certain brain regions (Mayer et al., 1990) and on NK cells (Zimmerman et al., 2006).

CD5 and CD6 are physically associated to the antigen-specific receptor present on T (TCR) and B1a (B-cell receptor) cells (Beyers et al., 1992; Lankester et al., 1994). In T cells, these two molecules are part of a macromolecular complex integrated also by other costimulatory molecules (CD2, CD4, CD8, CD45) (Carmo et al., 1999). CD6 has been shown to physically and independently associate to CD5 (Gimferrer et al., 2003) and to TCR/CD3 (Gimferrer et al., 2004); reports also described the colocalization of CD5 and CD6 with the

TCR/CD3 complex in the central area of the mature immune synapse (Brossard et al., 2003; Gimferrer et al., 2004; Zimmerman et al., 2006). This indicates that both receptors are well positioned to regulate activation or cell death signals promoted by specific antigen recognition; indeed, both molecules, in soluble form, are able to inhibit proliferative responses mediated by antibodies (anti-CD3) or mitogenic lectins (phytohemagglutinin) in T cells. It has also been shown that recombinant soluble human CD6 (rshCD6) inhibits the maturation of the immune synapse and the subsequent lymphocyte activation (Gimferrer et al., 2004; Hassan et al., 2004; Zimmerman et al., 2006), indicating that CD5 and CD6 possess important immunoregulatory properties.

A. Role in Lymphocyte Differentiation and Activation

Expression of CD5 and CD6 is increased throughout thymic differentiation (Azzam et al., 1998; Singer et al., 2002) and lymphocyte activation (Carrera et al., 1989; Cardenas et al., 1990; Lozano et al., 1990b) in a TCR-regulated manner.

The first functional studies on these receptors were carried out using specific anti-CD5/CD6 mAbs, and demonstrated an important role for them in lymphocyte activation, acting as costimulatory molecules (Ceuppens and Baroja 1986; Gangemi et al., 1989; Alberola-Ila et al., 1992; Bott et al., 1993). Later studies carried out in CD5-deficient mice (Tarakhovskiy et al., 1995; Bikah et al., 1996), showed that this molecule behaves as a negative modulator of the activation and differentiation signals mediated by antigen-specific receptors, depending on the cell type and on the cell maturation state (Lozano et al., 2000). Thus, CD5 could behave as a costimulatory molecule in mature T and B lymphocytes and as a negative signaling molecule in thymocytes and B1a lymphocytes. Expression of CD5 in thymocytes was shown to be regulated by the affinity of the TCR in studies with transgenic mice expressing high- and low-affinity TCRs (Azzam et al., 1998). In this way, CD5 was shown to be responsible for fine tuning of TCR signaling (Azzam et al., 2001). A CD6 knockout mice has not yet been developed, so whether this molecule also possesses similar dual modulating properties remains to be determined, although some studies seem to indicate that this could indeed be the case (Singer et al., 2002).

The intracellular regions of CD5 and CD6 lack intrinsic catalytic activity but possess a number of residues that are susceptible to phosphorylation and to further interaction with other cytoskeletal and signaling proteins (Kobarg et al., 1997; Vilà et al., 2001). Both molecules are constitutively phosphorylated, but lymphocyte activation causes them to become hyperphosphorylated (Cardenas et al., 1990; Lozano et al., 1990a). Although the CD5 signaling pathway is not entirely understood, CD5 cross-linking causes a rapid and transient release of diacylglycerol followed by the activation of PKC and an acid sphingomyelinase (Alberola-Ila et al., 1992; Si-

marro et al., 1999). Other elements further downstream of the CD5 signaling pathway include calcium/calmodulin-dependent kinase type IV (Gringhuis et al., 1997), phosphatidylinositol 3-kinase, Vav, Rac1 (Gringhuis et al., 1998), CKII (Raman and Kimberly, 1998), PKC- ζ , mitogen-activated protein kinase kinase, and c-Jun NH₂-terminal kinase (Simarro et al., 1999). A number of elements might also be recruited from other signaling pathways during CD5 activation, such as AKT and p38. With respect to CD6, it has been reported that crosslinking of this molecule by antibodies or its physiological ligand (CD166/ALCAM, for Activated Leukocyte Cell Adhesion Molecule) activated components of the MAP kinase pathway (extracellular signal-regulated kinase, c-Jun NH₂-terminal kinase, p38) as well as certain transcription factors (activator protein-1, nuclear factor κ B) (Ibáñez et al., 2006).

It is well established that CD6 binds CD166/ALCAM, an adhesion molecule from the Ig superfamily expressed in activated lymphocytes, epithelial thymic cells, and brain cells (Bowen et al., 1996). It has been reported that the CD6 domain implicated in ligand interaction (SRCR3) is deleted by alternative splicing mechanisms during lymphocyte activation, constituting a possible mechanism of negative regulation (Castro et al., 2007). However, the possible existence of alternative ligands for CD6 in nonhematopoietic cells has also been reported (Wee et al., 1994; Joo et al., 2000; Saifullah et al., 2004); these ligands are still awaiting characterization. With respect to CD5, the situation is particularly controversial, with several ligands reported: CD72 (Van de Velde et al., 1991), gp35-40 (Biancone et al., 1996), gp150 (Calvo et al., 1999b), the framework region of IgV_H (Pospisil et al., 2000), and CD5 itself (Brown and Lacey, 2010). These ligands have been questioned because of the inability of other groups to validate some of them and also because these ligands would mainly explain T-B or B-B interactions mediated by CD5 but not other interactions such as T-monocytes/macrophages, T-dendritic cells, T-epithelial cells, T-stromal cells, etc. It is noteworthy that CD5 expression is notably increased in regulatory cell types such as Treg (CD4⁺ CD5^{high} CD25^{high} FoxP3⁺) (Fehérvári and Sakaguchi, 2004) or regulatory B cells (CD19⁺ CD1d⁺ CD5⁺) (Yanaba et al., 2008), as well as in CD4⁺ T cells (Kassiotis et al., 2003), CD8⁺ T cells (Stamou et al., 2003), or B cells (Hippen et al., 2000), which have been anergized by repeated antigenic stimulation (with either endogenous or exogenous antigens). In fact, CD5 expression is necessary for B-cell production of IL-10, an autocrine cytokine for B1a cells (Gary-Gouy et al., 2002), which is a suppressant cytokine for some T cells and macrophage subsets. Accordingly, IL-10-producing B cells (also called B10 or regulatory B cells) play a relevant role in the control of experimental autoimmune processes such as experimental autoimmune encephalitis (Matsushita et al., 2008), collagen-induced arthritis (Mauri et al., 2003), inflam-

matory bowel disease (Mizoguchi et al., 2002), or contact hypersensitivity (Yanaba et al., 2008).

The presence of elevated levels of CD5 in regulatory T cells suggests that CD5 might be necessary to regulate the generation and/or function of these cells. In agreement with this, it has been reported that knockout mice for CD5 present an increased number of regulatory T cells both in the thymus and in the periphery (Ordoñez-Rueda et al., 2009), as well as enhanced suppressing activity of these cells (Dasu et al., 2008) possibly as a result of increased TCR signaling in the absence of negative regulation mediated by CD5. This could suggest a role for CD5 in the development of tolerance, both to self-antigens and to exogenous nonself antigens. To the best of our knowledge, there are no data concerning the relative expression of CD6 in regulatory or anergic cells.

