Title

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Journal

American Journal Of Pathology, 184(1)

ISSN

0002-9440

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Publication Date

2014

DOI

10.1016/j.ajpath.2013.08.029

Peer reviewed

The American Journal of Pathology, Vol. 184, No. 1, January 2014

ELSEVIER

The American Journal of
PATHOLOGY
ajp.amjpathol.org

REVIEW

LDL Receptor—Related Protein-1

A Regulator of Inflammation in Atherosclerosis, Cancer, and Injury to the Nervous System

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Accepted for publication August 2, 2013.

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Low-density lipoprotein receptor—related protein-1 (LRP1) is an endocytic receptor for numerous proteins that are both structurally and functionally diverse. In some cell types, LRP1-mediated endocytosis is coupled to activation of cell signaling. LRP1 also regulates the composition of the plasma membrane and may, thereby, indirectly regulate the activity of other cell-signaling receptors. Given the scope of LRP1 ligands and its multifunctional nature, it is not surprising that numerous biological activities have been attributed to this receptor. *LRP1* gene deletion is embryonic-lethal in mice. However, elegant studies using Cre-LoxP recombination have helped elucidate the function of LRP1 in mature normal and pathological tissues. One major theme that has emerged is the role of LRP1 as a regulator of inflammation. In this review, we will describe evidence for LRP1 as a regulator of inflammation in atherosclerosis, cancer, and injury to the nervous system. *(Am J Pathol 2014, 184: 18—27; http://dx.doi.org/10.1016/j.ajpath.2013.08.029)*

Low-density lipoprotein (LDL) receptor—related protein-1 (LRP1/CD91) is a type 1 transmembrane protein, which is processed by furin-like endoproteases in the *trans*-Golgi compartment to generate the mature two-chain structure.[1,2] The 515-kDa α-chain is entirely extracellular and coupled to the cell surface through strong noncovalent interactions with the transmembrane 85-kDa β-chain. Although LRP1 may localize transiently in lipid rafts, the receptor migrates in the plasma membrane to clathrin-coated pits, where it undergoes constitutive endocytosis and recycling with extremely high efficiency.[3—5] In most cells, including macrophages, hepatocytes, and neurons, LRP1-associated ligands dissociate in acidified endosomes and are transferred to lysosomes.[3,4,6] In endothelial cells, LRP1 ligands may undergo transcytosis.[7,8]

LRP1 is a member of the LDL receptor gene family, which includes receptors such as megalin/LRP2, apolipoprotein E receptor 2/LRP8, and the VLDL receptor. These receptors demonstrate similarities in domain organization and, in some cases, partially overlapping function.[9] As shown in Figure 1A, the LRP1 α-chain includes four clusters of complement-like repeats (CCRs), numbered from the N-terminus.[9,10] CCR2 and CCR4 contain 8 and 11 complement-like repeats, respectively, and are responsible for most of the ligand-binding activity of LRP1.[10] The LRP1 β-chain includes YxxL and dileucine motifs that serve as principal endocytosis signals[11] and two NPxY motifs that function as secondary endocytosis signals and as binding sites for signaling adapter proteins.[11—13]

The first identified LRP1 ligand was apolipoprotein E—containing β-VLDL.[14] Subsequently, LRP1 was identified as the receptor for activated α_2-macroglobulin (α_2M),[15] bringing forward a considerable body of literature in which LRP1 was referred to as the activated α_2M receptor. Figure 1B shows a model in which the 18-kDa LRP1-binding domain of α_2M (called the receptor-binding domain or RBD) is engaging tandem complement-like repeats from CCR2 of LRP1. As is typical for LRP1-ligand

Supported by NIH grants R01 HL060551 and R01 NS054671 (S.L.G.) and R01 NS057456 (W.M.C.).

