SERIES INTRODUCTION

Multiligand receptors and human disease

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By virtue of their specific interactions with extracellular ligands, cell surface receptors can transduce signals, carry out endocytosis and other forms of transport, and mediate the adhesion of cells to their substrata or to other cells. While it has generally been assumed that physiologic activities and appropriate responses to pathophysiologic states require that only one ligand be recognized by its cognate receptor, this "one ligand–one receptor" notion is now in need of extensive revision. This Perspective series focuses on several striking examples of multiligand receptors, molecules that interact specifically with classes of structurally related ligands or even with several structurally and functionally dissimilar ligands.

Such broad specificity raises intriguing problems for biological regulation that do not arise with classical, monospecific receptors. From the vantage point of the economy of host gene expression, it is expeditious to have a single protein subserve multiple roles, and for this reason, some authors have speculated that these proteins arose early in molecular evolution. However, the various functions are probably subject to precise regulation to avoid the possibility that a range of stimuli all activate a single cellular response, which might have disastrous consequences for the cell's ability to adapt to environmental challenges. How can one make sense of these types of receptor-ligand interactions? What basic principles have emerged from their study?

Varieties of multiligand receptors

Table 1 shows a selection of multiligand receptors, which are the focus of this Perspective series. Many of these receptors have been implicated in host defense or in the uptake of covalently modified proteins or lipoproteins. Others can be viewed as maintaining tissue homeostasis in some respect, either by shifting the balance of proteolysis in the extracellular space or by mediating the clearance of apoptotic cells and cell debris. In each case, although many of the ligands recognized by a given receptor may share a structural feature, none of the receptors shown can be described simply as a receptor for a particular peptide sequence or chemical moiety. For instance, the receptor for advanced glycation end products (RAGE), although it was initially defined by its affinity for proteins that have acquired covalent sugar linkages following extended periods of hyperglycemia (AGEs), also binds tightly and specifically to certain unmodified proteins. In their article in this series, Schmidt et al. (1) consider the ability of RAGE to interact with not only with pathological substances, the AGEs and the β amyloid fibrils found in plaques, but also with certain normal components of the extracellular environment. The latter ligands include amphoterin, a DNA-binding protein that is found outside the cell in tumors and during at least some phases of normal development, a family of calcium binding proteins, the S100/calgranins, and transthyretin. The ability of these ligands to upregulate RAGE expression and cause sustained cellular activation renders this receptor a potentially potent modulator of cellular properties in ligand-rich environments, such as inflammatory and atherosclerotic lesions, diabetic and tumor tissues, and amyloidoses.

Table 1
Ligand families of multiligand receptors

Receptor	Ligand classes
SR-A	modified lipoproteins (oxidized and acetylated LDL, oxidized HDL), maleylated albumin, LPS, lipoteichoic acid, Gram negative and positive bacteria, apoptotic cells, fucoidan, polyguanylic and polyinosinic acid
SR-BI	HDL, modified LDL (acetylated and oxidized), maleylated albumin, anionic phospholipids, apoptotic cells, native LDL, VLDL
CD36	thrombospondin, modified lipids (oxidized LDL), apoptotic cells, long chain fatty acids, modified LDL, retinal photoreceptor outer segments, *Plasmodium falciparum* malaria parasitized erythrocytes, sickle erythrocytes, anionic phospholipids
RAGE	advanced glycation endproducts (AGEs), β-sheet fibrils, S100/calgranulins, amphoterin, transthyretin
LRP	protease-inhibitor complexes, proteases, thrombospondin, bacterial toxins, rhinoviruses, chaperones (RAP, HSP-96)

Table 2
Disorders/homeostatic processes associated with expression of multiligand receptors