B. Role in Pathogen Recognition

An interesting contribution to the molecular interactions mediated by the extracellular regions of CD5 and CD6 is the recent discovery of the ability of both molecules to directly bind conserved PAMPs present in bacteria and fungi (Sarrias et al., 2007; Vera et al., 2009). Thus, the extracellular region of CD6 (but not CD5) interacts with LPS from Gram-negative bacteria and with LTA and peptidoglycan from Gram-positive bacteria. It is noteworthy that the affinity of the CD6-LPS interaction (K_D , $2.69 \pm 0.32 \times 10^{-8}$ M) is equivalent to that reported for CD14, the main known receptor for LPS in mammalian myeloid cells. On the other hand, the extracellular region of CD5 (but not CD6) interacts with β -glucans from fungal walls, with an affinity (K_D , 3.7 ± 0.2 nM) equivalent to that of Dectin-1, the main known receptor for β -glucans in mammalian cells. CD6, but not CD5, also showed the ability to aggregate bacteria, a property shared with other SRCR members such as Sp α and DMBT1, which could have importance in preventing transversion of bacteria through epithelial barriers and in facilitating their clearing from circulation.

Another relevant result from these studies is that the interaction of these microbial structures also occurs with membrane-bound forms of CD5 and CD6 inducing the activation of intracellular signaling pathways and allowing lymphocytes to detect the presence of an ample spectrum of pathogens. These data are in agreement with recent evidence demonstrating that lymphocytes possess PRRs (for example, TLRs) and that specific recognition of antigens (through TCR or B-cell receptors) in the presence of microbial ligands of these PRRs has important consequences for the expansion and function of different T and B cell types, with effector as well as regulatory function (Netea et al., 2004; Caron et al., 2005; Liu et al., 2006; Lampropoulou et al., 2008; Yanaba et al., 2009). It remains to be determined whether the binding of microbial products to coreceptors such as CD5 and/or CD6 contributes to the modulation

of adaptative immune responses mediated by PRRs—as occurs with TLR ligands.

C. Therapeutic Potential in the Control of Sepsis and Tolerance

The practical relevance of the pathogen-binding ability of CD5 and CD6 is illustrated by the fact that infusion of recombinant soluble human forms of CD5 (rshCD5) and CD6 (rshCD6) have notable beneficial effects (increase in survival, reduction in proinflammatory cytokine levels) in murine models of septic shock induced by zymosan and LPS, respectively (Sarrias et al., 2007; Vera et al., 2009), opening the door to a possible prophylactic or therapeutic use in human sepsis. As of 1998, septic shock was the tenth leading cause of death in Western countries and one of the main causes of death in intensive care units (Friedman et al., 1998). Because patients obtain little or no benefit from antibiotics or any other standard therapy, mortality rates currently range from 30 to 50% (Vincent et al., 2006). Infusion of recombinant soluble forms of CD5 and CD6 could then represent a valid therapeutic choice that could significantly improve survival of patients with septic shock.

Circulating soluble forms of CD5 and CD6 in human serum have been reported, albeit in small amounts (in the picomolar range), similar to what happens with other lymphocyte surface molecules; these seem to be released during the late phases of lymphocyte activation (Calvo et al., 1999a; Ramos-Casals et al., 2001), which could indicate the existence of a physiological immune response down-regulation mechanism. If confirmed, this finding would have important implications, including therapeutic ones, in autoimmune diseases that present lymphocyte hyperactivation. Although these soluble forms can be found in the serum of healthy persons, their levels are increased in patients suffering from pathological processes implicating lymphocyte hyperactivity/hyperactivation, such as primary Sjögren syndrome (Ramos-Casals et al., 2001) and in MRL-*Ipr/Ipr* mice (M. Ramos-Casals, unpublished data). Although the biological role of the soluble forms is largely unknown, it has been proposed that they could mediate negative feedback mechanisms to inhibit the inflammatory response, because they are able to interact with ligands located at a distance and to block the cell-cell contacts necessary to maintain such responses. Evidence for this is the demonstration that infusion of a chimeric soluble form of CD5 (CDR-Ig) shows beneficial effects in experimental murine models of antibody-induced glomerulonephritis (Biancone et al., 1996) or experimental autoimmune encephalitis (Axtell et al., 2004). So far, there are no similar data for soluble forms of CD6, chimeric or not. Taken together, these results strongly support a potential role for recombinant soluble CD5 in the modulation of autoimmune disease.

An early study described decreased tumor growth and improved survival in tumor-bearing mice treated with

nondepleting anti-CD5 antibodies (Hollander, 1984); this effect was not due to direct interaction of anti-CD5 antibodies with tumor cells; rather, it was mediated by enhancement of host T-cell response, in agreement with previously described CD5 functions. Studies with animal models have also shown that treatment with monoclonal anti-CD5 antibodies can indeed improve disease score and decrease severity of autoimmune disorders: this has been described for collagen-induced arthritis in mice (Plater-Zyberk et al., 1994) and also for mesangioproliferative glomerulonephritis in rats (Ikezumi et al., 2000). Translation of these results into the clinic, however, has met with mixed success: although preliminary studies had shown encouraging safety and activity profiles for an immunoconjugate of ricin A chain and anti-CD5 monoclonal antibody in rheumatoid arthritis (Strand et al., 1993; Fishwild and Strand 1994), a later, double-blind, placebo-controlled study failed to find a significant decrease in disease severity for the immunoconjugate-treated patients (Olsen et al., 1996). It should be noted, however, that an unusually high placebo response was observed in this study. Likewise, although an early study suggested some activity for this immunoconjugate in SLE (Stafford et al., 1994), no further efforts have been carried out along this line of treatment.

An important thing to consider when dealing with CD5-related therapies is that although inducing expression of CD5 on lymphocytes may have a protective effect in autoimmune disorders, it might also result in increased risk of tumor development (Dalloul, 2009). This effect might be mediated through IL-10 production induced by CD5, which decreases tumor-specific T-cell immunity, or by a decrease in antitumor efficacy of CD5-expressing T cells, which seems to be inversely proportional to the levels of expressed CD5 (Dorothee et al., 2005).

Regarding the therapeutic use of anti-CD6 antibodies, a successful application for them has been found in the prevention of graft-versus-host disease in patients undergoing bone marrow transplant. Anti-CD6 antibodies have been used to deplete mature T cells *ex vivo* from bone marrow from syngeneic or allogeneic donors before its transplant into recipients (Soiffer et al., 1992, 1997; Patel et al., 2008). The claimed advantage of anti-CD6 was that it specifically removes mature T cells without significantly affecting NK cells, B cells, or myeloid precursors; the *ex vivo* therapy also reduced patient morbidity and permitted bone marrow transplants in older patients. Bone marrow depletion with anti-CD6 has also been used in the treatment of hematological malignancies such as multiple myeloma (Seiden et al., 1995) and non-Hodgkins lymphoma (Soiffer et al., 1998). Because the use of CD6-depleted bone marrow carries a low risk of transplant-related complications, it has become a valid treatment alternative for patients at high risk of relapse after autologous transplant.