Disclosure: S.L.G. is a consultant for Angiochem.

http://dx.doi.org/10.1016/j.ajpath.2013.08.029

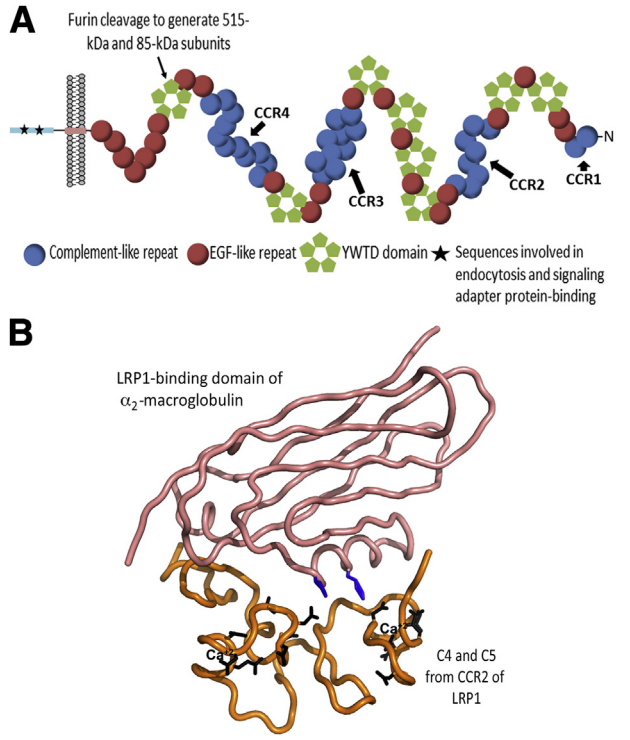

Figure 1 Molecular models showing the organization of structural domains in LRP1 and the docking of a representative ligand to complement-like repeats in LRP1. **A:** The depicted domains in LRP1 are common to the LDL receptor family. **Stars** are present in the intracellular region of LRP1 to represent motifs that function as endocytosis signals and/or as docking sites for cell-signaling proteins including NPXY, YxxL, and dileucine. **B:** A representative LRP1 ligand, the 18-kDa receptor-binding domain of α_2-macroglobulin, which is a free-standing domain in the activated state of the protein, is shown in pink. Two lysine residues in a single α-helix, highlighted in blue, are essential for binding to LRP1. These lysine residues interact with acidic amino acids in the LRP1 complement-like repeats. The fourth and fifth complement-like repeats in CCR2 are shown in orange, and the acidic amino acids in these domains are highlighted in black. The approximate positions of calcium are shown. EGF, epidermal growth factor.

interactions, Lys residues in the structure of the RBD, positioned in parallel orientation within the same α-helix, interact with negatively charged amino acids in the complement-like repeats.[16,17] Hydrophobic residues exposed on the surface of the RBD also may be involved.[16] The integral association of calcium with the complement-like repeats is necessary for structural integrity and function.[1,17]

Currently identified LRP1 ligands include proteases, protease inhibitor complexes, extracellular matrix proteins, growth factors, toxins, and viral proteins.[9] LRP1 ligands are present in myelin, including myelin basic protein and myelin-associated glycoprotein (MAG),[18,19] explaining why in the injured central nervous system, LRP1 may participate in the phagocytosis of myelin debris.[18] By binding calreticulin, LRP1 associates with members of the collectin family, including C1q and mannose-binding lectin, and participates in the phagocytosis of apoptotic cells.[20,21] LRP1 also serves as an endocytic receptor for many intracellular proteins released by necrotic cells.[22] These LRP1 activities are important because failure to efficiently clear intracellular proteins, apoptotic cells, and cell debris may be associated with the onset of autoimmune disease.[23]