Receptor	Disorders/homeostatic processes
SR-A	atherosclerosis, Alzheimer disease, protection from Gram positive/negative sepsis
SR-B1	HDL and cholesterol metabolism, steroidogenesis, atherosclerosis, development of oocytes and red blood cells
CD36	atherosclerosis, angiogenesis/anti-angiogenesis, fatty acid metabolism, insulin resistance, antigen presentation (priming to tumor or viral antigens)
RAGE	atherosclerosis, diabetic complications, chronic inflammatory disorders (rheumatoid arthritis, etc.), amyloidoses, local tumor growth and metastasis
LRP	embryonic development (migration of neurons during brain development), Alzheimer disease, viral (rhinoviruses) and bacterial toxin-associated diseases, hepatic remnant metabolism

The macrophage scavenger receptors SR-AI and SR-AII, discussed by Platt and Gordon in this series (2), likewise make a mockery of any attempt to define ligand specificity in a single phrase. Although all SR-AI/II known ligands are negatively charged, the SR-As are not indiscriminate polyanion receptors, since many polyanions fail to bind. The known SR-A ligands are also notably heterogeneous in their presumed biological functions, since they range from covalently modified forms of several proteins and lipoproteins to the surface components of a diverse array of bacteria.

In their review, Platt and Gordon (2) grapple with the issue of whether SR-A is indeed multifunctional, as had been suggested by this range of ligands. As they indicate, this question may be harder to answer now, with several conflicting reports of the phenotypes of SR-A–deficient mice in the literature, than it seemed before these animals were described. The macrophage-specific expression and broad ligand repertoire of the SR-As raised the possibility that they serve as pattern recognition endocytic receptors for host defense. Indeed, their ability to bind and internalize a variety of pathogenic surface components from microorganisms (e.g., LPS) and lipoteichoic acid, and the consequences of inactivating mutations on the susceptibility of mutant mice to a wide variety of pathogens strongly suggest that SR-AI/II plays an important role in the innate immune system. As such, it probably forms part of the first line of defense against invading organisms and promotes engagement of adaptive immunity, potentially through the processing of internalized macromolecules for presentation by MHC molecules on the macrophage surface. The physiologic significance of SR-AI/II binding to asbestos fibers, amyloid fibrils, and apoptotic cells, on the other hand, remains to be established.

Expression cloning to identify a novel modified lipoprotein receptor resulted in the cloning of another scavenger receptor, called SR-BI, the topic of the review by Krieger (3) in this series. This receptor engages modified lipoproteins and, like several of the receptors shown in Table 1, it serves as a receptor for the anionic phospholipid phosphatidylserine. As discussed at length by Fadok et al. (4), phosphatidylserine is normally most abundantly expressed on the inner leaflet of the plasma membrane but is exposed on the outer leaflet of apoptotic cells, where it promotes recognition by phagocytes. SR-AI/II, SR-BI, and CD36 are expressed on the surfaces of macrophages and can mediate binding of apoptotic cells to receptor-expressing cells. Other receptors that recognize apoptotic cells include the integrin $\alpha_v\beta_3$ (which is discussed only in passing in this series by Febbraio et al. (5) but which offers another fine example of a multiligand receptor) and a recently identified specific phosphatidylserine receptor. The critical importance of such receptors for development and homeostasis is clear. Nevertheless, while there are a plethora of potentially important receptors identified by in vitro studies, there have been relatively few in vivo experiments that address the functional significance of any one of these receptors in mammalian systems.

Much of the analysis of SR-BI has focused on an entirely unanticipated activity for a scavenger receptor, the recognition of unmodified lipoproteins. As Krieger indicates (3), SR-BI serves as an HDL (and LDL) receptor that mediates the delivery of lipids to cells by a distinctive process called selective lipid uptake. In this process, the lipid components of receptor-bound lipoproteins are internalized, whereas the apoprotein component is released from the cell. Studies with rodents have shown that SR-BI contributes importantly to the transport of HDL cholesterol to the liver and steroidogenic tissues, and that it protects against atherosclerosis in disease-prone murine knockout models. SR-BI has also been shown to significantly influence, either directly or indirectly, oocyte and red blood cell development.