VIII. CD163: the Hemoglobin Receptor and More

CD163 is a macrophage-specific transmembrane type I glycoprotein identified in a number of species (Kishimoto et al., 1997). Structurally, CD163 has an ectodomain consisting of 9 SRCR domains in tandem, with SRCR domains 6 and 7 separated by a PST-rich interdomain segment. A short linker section then connects SRCR domain 9 with a transmembrane domain and an intracellular cytoplasmic tail. This structure is reminiscent of that of CD163-L1 (Gronlund et al., 2000), except that the latter possesses 12 SRCR domains. It is believed that CD163 could have arisen from CD163-L1 through loss of the first three SRCR domains (Gronlund et al., 2000; Stover et al., 2000). The cytoplasmic tail of CD163 is subjected to alternative splicing, generating three variants of different length: the most abundant form has a tail of 49 amino acids, while longer forms of 84 or 89 amino acids exist (Law et al., 1993; Ritter et al., 1999). The first 42 amino acids of this tail are preserved in all existing forms and contain phosphorylation target sequences for creatine kinase and protein kinase C; additional phosphorylation sites are also present in the longer cytoplasmic tail forms (Van Gorp et al., 2010). Alternative splicing forms affecting the extracellular part of CD163 have also been reported, one of them possessing a stop codon after the first SRCR domains, generating a truncated, possibly secreted form, and the second one giving rise to a protein with an additional 33 amino acids in between SRCR domains 5 and 6 (Law et al., 1993). The cDNA sequence predicts 11 putative *N*-glycosylation sites; accordingly, there is a reduction in molecular weight after treatment with *N*-glycosidase (Högger et al., 1998; Fabriek et al., 2007).

CD163 is a monocyte/macrophage-specific protein, in contrast to other members of the SRCR superfamily. Expression is strongly up-regulated by anti-inflammatory inducers (such as glucocorticoids, IL-6, and IL-10) and down-regulated by proinflammatory agents (such as LPS, TNF- α , and IFN γ). The presence in the 5'-flanking region of glucocorticoid responsive elements and binding sites for a number of transcription factors involved in myeloid-specific gene expression and differentiation (Ritter et al., 1999) explains how those agents can regulate CD163 expression (Morganelli and Guyre 1988; Zwadlo-Klarwasser et al., 1990; Högger et al., 1998; Van den Heuvel et al., 1999). CD163 expression correlates with the degree of cell differentiation and activation; indeed, tissue macrophages have increased expression of CD163 compared with levels found in monocytes (Sánchez et al., 1999). CD163 has therefore been proposed as a marker of monocyte differentiation. Expression of CD163 could also correlate with the degree of macrophage activation, because newly infiltrating macrophages are CD163-negative but up-regulate their expression during the healing phase of acute inflammation, in chronic inflammation, and also in wound-healing tissue

(Zwadlo et al., 1987; Verschure et al., 1989). However, the mechanisms of CD163 expression are regulated in a complex way: for example, LPS binding to TLR4 induces expression of IL-6 and IL-10, which in turn induce CD163 expression (Weaver et al., 2006, 2007). LPS is then able to indirectly induce expression of CD163. Likewise, reduction in CD163 expression mediated by LPS is not a consequence of synthesis inhibition or increased turnover, but rather of induced ectodomain shedding.

The CD163 ectodomain shedding leads to a soluble form circulating in plasma (Droste et al., 1999; Møller et al., 2002). Soluble CD163 (sCD163) is not generated by alternative splicing but is the product of membrane-bound CD163 cleavage by ADAM17 (Etzerodt et al., 2010); whether sCD163 can also be generated by alternative splicing has not yet been determined. The molecular weight of sCD163 suggests that this form contains almost the entire extracellular region of membrane-bound CD163 (Møller et al., 2002). Shedding can be induced by mitogens such as phorbol 12-myristate 13-acetate (PMA) (Droste et al., 1999), endotoxins such as LPS (Hintz et al., 2002; Weaver et al., 2006), mediators of oxidative stress (Timmermann and Högger, 2005), and Fc γ receptor cross-linking (Sulahian et al., 2004).

The physiological role of sCD163 is unknown, but it seems to be of lesser importance in the binding of Hb-Hp complexes, the best-studied role of CD163 (see section VIII.A), which bind preferentially to membrane-bound CD163 (Møller et al., 2010). It is noteworthy that levels of sCD163 are increased in patients suffering from infections and autoimmune disorders (Van Gorp et al., 2010) and sCD163 has been reported to exert a strong anti-inflammatory effect on T cells, inhibiting their activation and proliferation (Högger and Sorg, 2001). This could point to a role for sCD163 in controlling and reducing inflammation.

A regulatory role has been suggested for CD163 during erythropoiesis because of its reported ability to bind erythroblasts and promote erythroid expansion *in vitro* (Fabriek et al., 2007). The role of CD163 in the immune response, however, is still unclear, because this receptor seems to elicit different reactions depending on stimuli and context. On the one hand, expression of CD163 is up-regulated in macrophages by anti-inflammatory compounds such as IL-10 and glucocorticoids; this in turn results in induction of IL-10 production by stimulated macrophages, creating a positive loop. IL-10-producing macrophages, also known as alternatively activated macrophages or M2 macrophages, are involved in Th2-type responses, inhibit T-cell proliferation, and possess anti-inflammatory properties (Fairweather and Cihakova, 2009). This has led CD163 to be considered a marker of M2 anti-inflammatory macrophages. Furthermore, products of heme degradation after endocytosis by CD163 have strong anti-inflammatory and antioxidative activity (Otterbein et al., 2003). This

points to a role for CD163 in preventing and controlling excessive inflammatory reaction, and helps to explain the presence of high levels of CD163 during the late phase of inflammation or in chronically inflamed tissues (Zwadlo et al., 1987; Topoll et al., 1989). However, cross-linking of CD163 with antibodies elicits a different type of response from macrophages, namely the synthesis of pro-inflammatory cytokines such as IL-1 β and TNF α (Van den Heuvel et al., 1999; Polfliet et al., 2006). Furthermore, binding of CD163 to bacteria also induces a similar pro-inflammatory response (Fabriek et al., 2009). These data indicate that CD163-mediated modulation of the immune response depends on the type of ligand bound and the presence of different cytokines in the environment.

CD163⁺ macrophages are also found infiltrating tumor tissue (Peng et al., 2009). As mentioned previously, CD163 expression is particularly high in alternatively activated macrophages, which are known to secrete angiogenic factors (Kodelja et al., 1997). Enhanced angiogenesis is found in follicular lymphoma near sites of CD163⁺ macrophage infiltration (Clear et al., 2010). The presence of an increased number of CD163⁺ macrophages infiltrating the tumor was found to correlate with neoangiogenesis and poor prognosis. These results were supported by work on intrahepatic cholangiocarcinoma, which revealed that CD163 was a prognostic marker for the disease (Hasita et al., 2010). CD163 can also bind to and sequester TNF-like weak inducer of apoptosis from the environment, inhibiting its ability to induce apoptosis of tumor cells (Bover et al., 2007).