Trafficking of Membrane Proteins and Foreign Antigens

LRP1 associates with and regulates the abundance of other proteins in the plasma membrane.[24,25] Some plasma membrane proteins, such as Plxdc1/TEM-7, which has been implicated in angiogenesis, may be co-immunoprecipitated with LRP1, suggesting a possible direct interaction.[25] However, more frequently, plasma membrane proteins are bridged to LRP1 by bifunctional ligands or intracellular adaptor proteins, such as Fe65 and postsynaptic density protein 95 (PSD-95).[26–28] Fe65 bridges LRP1 to β-amyloid precursor protein (APP), promoting APP endocytosis and regulating APP processing to form β-amyloid peptide (Aβ).[26,27] PSD-95 links LRP1 to the N-methyl-D-aspartate receptor and may regulate bidirectional cross talk between these two receptors.[28] Bridging of LRP1 to the urokinase receptor (uPAR) by the bivalent ligand, urokinase-type plasminogen activator (uPA)—plasminogen activator inhibitor-1 complex, promotes uPAR internalization and regulates uPAR-initiated cell signaling.[29] A similar mechanism is involved in the pathway by which LRP1 clears tissue factor from cell surfaces.[30]

A hallmark of the pathway in which LRP1 regulates the abundance of other proteins in the plasma membrane by facilitating their endocytosis is the ability to inhibit this process with the LRP1 ligand-binding antagonist, receptor-associated protein (RAP).[31] When RAP is added to cultured cells over 3 to 5 days, the abundance of the LRP1-regulated protein in the plasma membrane gradually increases until a new equilibrium is achieved. Receptors that are increased in abundance at the cell surface in RAP-treated cells include uPAR,[29] APP,[26] and semaphorin4D.[25]

LRP1 has been implicated in antigen presentation and in stimulation of $CD8^+$ T cells. Diverse heat shock proteins (HSPs), which function as chaperones for antigenic peptides, bind to LRP1 when these HSPs are released from the cell.[32] HSP-peptide complexes that are internalized by LRP1 traffic to major histocompatibility complex I for representation by antigen-presenting cells.[33] Extracellular peptides also may be presented to T cells when bound to α_2M and internalized by LRP1.[34] These pathways, particularly those involving HSPs, may be extremely important in pathological conditions associated with extensive cell death, which promotes release of HSPs from intracellular pools.

LRP1 Couples Endocytosis to Cell Signaling

The broad continuum of ligands that bind LRP1 empowers this receptor to serve as a sensor of the cellular microenvironment. By multiple mechanisms, LRP1 regulates cell signaling and, ultimately, cell physiology and gene expression

in response to numerous extracellular proteins. A simple mechanism by which LRP1 regulates cell signaling involves competitive binding of proteins that activate other signaling receptors so that the concentration of the protein in the cellular microenvironment is decreased. Together with glypican-3, LRP1 mediates the internalization of hedgehog, decreasing the concentration of hedgehog available to bind to its main signaling receptor, patched.[35] LRP1 also regulates cell signaling by trafficking preformed receptor-ligand complexes into endosomes, as has been observed with bone-morphogenic protein-4 in association with Bmper and its cellular receptors.[36] The association of LRP1 with platelet-derived growth factor (PDGF) receptor in endosomes regulates the phosphorylation events observed when cells are treated with PDGF.[37–39]

As previously described, LRP1 may regulate the activity of other signaling receptors simply by controlling the abundance of these receptors in the plasma membrane.[24] In some cells, including neurons, neurite-generating cell lines, Schwann cells, and interstitial fibroblasts, direct binding of ligands to LRP1 activates cell signaling.[19,40–47] Activation of cell signaling in response to ligand binding is not ubiquitous in all cells and tissues in which LRP1 is expressed. Instead, coupling of cell signaling to ligand binding may depend on whether a specific cell type expresses necessary LRP1 co-receptors. In neurons and neurite-generating cell lines, N-methyl-D-aspartate receptor functions as an LRP1 co-receptor, physically linked to LRP1 by PSD-95, activating signaling factors such as extracellular signal–regulated kinase 1/2 (ERK1/2).[28,37,44,46] Trk receptors also have been described as LRP1 co-receptors, essential for activation of Src, ERK1/2, and Akt in response to activated α_2M and tissue-type plasminogen activator.[47] p75 neurotrophin receptor is recruited into a complex with LRP1 by MAG.[19] This event is followed by activation of downstream cell-signaling factors such as RhoA, which are distinct from those activated by other LRP1 ligands.[19] The LRP1-dependent cellular response to MAG raises the hypothesis that the cell-signaling activity of LRP1 may be ligand specific.