The still-unfolding story of CD36, a member of the class B scavenger receptor family, is emblematic of the multiligand receptors. Initially recognized as an abundant platelet integral membrane glycoprotein, CD36 was subsequently shown to bind the matrix protein thrombospondin (Tables 1 and 2). Further analysis has established that it can function in antigen presentation, as a long chain fatty acid and lipid transporter, as a cellular adhesion molecule, and as a signaling protein. The interaction of thrombospondin with CD36 on microvascular endothelial cells activates a kinase cascade, ultimately forcing the cells down an apoptotic pathway. Thus, thrombospondin binding to CD36 exerts an anti-angiogenic effect in normal and neoplastic tissues. The latter properties of CD36 are complemented by its ability to bind and internalize apoptotic cells. Engagement of apoptotic cells by CD36 is responsible, at least in part, for the generation of inflammatory mediators, such as prostaglandin E2, IL-1, platelet activating factor and TGF-β1. CD36 biology is the subject of the contribution by Febbraio et al. (5) to this series.

The discovery of low-density–lipoprotein receptor related protein (LRP) derived from cloning of other members of the LDL receptor family. Because of its placement in this family and its high-level expression in the liver, it was initially suspected to be predominately involved in lipoprotein metabolism (see contri-

bution by Herz and Strickland in this series, ref. 6). It soon became apparent that although LRP contributes to hepatic metabolism of chylomicron remnants, its influence stretches well beyond lipoprotein biology. Its extracellular ligands include proteinases and proteinase-inhibitor complexes, as well as ECM components such as thrombospondin, and it has been co-opted as a receptor for several viruses and bacterial toxins. Studies in LRP-knockout mice indicate that it plays an important role in embryonic development, but as with other receptors considered in this series, the full range of physiological roles of this polymath receptor may be difficult to demonstrate by gene targeting.

Versatility reconsidered

The multiligand receptors challenge us to reconsider both the structural basis of receptor-ligand interactions and the value of molecular specificity in biological systems. In general, we do not yet understand how these receptors combine high affinity with a broad but not indiscriminate binding specificity. The physiologic and evolutionary value of these molecules also remains uncertain in most regards, but some general observations can be made.

First, certain aspects of a receptor's ligand profile may simply be fortuitous: An endogenous or exogenous ligand may mutate to co-opt an existing receptor or vice versa. This arrangement may complicate the job of regulating receptor function, but it may not prove deleterious, especially if the receptor pathways are relevant to different cells so that they can be regulated independently. For example, the interaction of endothelial cell CD36 with thrombospondin may force the cell down an apoptotic pathway, whereas when the same receptor, expressed on a macrophage, binds modified lipoproteins, the result may be foam-cell formation, cellular activation, and the beginnings of atherosclerosis. Moreover, even if this arrangement compromises the organism's ability to regulate a given receptor pathway, it may be selectively neutral if it causes diseases only late in life. Alzheimer disease, atherosclerosis, and diabetic complications — the disorders shown in Table 2 as possibly associated with SR-A and RAGE — are all late-onset conditions with modest effects on reproductive fitness.

Alternatively, broad binding specificity may be valuable for any of several reasons. Multiligand receptor-mediated clustering of ligands could generate novel molecular assemblies with distinctive properties. The colocalization of multiple ligands of a single receptor could be significant for normal function, but also perhaps in disease. For instance, in vascular lesions, both AGEs and S100/calgranulin ligands are juxtaposed to RAGE-bearing mononuclear phagocytes, smooth muscle, and endothelial cells. Intercepting RAGE-ligand interaction suppresses the development of accelerated atherosclerosis associated with diabetes, preventing vascular activation and helping to clear RAGE ligands from the tissues. In some cases, multiligand signaling receptors may allow any of several structurally diverse extracellular messengers to deliver a single appropriate signal to the cell. For instance, the ability of the SR-As (and other putative pattern recognition receptors such as CD14, the mannose-binding protein, and the Toll-like receptors) to recognize multiple bacterial surface components has probably been under continuous selection, as this feature is key to their function in innate immunity.

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