A. Role in Hemoglobin Clearance

The most established function of CD163 is its ability to bind and endocytose Hb-Hp complexes (Kristiansen et al., 2001). Hemoglobin is released into the circulation after intravascular hemolysis of reticulocytes or senescent red blood cells but also during autoimmune, infectious, or inherited disorders causing accelerated hemolysis. Removal of hemoglobin is of key importance as a result of the toxicity and oxidative potential of iron-containing heme. Haptoglobin is a protein produced by the liver and circulating in plasma; it is able to bind free hemoglobin and experiences a conformational change that reveals a neoepitope, allowing it to bind CD163 (Kristiansen et al., 2001). Haptoglobin is present in humans in two allelic forms, Hp-1 and Hp-2; CD163 has higher functional affinity for Hp 2-2 or Hp 2-1 multimers than for Hp 1-1 dimers (Kristiansen et al., 2001). Interaction between CD163 and Hb-Hp complexes is of very high affinity and is calcium-dependent (Madsen et al., 2004). Hb-Hp complexes are subsequently endocytosed, and the heme group is converted intracellularly into iron and bilirubin by heme oxygenase-1 (HO-1) (Nielsen et al., 2010). It is noteworthy that HO-1 expression can be induced by glucocorticoids and IL-10, the very same compounds known to induce CD163 expression (Wagener et al., 2003; Philippidis et al., 2004). Further-

more, binding of CD163 to Hb-Hp complexes triggers macrophage secretion of cytokines, among them IL-10. These data point to a coordinated up-regulation of the system that is activated upon the release of hemoglobin into the circulation and can help protect tissues from toxic and oxidative heme-mediated damage. As mentioned previously, the response induced by CD163 depends on the stimulus; in this way, cross-linking of CD163 by Hb-Hp induces a different cytokine profile than cross-linking with anti-CD163 antibodies (Van den Heuvel et al., 1999; Ritter et al., 2001; Madsen et al., 2004).

Besides its protective function, heme clearance from the circulation could reduce the availability of iron to pathogens, thereby helping to fight infection (Madsen et al., 2004; Weaver et al., 2006).

B. Role in Pathogen Recognition

Like other SRCR superfamily members, CD163 has been recently reported to bind to Gram-positive and Gram-negative bacteria, acting as a pattern recognition receptor (Fabriek et al., 2009). The binding site was mapped to a consensus sequence including the GRVEVxxxxxW motif—already implicated in bacteria binding in gp340/SAG/DMBT1 (Bikker et al., 2004a)—within the second SRCR domain. Similar to results obtained in DMBT1, the consensus peptide alone was able to induce aggregation of bacteria. It is noteworthy that the same domain has been reported to be implicated in adhesion to erythroblasts (Fabriek et al., 2007), whereas binding to Hb-Hp complexes, however, has been mapped to the third SRCR domain (Madsen et al., 2004). Binding of bacteria to CD163 triggered the production of proinflammatory cytokines such as TNF α (Fabriek et al., 2009). However, CD163 did not seem to have functional implications in phagocytosis, which led authors to postulate a role for this receptor as a bacteria sensor.

A broader role for CD163 in the defense against pathogens can be gathered from evidence that this gene is up-regulated in central nervous system macrophages in a neuroAIDS model (Roberts et al., 2003), in liver macrophages from patients with chronic hepatitis (Hiraoka et al., 2005a), and in brain macrophages and microglia of monkeys infected with the simian immunodeficiency virus (SIV) (Borda et al., 2008). Furthermore, CD163 mediates infection by the African swine fever virus (Sánchez-Torres et al., 2003); indeed, CD163 was found to be necessary for infection of macrophages by this virus. Supporting the role of CD163 as a possible viral entry target, transfection of full-length CD163 conferred susceptibility to porcine reproductive and respiratory syndrome virus (PRRSV) infection to porcine macrophages (Calvert et al., 2007). Sialoadhesin was later found to be a necessary partner of CD163 in PRRSV infection (Van Gorp et al., 2008). Interaction with PRRSV was mapped to the fifth SRCR domain (Van Gorp et al., 2010), in contrast with the sites reported to bind bacteria and Hp-Hb complexes. More recent studies have suggested

that CD163 is not only implicated in PRRSV entry, but also in its replication efficiency (Patton et al., 2009); indeed, recombinant CD163 lacking the cytoplasmic tail was shown to promote viral replication in PRRSV-infected macrophages to a higher extent than that of full-length CD163 (Lee and Lee, 2010).

C. Diagnostic and Therapeutic Potential: Utility as Serum/Cell Marker of Inflammatory Status during Infectious and/or Malignant Disorders

As previously mentioned, sCD163 levels are increased in serum in response to a number of pathological conditions; this suggests a potential use as a marker of disease severity and progression. An early report on this potential capacity failed to distinguish healthy patients from those with infection, different degrees of sepsis and bacteremia on the basis of their sCD163 serum levels (Gaïni et al., 2006). However, bacterial and nonbacterial infections in patients suspected of meningitis could be distinguished on the basis of elevated sCD163 serum levels (Knudsen et al., 2007). Likewise, sCD163 levels were found to be significantly elevated in patients with *S. pneumoniae* bacteremia compared with healthy control subjects (Møller et al., 2006); furthermore, sCD163 levels were predictive of fatal outcome in older patients. A decreased survival rate was also found for patients with tuberculosis with levels of sCD163 above the reference upper limit; correlation was independent of age and gender (Knudsen et al., 2005). Concomitant HIV infection further increased sCD163 levels. This could indicate that sCD163 serum levels could be used as markers to follow-up infectious disease for certain pathogens.

It has been shown that heme-mediated toxicity is associated with bacterial infection, and that the release of excessive amounts of heme during infection could induce lethal sepsis (Larsen et al., 2010). In a manner similar to that shown for Hp (Boretti et al., 2009) and hemopexin (Lin et al., 2010), exogenous administration of sCD163 could then enhance the clearing of free heme from the circulation and thus prevent the development of sepsis or improve its outcome. Although Hb-Hp complexes bind preferentially to membrane-bound CD163, this protein could prove useful in the scavenging of free heme.

Reflecting the involvement of CD163 in viral pathogenesis, CD163⁺ monocytes are increased in patients with HIV-1 compared with healthy controls or with patients infected with HIV-1 but with undetectable viral load, and their number correlates with viral load more accurately than the number of CD4⁺ T cells (Fischer-Smith et al., 2008). CD163⁺ monocytes were also found to be inversely correlated to the number of CD4⁺ T cells, suggesting that, as is the case with PRRSV, CD163 could be involved in HIV-1 infection of monocytes as well as disease progression and might be a useful marker for disease follow-up. This may also apply to the use of sCD163 in liver disease: compared with healthy patients, levels of sCD163 were increased in patients with

acute and chronic hepatitis but were highest in patients with fulminant hepatic failure (FHF) (Hiraoka et al., 2005b). sCD163 progressively decreased in survivors of FHF, but not in nonsurvivors, suggesting a link with disease outcome.