It is reasonable to speculate that novel LRP1 co-receptors remain to be identified. Such receptors may function individually with LRP1 or, more likely, as part of a multiprotein receptor system, with conserved and variable members in any given cell type. In a complex cellular microenvironment, LRP1 may be engaged as a primary signaling receptor by extracellular ligands and simultaneously function by the other mechanisms previously described. LRP1 also may regulate cell signaling by undergoing regulated intramembrane proteolysis (RIP).[48] Both the shed form of LRP1, which is released in the first step of RIP, and the cytoplasmic tail, which is released intracellularly in the second step of RIP, have been implicated in cell signaling.[48–51]

LRP1 gene deletion is embryonic-lethal in mice.[52] Nevertheless, the diverse scope of LRP1 ligands and the multifunctional nature of this receptor in cell signaling necessitates a broadening of the classic definition of specificity used by the receptor biology field. LRP1 did not evolve to respond to a single or even a small family of ligands. Instead, numerous interactions and a diverse spectrum of physiologically significant cellular responses are observed. The complexity of LRP1 is appreciated by applying programs such as Interactive Pathway Analysis (IPA) by Ingenuity (Redwood City, CA). Figure 2 shows an IPA map for LRP1. Various forms of interaction, reported by IPA, include, but are not limited to, direct binding events, interactions within the plasma membrane, effects on protein phosphorylation, and effects on cellular localization. The data were restricted so that the displayed interactions include only those that have been associated with neuroinflammation. Without applying functions to limit the data set, the LRP1 IPA map is too dense to read. The results shown in Figure 2 are stratified according to the location of the LRP1-interacting gene products, including those outside the cell, in the plasma membrane, or in the cell interior.

Because of the complexity of LRP1 and its diverse interactions, understanding the function of LRP1 in a specific context or disease process cannot be assumed from analysis of specific molecular interactions. Instead, it has been informative to analyze *in vitro* studies together with experiments in mouse model systems. Conditional gene deletion studies have identified LRP1 as a major regulator of inflammation. In the remainder of this review, the function of LRP1 in inflammation is considered in the context of atherosclerosis, cancer, and injury to the nervous system. Although these are different forms of pathology, common activities emerge for LRP1, which may be explained based on our understanding of this receptor at the molecular level.

LRP1 in Atherosclerosis

Atherosclerosis is a complex chronic disorder, which progresses at a rate that is regulated by inflammatory cells that enter the arterial wall and vascular smooth muscle cells (VSMCs) that migrate from the arterial media into the neointima.[53–55] Despite early studies suggesting that, in cell culture, direct binding of ligands to LRP1 may promote VSMC proliferation,[56] conditional deletion of LRP1 in VSMCs in mice has shown that the dominant activity of LRP1 in VSMCs *in vivo* is antiatherogenic, by limiting activation of PDGF receptor-β signaling.[37] In macrophages, LRP1 also inhibits atherogenesis and several related mechanisms have been described, including its effects on expression of inflammatory mediators, regulation of local matrix metalloprotease-9 (MMP9) activity, effects on transforming growth factor β activity, and regulation of extracellular matrix deposition.[57–60]

The activity of LRP1 in macrophage cell signaling provides an explanation for its activity in atherosclerosis. When LRP1 undergoes RIP, the cytoplasmic fragment may relocate to the nucleus, where it binds to interferon regulatory factor-3, promoting export of interferon regulatory factor-3

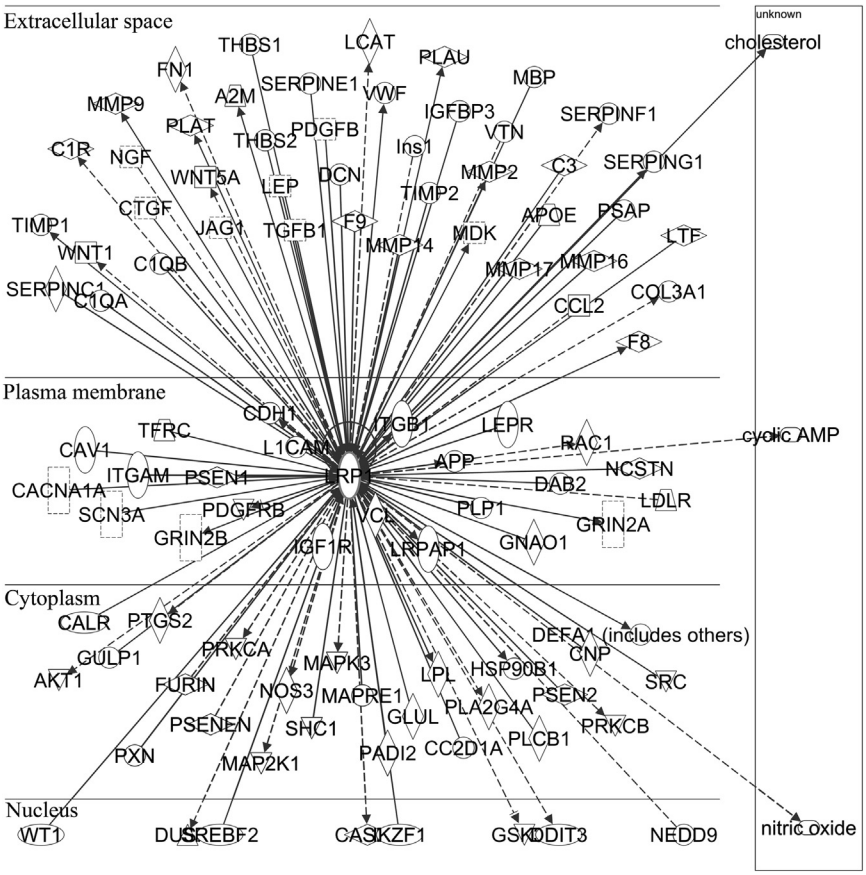

Figure 2 LRP1 interaction map generated using the Ingenuity IPA System. The map was limited to interactions involving the nervous system in inflammatory disease and in the inflammatory response. Interactions are stratified in relation to the location of the LRP1-interacting gene product relative to the cell. Interacting gene products include cytokines (**closed square**), growth factors (**broken square**), proteases (**horizontally elongated diamond**), other enzymes (**vertically elongated diamond**), proteins involved in transport (**trapezoid**), transmembrane receptors (**vertically elongated oval**), ion channel subunits (**broken vertically elongated rectangle**), kinases (**inverted triangle**), transcription regulators (**horizontally elongated oval**), and phosphatases (**triangle**). Other categories of gene products are shown as **circles**. Direct interactions are shown with a solid line and indirect interactions with a broken line. A solid line without an arrow implies a binding interaction. An **arrowhead** at the end of a **broken line** implies that one gene product acts on the other. A perpendicular bar implies an inhibitory interaction.

from the nucleus and suppressing expression of pro-inflammatory lipopolysaccharide target genes.[49] Because lipopolysaccharide and other inflammatory mediators promote LRP1 shedding,[51] which is the first step of RIP, the activity of the LRP1 cytoplasmic fragment may constitute an important feedback inhibition pathway, limiting amplification of inflammation in already inflamed tissues. Increased levels of shed LRP1 are observed in the plasma of patients with rheumatoid arthritis and systemic lupus erythematosis.[51]