Consistent with the fact CD163 is associated with M2 macrophages, which play an important role in defense against pathogens eliciting a Th2 response, such as parasites (Fairweather and Cihakova, 2009), sCD163 is found elevated in the serum of patients with malaria compared with healthy persons (Kusi et al., 2008). sCD163 levels were higher in patients with uncomplicated malaria than in those with cerebral malaria or severe malarial anemia, suggesting that the anti-inflammatory properties of sCD163 protect these patients from further inflammation-related damage.

Some noninfectious disorders have also shown an increase in sCD163 levels, particularly autoimmune diseases. Potential for use of sCD163 as a marker of disease severity and progression, as well as for initial diagnosis, has been suggested for autoimmune arthritis (Matsushita et al., 2002; Baeten et al., 2004), reactive hemophagocytic syndrome (Schäfer et al., 2005), macrophage activation syndrome (Blesing et al., 2007), and multiple sclerosis (Fabriek et al., 2007).

Besides the potential use of sCD163 as a marker of macrophage activity in disease, it has also been proposed to exploit CD163 in therapy by using this receptor for targeting drugs to macrophages (Nielsen and Moestrup, 2009). This has rather intriguing perspectives because macrophages, as the main producers of TNF- α and other proinflammatory cytokines, are a main effector cell in many inflammatory diseases such as rheumatoid arthritis and chronic intestinal inflammation. CD163 is also highly expressed in tumor-associated macrophages, which at present is a focus in cancer research and treatment because of their importance in maintaining and supporting cancer growth.

IX. DMBT1/gp340/Salivary Agglutinin: an Antioncogene with Broad Protective Functions

DMBT1 (for deleted in malignant brain tumors 1) is a mosaic protein highly conserved among different species and found as a secreted protein, although isoforms may exist that function as transmembrane receptors. Three proteins found in human tissue—DMBT1, gp340 and SAG (for salivary agglutinin)—have all been found to be products of the same gene, termed *DMBT1* (Holmskov et al., 1999; Prakobphol et al., 2000). Meanwhile, species homologs have been described in mouse (CRP-ductin, vomeroglandin and muclin), rabbit (hensin), rat (ebnerin), cow (bovine gallbladder mucin), and rhesus monkey (H3) (Sarrias et al., 2004a). All these proteins share a common structure of a defined number of group B SRCR domains separated by stretches of 20 to

23 amino acid residues [SRCR interspersed domains (SIDs)], as well as of CUB and ZP domains. The CUB domain can be found in complement proteins such as C1s/C1r, whereas the ZP domain is present in glycoproteins from the *zona pellucida* of oocytes. Both CUB and ZP domains have been implicated in protein-protein interactions. ZP domains are also involved in protein oligomerisation, a function they could also perform in DMBT1/gp340/SAG, in that this protein seems to form aggregates (Young et al., 1997; Oho et al., 1998).

Three transcripts have been described for DMBT1/gp340/SAG, with lengths of 6, 7.5, and 8 kb; all three are expressed in fetal lung, whereas only the 8-kb transcript was detected in adult lung. The 6- and 7.5-kb transcripts were also present in adult small intestine (Mollenhauer et al., 1997). DMBT1/gp340/SAG possesses 8 to 13 tandem-repeated highly homologous SRCR domains separated by SIDs and a lower homology 14th domain separated from the others by a Thr-rich region and a CUB domain (Mollenhauer et al., 1997, 1999; Holmskov et al., 1999). It was later found that the number of tandem repeat SRCR domains can vary between 8 and 13 in naturally occurring alleles (Mollenhauer et al., 2002; Ligtenberg et al., 2007). Further toward the C terminus are a second CUB domain and the ZP domain. Exon 55 of the DMBT1 genomic DNA encodes for a potential transmembrane sequence, but so far, no transcript containing this exon has been detected in humans (Mollenhauer et al., 1999). Twelve potential *N*-glycosylation sites are predicted from the DMBT1/gp340/SAG protein sequence; sites of *O*-glycosylation within the SIDs have also been proposed (Bikker et al., 2002). Glycosylation accounts for a substantial proportion—approximately 25%—of the total molecular weight of the protein (Oho et al., 1998).

Expression of DMBT1/gp340/SAG has been detected in several different types of tissue, mostly of epithelial origin, such as lung, trachea, salivary gland, small intestine, and stomach. Lower levels have been found in brain, testis, uterus, prostate, pancreas, and mammary glands (Holmskov et al., 1999); DMBT1 expression in rat and monkey endometrial tissue was found to be estrogen-dependent (Tynan et al., 2005). Another report found DMBT1/gp340/SAG to be expressed across the immune system, in T- and B-cell lines, spleen, thymus, lymph nodes, bone marrow, and alveolar macrophages (Mollenhauer et al., 2000).

A. Role in Epithelial Cell Differentiation and Pathogen Recognition

DMBT1/SAG/gp340 was originally reported based on deletions in malignant brain tumors (Mollenhauer et al., 1997), hence its name. However, it was later found that inactivating mutations of the gene in astrocytic gliomas were small and infrequent (Mueller et al., 2002). There are hints that the repetitive SRCR/SID region of

DMBT1/gp340/SAG shows various different rearrangements in cancer cells, but these are difficult to resolve and to discern from already existing interindividual polymorphisms (Mollenhauer et al., 1999, 2000, 2002). Furthermore, certain subpopulations of glioblastoma multiforme were actually shown to overexpress the protein (Mollenhauer et al., 2000). However, most cancer types that have been analyzed displayed a down-regulation of DMBT1/gp340/SAG expression levels, so that this might represent a more common mechanism of inactivation (Mori et al., 1999; Takeshita et al., 1999; Wu et al., 1999; Mollenhauer et al., 2000, 2001). A clearer role for DMBT1/gp340/SAG in the development, regeneration, and homeostasis of epithelia is now emerging thanks to recent reports.

DMBT1/gp340/SAG levels in the adult were found to be much lower than those of the fetus, whereas the spatial location and the subcellular distribution of the protein also varied according to the developmental stage (Mollenhauer et al., 2000). Studies on the DMBT1/gp340/SAG mouse and rabbit homologs, CRP-ductin and hensin, respectively, first indicated that these proteins could be involved in epithelial differentiation. Hensin has been shown to mediate terminal differentiation of kidney epithelial cells (Al-Awqati et al., 1998, 2000; Vijayakumar et al., 1999); it has been hypothesized that hensin might also influence differentiation of other epithelia, given its expression pattern. A recent report described that expression of DMBT1/gp340/SAG was induced in gastric cells undergoing G₀/G₁ arrest and down-regulated after the cells had finished their differentiation process (Kang et al., 2005), implicating DMBT1/gp340/SAG in cell fate decisions.

Expression of this protein has in several species been readily detected in the crypt cells of the small intestine (Cheng et al., 1996; Takito et al., 1996; Mollenhauer et al., 2000), an area composed mostly of stem and progenitor cells. The conserved expression of this protein at such an area in different species suggests a role for DMBT1/gp340/SAG in small intestine epithelial regeneration. Further evidence on the role of DMBT1/gp340/SAG in epithelia regeneration came from a study on the rat homolog of this protein, ebnerin: proliferation of duct-located stem cells, possessing the ability to differentiate into hepatocytes and thus regenerate liver tissue affected by toxins or injury, was associated with induction of ebnerin expression in these cells (Bisgaard et al., 2002). A possible mechanism for DMBT1/gp340/SAG in tissue regeneration could involve interaction with trefoil factors: these have been shown to promote the regeneration and healing of the gastrointestinal tract. Mouse *Dmbt1* has an expression pattern very similar to that of trefoil factor 2; furthermore, porcine DMBT1 was found to interact with trefoil factor 2 (Thim and Mørtz, 2000).