A second pathway by which macrophage LRP1 may limit inflammation has been described. In some cells, including macrophages, LRP1 decreases the cell-surface abundance of tumor necrosis factor receptor-1 and attenuates activation of IκB kinase−NF-κB signaling.[61] NF-κB activation results in increased expression of complement proteases, plasminogen activators, and inflammatory mediators, such as inducible nitric oxide synthase and IL-6. In LDL receptor−deficient mice with LRP1-deficient monocytes and macrophages, atherosclerotic lesions demonstrate increased levels of monocyte chemoattractant protein-1/chemokine ligand (CCL) 2.[58] The increase in CCL2 is associated with an increase in macrophage density in the plaques. We showed that expression of CCL2 by LRP1-deficient bone marrow−derived macrophages is increased because of activation of NF-κB signaling.[61] Thus, it is reasonable to hypothesize that the ability of LRP1 to suppress NF-κB signaling may limit monocyte recruitment into atherosclerotic plaques and the adverse effects of macrophage-generated mediators in the arterial wall. LRP1 signaling to Akt in macrophages also may be antiatherogenic by preventing macrophage apoptosis within plaques.[62]

The studies showing that macrophage LRP1 limits atherosclerosis in mice used a variety of model systems, including Cre-mediated LRP1 knockout in myeloid cells in an LDL receptor−deficient or apolipoprotein E/LDL receptor double-deficient background and transplantation of bone marrow from mice with LRP1-deficient macrophages into LDL receptor−deficient mice.[57−60] LRP1 emerged as antiatherogenic in all these studies. The relevance of studies in which the *LRP1* gene is deleted in macrophages may be found in a body of literature demonstrating that, in monocytes and macrophages, LRP1 expression is highly regulated.[51,63−67] Inflammatory mediators present in atherosclerotic plaques may combine to substantially decrease LRP1 expression. The same inflammatory mediators also promote LRP1 shedding.[51] The effects of these events on expression of important mediators, such as CCL2, may be additive. Loss of cell-surface LRP1 in monocytes and macrophages may increase expression of CCL2 by activation of NF-κB signaling, whereas shed LRP1 further induces CCL2 expression by its direct effects on cells.[51,58,61] Therapeutic agents that antagonize inflammation may sustain LRP1 expression at the macrophage cell surface and inhibit LRP1 shedding, thereby counteracting progression of atherosclerosis.

Although we have focused mainly on mechanisms by which LRP1 in VSMCs and macrophages regulates atherogenesis, the liver is a rich source of LRP1. Early work demonstrated that inactivation of hepatic LRP1 increases levels of circulating chylomicron remnants.[68] More recently, it has been reported that loss of hepatic LRP1 is associated with increased atherosclerosis in rodent models because of the accumulation of proatherogenic mediators in the plasma.[69]

LRP1 in Cancer

Early studies, focused mainly on tumor cell lines, suggested that malignant transformation may be associated with loss of LRP1 expression.[70–72] However, we now understand that LRP1 expression is substantially increased by hypoxic conditions that are common in malignancies *in vivo*.[73] Thus, tumor cells cultured in ambient oxygen may not accurately report LRP1 expression and activity as they occur in cancer. The effects of LRP1 expression in tumor cells on progression of malignancy remain unresolved. In prostate cancer, LRP1 expression is observed mostly in high Gleason grade tumors, which are the most aggressive tumors, whereas in hepatocellular carcinoma, loss of LRP1 expression may correlate with tumor progression.[71,72,74,75]

From the mechanistic standpoint, LRP1 demonstrates numerous activities that may regulate cancer cell physiology *in vitro* and in preclinical mouse model systems. Some of the reported activities of LRP1 may actually yield opposing effects on cancer progression. Thus, understanding the role of LRP1 in cancer requires model systems that report diverse LRP1 activities in an integrated manner. In fibrosarcoma cells and astrocytic tumor cells, LRP1 affects cell migration and invasion by regulating the proinvasive uPA-uPAR system.[29,76,77] The interaction of LRP1 with uPA and uPAR is complex and has been recently reviewed.[29] LRP1 attenuates the activity of uPA as an activator of extracellular proteases that facilitate cellular penetration of tissue boundaries. At the same time, LRP1 regulates uPAR signaling to factors such as ERK1/2, which promote tumor cell survival, proliferation, migration, and invasion. Whether LRP1 inhibits or promotes uPAR signaling probably depends on whether plasminogen activator inhibitor-1 is available and on the abundance of uPAR in the plasma membrane.

Direct binding of ligands to LRP1, including protease nexin-1, Hsp90, and midkine, may directly activate cell signaling in cancer cells, as has been observed in non-transformed cells such as neurons and interstitial fibroblasts.[78–80] When ERK1/2 is activated downstream of LRP1, MMP9 and MMP2 are expressed at increased levels.[41,78,81] Because these MMPs are implicated in cancer cell invasion and metastasis, ERK1/2 activation downstream of LRP1 may promote cancer progression. Another LRP1 ligand, apolipoprotein E, inhibits tumor cell invasion and metastasis by a pathway that also requires LRP1.[82] We have observed that *LRP1* gene silencing in CL16 cancer cells has no effect on xenograft formation, growth of tumors in mice, or the ability of these tumor cells to metastasize to the lungs; however, when LRP1 is silenced, pulmonary metastases formed by CL16 cells fail to grow.[73] How LRP1 may selectively facilitate growth or survival of tumor cells in metastases without having the equivalent effect on cells in the primary tumor is a topic for future investigation.

A clearer picture has emerged regarding the role of macrophage LRP1 in cancer progression. It is well accepted that monocytes and macrophages that infiltrate tumors may promote cancer progression and metastasis by expressing growth factors and proteases that are exploited by the malignant cells.[83] Macrophages also have been linked to tumor angiogenesis. We found that monocytes in which LRP1 is deleted by Cre-LoxP recombination migrate in increased numbers into orthotopic and s.c. isografts of PanO2 pancreatic cancer cells in mice.[84] The increase in tumor infiltration by LRP1-deficient macrophages provides an interesting parallel to atherosclerotic plaques, which also are infiltrated more aggressively by LRP1-deficient macrophages.[58] In addition to CCL2, we identified novel chemokines involved in recruitment of inflammatory cells that are expressed at increased levels by LRP1-deficient macrophages.[84] Most significantly, increased expression of macrophage inflammatory protein-1α/CCL3 and macrophage inflammatory protein-1β/CCL4 was observed. These chemokines are known to amplify inflammation. The increase in tumor infiltration by LRP1-deficient macrophages was accompanied by an increase in tumor angiogenesis,[84] most likely reflecting vascular endothelial growth factor and other proangiogenic proteins released by the macrophages.[83]

LRP1 in Injury to the Nervous System

In the healthy central nervous system and in the uninjured peripheral nervous system (PNS), multiple groups of neurons express LRP1.[85,86] Figure 3A shows an immunohistochemical (IHC) analysis identifying intense LRP1 immunoreactivity in the cell bodies of pyramidal neurons from the mouse cerebral cortex. Although astrocytes in the healthy brain demonstrate limited LRP1 expression, reactive astrocytes, responding to injury or disease, are robustly LRP1 immunopositive.[87] Similarly, Schwann cells, which provide myelination and trophic support to axons in the uninjured PNS, demonstrate substantially increased LRP1 expression in response to nerve injury.[86] Figure 3B is an IHC analysis showing robust LRP1 immunoreactivity in activated Schwann cells in crush-injured rat sciatic nerve, 3 days after injury. At this time point, macrophages have begun to infiltrate the injured nerve. These cells also are LRP1 immunopositive.

Earlier in this review, we discussed the possible relationship of abnormal phagocytosis of cellular debris to the development of autoimmune disease. In multiple sclerosis