As well as being deregulated in epithelial malignancies, expression of DMBT1/gp340/SAG can be affected by inflammation and infection. Indeed, high levels of DMBT1/gp340/SAG were found in the tracheal aspirates

and lung tissue sections of newborn infants with bacterial infections (Müller et al., 2007) and in the A549 lung cell line after pro-inflammatory stimulation with PMA (Kang et al., 2002). Inflammation—whether induced by TNF α , by LPS, or by inflammatory bowel disease—also up-regulated DMBT1/gp340/SAG expression in intestinal epithelial cells (Renner et al., 2007; Rosenstiel et al., 2007). Moreover, a polymorphism of DMBT1/gp340/SAG giving rise to a protein with fewer SRCR domains was associated with increased risk of Crohn's disease. Confirming the involvement of this protein in intestinal inflammation, knockout mice for *dmbt1* were more susceptible to dextran sulfate-induced colitis (Renner et al., 2007). However, two further *dmbt1* knockout mouse models display different phenotypes: one of them showed a severe phenotype with embryonic lethality as a result of developmental defects (Takito and Al-Awqati, 2004), whereas the other was viable but did not display enhanced susceptibility to induced colitis (De Lisle et al., 2008). Although the reasons for the differences in viability remain unclear, it was subsequently shown that high concentrations of dextran sulfate level out the protective effect of DMBT1 because of a direct interaction between DMBT1 and dextran sulfate (End et al., 2009).

The first reported function for DMBT1/gp340/SAG was that of a salivary agglutinin for *Streptococcus mutans*, the main causative agent of dental caries (Ericson and Rundegren, 1983). Subsequently, it was shown that this binding was calcium-dependent and extended to a number of different Gram-positive and Gram-negative bacteria, including *E. coli*, *Lactobacillus casei*, *Helicobacter pylori*, *S. aureus*, *S. pneumoniae*, and *Haemophilus influenzae* (Prakobphol et al., 2000; Bikker et al., 2002; Madsen et al., 2003); the protein was also shown to inhibit cytoinvasion of intestinal epithelial cells by *Salmonella enterica* (Rosenstiel et al., 2007). Specific components at the bacterial surface were found to be ligands for DMBT1/gp340/SAG, namely a group of receptors on the surface of streptococci termed antigen I/III polypeptides (Jenkinson and Demuth, 1997); however, DMBT1/gp340/SAG also bound to *H. pylori* and *S. aureus*, which do not possess these polypeptides. Binding of DMBT1/gp340/SAG to bacteria has been shown to depend on fucose and sialic acid residues (Demuth et al., 1990; Oho et al., 1998), suggesting that carbohydrate moieties are of primary importance in the interaction with bacteria. However, other studies put this theory in doubt by reporting that binding of DMBT1/gp340/SAG to bacteria is unaffected by chemical modification of carbohydrate residues in the protein (Oho et al., 1998; Ligtenberg et al., 2000). Indeed, the peptidic region of DMBT1/gp340/SAG has been shown to be involved in bacterial binding. Chemical fragmentation and peptide mapping, followed by synthesis of peptides representing the consensus sequences of SRCR domains and SIDs, showed that an 11-mer peptide (GRVEVLYRGSW) present in a loop in a SRCR domain was the only DMBT1/gp340/SAG peptide

sequence able to agglutinate *S. mutans* in a calcium-dependent fashion and to bind different types of bacteria (Bikker et al., 2002). This peptide is present in eight SRCR domains of DMBT1/gp340/SAG, explaining its ability to aggregate bacteria through multiple binding sites. However, the peptide was also able to induce agglutination of bacteria on its own, possibly by mimicking the multivalent structure of the protein by self-aggregation.

DMBT1/gp340/SAG has also been reported to protect mucosae against viruses by directly binding, agglutinating, and neutralizing them. Indeed, DMBT1/gp340/SAG present in alveolar fluid was shown to inhibit the infectivity of influenza A virus (Hartshorn et al., 2003); in this case, the antiviral effects were found to be mediated by interactions between virions and sialic acid residues present on the surface of DMBT1/gp340/SAG. Resistance to infectivity was shown to depend on the number of sialic acid residues (Hartshorn et al., 2006), remarking the importance of this type of glycosylation in the antiviral activity of DMBT1/gp340/SAG. This antiviral activity was also found to extend to equine and porcine influenza viruses as well as the human variety. HIV-1 infectivity is also inhibited by binding in a calcium-dependent fashion to DMBT1/gp340/SAG through the surface glycoprotein gp120 (Wu et al., 2003); interestingly, the binding was shown to be dependent on carbohydrate moieties and the N-terminal SRCR found to be directly implicated in the interaction (Wu et al., 2006). gp120 binds to DMBT1/gp340/SAG through a different site than that implicated in CD4 binding (Wu et al., 2004). In fact, CD4 binding to gp120 seems to enhance the interaction between gp120 and DMBT1, suggesting that DMBT1 specifically blocks entry of HIV-1 into T cells. In stark contrast with these results, recent studies reported that DMBT1/gp340/SAG expression in macrophages and genital epithelial cells actually facilitates HIV-1 infection, which was proposed to be based on DMBT1/gp340/SAG simultaneously promoting transfer of HIV-1 to T cells (Stoddard et al., 2007; Cannon et al., 2008).

In addition to directly binding bacteria and viruses, DMBT1/gp340/SAG is also able to bind soluble IgA, which results in a cooperative effect in bacteria agglutination (Rundegren and Arnold, 1987; Armstrong et al., 1993). Enhanced clearance of pulmonary bacteria and viruses is also achieved by DMBT1/gp340/SAG in cooperation with surfactant proteins SP-A and SP-D, involved in the innate defense of lung mucosae (Ligtenberg et al., 2001; Hartshorn et al., 2003); in this case, although gp340 can bind to SP-D/A at a site distinct from the mannan-binding site, the cooperative effect was achieved not by binding of DMBT1 to the surfactant proteins but rather by the combined effects of each protein working independently (White et al., 2005). Binding of DMBT1/gp340/SAG to the complement protein C1q activates the classic complement pathway, inducing inflammatory response (Boackle et al., 1993); DMBT1/gp340/SAG also seems to activate the lectin path-

way of complement through interaction with mannose-binding lectin (A. Ligtenberg, personal communication). DMBT1/gp340/SAG has further been reported to stimulate migration of alveolar macrophages (Tino and Wright, 1999), suggesting that its protective functions exceed those that involve direct binding of pathogens. Thanks to interactions with other proteins – whether direct or in cooperation - DMBT1/gp340/SAG is able to carry out its protective functions in a versatile fashion.

Taken together, these results indicate that DMBT1/gp340/SAG is able to bind, agglutinate and/or neutralize a variety of bacteria and viruses, either directly or in cooperation with other innate immunity proteins, providing a clear role for this protein in the protection of epithelia and mucosae from pathogens. Coupled with its role in innate defense of epithelia and mucosae, DMBT1 involvement in epithelia regeneration and homeostasis puts this protein in a key position to integrate signals from the environment and maintain epithelial integrity through interaction with pathogens, host proteins, and growth factors or surface molecules in the stem-cell compartment, possibly through its CUB and ZP domains.

In this context, it is conceivable that alterations in DMBT1/gp340/SAG could lead to tumor development. Indeed, deregulation of DMBT1 expression has been reported for a number of tumors, including gliomas (Lin et al., 1998), small- and non-small-cell lung cancer cell lines and tumors (Takeshita et al., 1999; Wu et al., 1999; Mollenhauer et al., 2002), carcinoma of the esophagus (Mori et al., 1999; Mollenhauer et al., 2001), epithelial skin cancer (Mollenhauer et al., 2003), intrahepatic cholangiocarcinoma (Sasaki et al., 2003), breast cancer (Braidotti et al., 2004; Mollenhauer et al., 2004; Blackburn et al., 2007), salivary gland tumors (Bikker et al., 2004b), pancreatic ductal adenocarcinomas (Hustinx et al., 2004; Cheung et al., 2008), oral squamous cell carcinoma (Imai et al., 2005), gastric cancer (Conde et al., 2007), and cutaneous melanoma (Helmke et al., 2009). In many cases, expression of DMBT1/gp340/SAG was deregulated not only at the tumor site but also in flanking tissue, which could arise as a consequence of the proinflammatory environment generated by the tumor. The high number of repetitive sequences in the DMBT1/gp340/SAG gene could be responsible for instability of the gene and the subsequent arising of alterations.

B. Therapeutic and Diagnostic Potential

The deregulation of DMBT1/gp340/SAG expression in a number of different tumor types makes this protein an attractive candidate for use as a tumor biomarker. Diagnosis of early pancreatic cancer is complex because of the absence of clear symptoms and the lack of effective screening tests (Li and Abbruzzese, 2010); this is one of the reasons why pancreatic cancer has a 5-year survival rate of less than 5%. Two independent studies have identified DMBT1/gp340/SAG

as a gene consistently overexpressed in pancreatic tumors compared with normal pancreatic tissue (Hustinx et al., 2004; Cheung et al., 2008). Both studies used different approaches to identify biomarkers, which further supports the differential expression of DMBT1/gp340/SAG in normal and malignant pancreatic tissue. This could allow for the development of DMBT1/gp340/SAG screening tests as part of pancreatic cancer diagnosis.

Breast cancer is the most frequent malignancy among women. Studies with mice have suggested that DMBT1/gp340/SAG expression is related to breast cancer susceptibility, being significantly reduced in tumor compared with normal breast tissue (Blackburn et al., 2007). These results have been further confirmed by the identification of two polymorphisms associated with increased risk of breast cancer in women older than 60 years old (Tchatchou et al., 2010). It is noteworthy that one of the polymorphisms was located at the promoter region of the *DMBT1* gene and was associated with a significantly reduced promoter activity in vitro. Detection of these polymorphisms could single out persons at risk and provide them with extra vigilance and an early diagnosis that would reduce morbidity and mortality. Finally, heterogeneity of DMBT1/gp340/SAG expression in different tumor types could help to distinguish them, as in the case of anorectal and cutaneous melanoma: while cutaneous melanoma is the most common skin malignancy and has a mean 5-year survival of 80%, anorectal melanoma is rare but is associated with an extremely poor prognosis. Moreover, both types of melanoma seem to express different levels of DMBT1/gp340/SAG. These two tumor types can then be discriminated on the basis of their DMBT1 expression (Helmke et al., 2009), facilitating diagnosis and ensuring that the right treatment for the disease is used in each case.

Apart from the use of DMBT1/gp340/SAG as a tumor biomarker, there is undoubted potential for this protein in the treatment and management of infections—especially oral (as in dental cavities), intestinal, and pulmonary—through its recognized activity as a pathogen-neutralizing agent. More speculatively, this protein might also be of use in the management of chronic inflammatory disorders such as inflammatory bowel disease and Crohn's disease.

X. Sp α /AIM/Api6/CD5L: An Antiapoptotic Protein Secreted by Macrophages

Sp α (secreted protein α) and AIM (apoptosis inhibitory molecule; also known as Api6 and CD5L) are homologous human and murine secreted proteins belonging to group B of the SRCR superfamily. AIM is generally considered to be the murine homolog of Sp α (Gebe et al., 2000). They both possess a secretory signal followed by three SRCR domains, a structure that closely resembles that of CD5 and CD6; however, these

proteins display higher homology with fellow group B members T19/WC1 and CD163/M130. Although Sp α and AIM share a high level of sequence homology (70%), their glycosylation patterns differ considerably; although the Sp α sequence contains no putative *N*-linked glycosylation sites (Gebe et al., 1997), three of these sites have been found in the AIM amino acid sequence (Gebe et al., 2000). Sp α , however, has been shown to possess terminal sialic acid residues presumably attached to O-linked carbohydrate moieties bound to a PST-rich polypeptide that separates SRCR domains 1 and 2 (Sarrias et al., 2004b). Divergent glycosylation patterns could account for functional differences reported for these proteins.

Expression of Sp α mRNA is found mostly in lymphoid tissues, including spleen, lymph nodes, thymus, bone marrow, and fetal liver, but not in peripheral blood leukocytes. In contrast, expression of AIM is restricted to tissue macrophages, although only a fraction of these express the protein (Miyazaki et al., 1999). Subpopulations of AIM-expressing macrophages are found at inflammation sites and at the thymic cortex, suggesting that AIM is involved in both regulation of the inflammatory response and in thymocyte development. Expression of AIM has been found to be increased by the inflammatory environment but not by common stimuli such as PMA, LPS, and cytokines such as IFN- γ or interleukins (Miyazaki et al., 1999). Both Sp α and AIM are found circulating in serum (Gebe et al., 2000; Sarrias et al., 2004b), where Sp α associates with IgM but not IgG or IgA (Tissot et al., 2002; Sarrias et al., 2005).

A. Role in Apoptosis, Arteriosclerosis, and Pathogen Recognition

AIM has been reported to bind strongly to murine macrophages and weakly to T-cell lines, but not to B-cell lines or to peripheral blood mononuclear cells (Gebe et al., 2000). Despite its apparent lack of binding to B-cell lines, AIM was shown to strongly inhibit the proliferation and antibody production of spleen B cells stimulated with LPS (Yusa et al., 1999); this inhibition, however, was only observed when cells were incubated with AIM in the presence of TGF- β , suggesting a complex interaction between SRCR members and cytokines. AIM has also been shown to increase phagocytosis in macrophages, probably by acting as an opsonin (Haruta et al., 2001), but it was the development of AIM knockout mice that shed light on the function of this protein: AIM(-/-) mice were shown to harbor significantly lower amounts of CD4/CD8 double-positive thymocytes compared with wild-type mice. Accordingly, AIM(-/-) double-positive thymocytes showed increased sensitivity to apoptosis induced by dexamethasone, irradiation, and CD95/Fas crosslinking (Miyazaki et al., 1999). Indeed, AIM has also been shown to protect macrophages from bacterial pathogens such as *L. monocytogenes* (Joseph et al., 2004), *Bacillus anthracis*, *E. coli*, and *S. typhimurium*

(Valledor et al., 2004). Furthermore, addition of recombinant AIM was shown to rescue monocytes and thymocytes at different maturation states from apoptosis (Miyazaki et al., 1999), indicating that AIM binding results in a survival stimulus in different cell lines. It was later shown that AIM(-/-) challenged with heat-killed *Corynebacterium parvum* also had lower numbers of T and NK T cells within granulomas (Kuwata et al., 2003), suggesting that these cells were also rescued from apoptosis by AIM. This could have a significance at inflammation sites, where AIM-expressing macrophages would be more resistant to apoptosis and could therefore facilitate the clearance of the stimulus responsible for inflammation.

Overexpression of AIM, however, can also be damaging to mice: transgenic mice engineered to express high levels of AIM showed enhanced inflammatory response to experimentally induced hepatitis (Haruta et al., 2001), with large numbers of infiltrating cells and increased tissue destruction. Moreover, transgenic mice overexpressing myeloid-specific AIM show severe inflammation in the lung, resulting in increased incidence of lung adenocarcinoma compared with wild-type mice (Qu et al., 2009). Increased numbers of neutrophils and macrophages, resulting from increased proliferation and diminished apoptosis, infiltrated and accumulated in the lung, changing the microenvironment by decreasing expression of proapoptotic molecules and increasing the levels of enzymes involved in tissue remodelling: this has led researchers to believe that AIM can act as an oncogene.

Macrophages are at the heart of atherosclerotic lesions, where they take up oxidized lipid products from the bloodstream and develop into foam cells; the environment in these lesions is known to be highly proapoptotic (Geng and Libby, 2002). Uptake of oxidized LDL has been reported to induce AIM expression in macrophages (Arai et al., 2005), which in turn results in decreased apoptosis and extended atherosclerotic lesions. Furthermore, lesions in AIM(-/-) mice are dramatically reduced compared with their AIM(+/+) counterparts: this indicates that AIM enhances atherosclerosis, at least in the early stages of the disease, suggesting that deletion/blockade of this protein could prevent the development of atherosclerotic plaques. In the late stages of atherosclerosis, however, AIM deletion might prove detrimental because increased macrophage apoptosis could destabilize plaques and cause acute vascular occlusion and tissue infarction.

A new role for AIM in lipid metabolism has recently been described (Kurokawa et al., 2010). AIM was shown to be endocytosed into adipocytes via CD36 and to subsequently bind to fatty acid synthase, decreasing its activity and stimulating the efflux of fatty acids and glycerol from adipose cells. This effect resulted in decreased lipid droplet size, lower numbers of mature adipocytes, and decreased weight and fat mass induced by

high-fat diet, without any visible alteration in metabolic rates. The role of an innate immunity molecule such as AIM in obesity is explained by the fact that adipose tissues in obesity are in a state of chronic inflammation induced mostly by recruitment of macrophages (Olshansky et al., 2005; Baker et al., 2007).

Although a definite function for Sp α has not yet been reported, this human protein has been shown to bind to resting myeloid cell lines, as well as to peripheral blood monocytes and some B and T cell lines (Gebe et al., 1997); the significance of this binding remains unknown, although the pattern of Sp α expression suggests that this protein could be implicated in development and maintenance of the lymphoid compartment, as well as in immune surveillance. Like other SRCR family members, Sp α can also act as a PRR (Sarrias et al., 2005) by binding LPS and LTA through nonoverlapping sites. It is noteworthy that a single SRCR domain from Sp α retained the ability to interact with bacteria, which directly implicates SRCR domains in the PRR function. There is evidence that AIM also acts as a pattern recognition receptor (V. G. Martinez, unpublished results); this could explain AIM expression in areas exposed to blood-borne pathogens.

B. Therapeutic and Diagnostic Potential

Sp α has been shown to be a valuable marker for autoimmune disease (atopic dermatitis, asthma) and hepatitis-induced liver fibrosis. In the case of atopic dermatitis, Sp α was found to be increased in the serum of patients with the disease compared with healthy control subjects (Kim et al., 2008). Eosinophilia is one of the hallmarks of atopic dermatitis, and increased levels of Sp α could protect eosinophils from apoptosis, thus increasing their numbers and enhancing their activity as effectors of allergic reactions. Sp α was also found to be up-regulated in response to antigen challenge in the bronchial lavage fluid of asthmatic patients compared with nonasthmatic ones (Wu et al., 2005); in this case, Sp α could also increase the numbers of eosinophils, as well as induce the expression of tissue remodelling enzymes involved in the pathogenesis of asthma. As a possible marker of nonautoimmune disease, Sp α serum levels were found to be increased in patients suffering from liver fibrosis as a result of hepatitis C virus infection compared with healthy control subjects (Gangadharan et al., 2007); if validated, these markers could replace liver biopsy as the method of choice for the diagnosis and follow-up of liver fibrosis. All together, these results indicate that serum levels of Sp α directly relate to the development and progress of autoimmune and inflammatory disease; this would make Sp α an attractive marker for use in diagnosis and patient monitoring.

XI. Concluding Remarks

The SRCR-SF is composed of a heterogeneous set of proteins involved in a myriad of different functions. A

significant number of proteins in this superfamily act as pattern recognition receptors, working as pathogen sensors and constituting a first line of defense against microbes. It is noteworthy that pattern recognition is the earliest event in the immune response, making these receptors valuable targets for anti-inflammatory therapy both during infection and in autoimmune diseases. Interfering with the function of these receptors with blocking antibodies or small molecule antagonists inhibiting signal transduction could be a useful tool in the treatment of chronic inflammation. Furthermore, soluble forms of these receptors could be used in the management of infections, to aggregate and/or to facilitate removal of bacteria from infected tissues, or even to sequester LPS or zymosan—known septic shock-inducing factors—from the bloodstream. Other members of this superfamily, such as CD5 and CD6, seem to be implicated in the regulation of the immune response, both innate and adaptive, thus providing further opportunity to modulate the immune response through pharmacological targeting of these proteins. Indeed, there is great potential for the targeting of CD5 in patients with septic shock, as preliminary studies suggest.

Deregulated expression of certain superfamily members, such as DMBT1 or SCARA5, also seems to be associated with cancer, whereas SR-A/II plays a role in the pathogenesis of atherosclerosis and possibly also Alzheimer's disease. The association of these proteins with a pathological state makes them useful markers for disease diagnosis and prognosis. Screening for polymorphisms or mutations in these proteins could also identify populations at risk of disease development before any symptoms or signs appear, thus playing an important role in disease prevention.

All together, these proteins seem to contribute significantly to the regulation of the internal environment of multicellular organisms, maintaining tissue homeostasis. Although further research is needed to shed light on some functional aspects of the SRCR-SF, their involvement in a number of physiological and pathological situations makes them attractive targets for diagnosis and therapy.

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