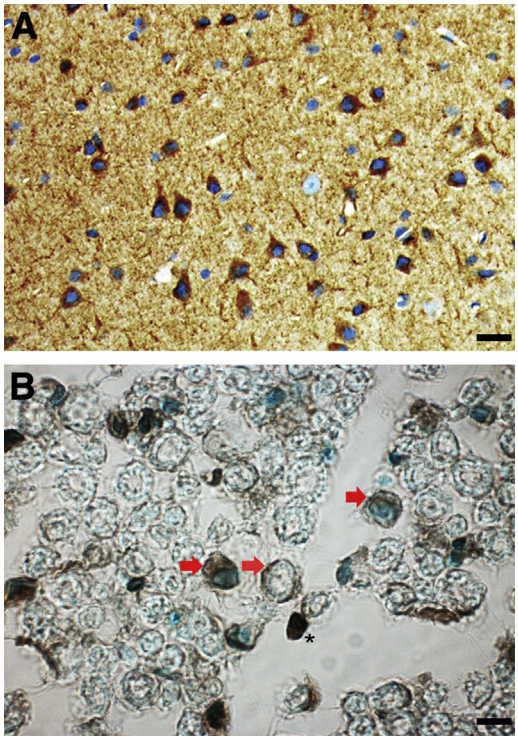

Figure 3 IHC analysis to detect LRP1 in the nervous system. **A:** LRP1 immunostaining of mouse cerebral cortex. LRP1 was detected with a primary polyclonal antibody that detects the β-chain (Sigma-Aldrich, St. Louis, MO). Staining was conducted using a Ventana System (Tucson, AZ). **B:** A section of rat sciatic nerve distal to a crush injury site, which was recovered 3 days after nerve injury. LRP1 was detected using polyclonal antibody R2629. The section is counterstained with methylene green. Representative LRP1-immunopositive Schwann cells are marked with **arrows**. The **asterisk** marks a macrophage. Scale bars: 35 μm (**A**); 12 μm (**B**).

(MS), failure to clear products of degenerated myelin may be important in initiating the immune response.[88] Thus, the function of LRP1 as a phagocytic receptor for apoptotic cells, cellular debris, and degenerated myelin may be important in the pathophysiological characteristics of MS.[18–22] Consistent with this model, LRP1 expression is up-regulated in the rims of chronic active MS lesions in humans.[89]

LRP1 and other members of the gene family, including apolipoprotein E receptor 2 and the VLDL receptor, have been implicated in Alzheimer disease.[90] Animal models and *in vitro* experiments have revealed numerous mechanisms by which LRP1 may regulate Alzheimer disease onset and progression. Among these are the role of LRP1 as an endocytic and signaling receptor for apolipoprotein E and its function as a receptor for Aβ peptide. Neuroinflammation may contribute to the pathogenesis and progression of Alzheimer disease.[91] It is, thus, interesting that the ε4 allele of apolipoprotein E, which is associated with increased risk for Alzheimer disease, is more proinflammatory than the ε3 allele.[91] Both forms of apolipoprotein E are ligands for LRP1.[90]

The PNS is distinguished from the central nervous system by a substantially greater capacity for regeneration after injury,[92] and recent studies suggest a major role for LRP1 in this process. Schwann cells function as the first responders to acute PNS injury. Activated Schwann cells dedifferentiate, proliferate, migrate, participate in the phagocytosis of myelin and cellular debris, and establish scaffolds that allow for eventual axonal regeneration.[93] Successful nerve regeneration requires the recruitment of monocytes from the blood. These cells further facilitate the clearing of debris; however, as in other forms of injury, the extent of macrophage infiltration and inflammation must be highly regulated in the injured nerve, both temporally and in amplitude.

LRP1 is rapidly up-regulated in Schwann cells *in vivo* in the injured peripheral nerve and functions as a robust cell-signaling receptor in this cell type, activating pathways that support Schwann cell survival under stressful conditions.[86,94,95] LRP1-initiated cell signaling also regulates Schwann cell migration by its effects on activation of ERK and the activity of Rho GTPases.[45,96] Thus, LRP1 has emerged as an orchestrator of key events occurring in Schwann cell physiological characteristics in PNS injury. As a first approach to study the effects of LRP1 on Schwann cell expression of inflammatory mediators in PNS injury, we treated Schwann cells in culture with activated α_2M. This LRP1 ligand is present at low levels in the uninjured peripheral nerve but greatly increased in concentration in the injured nerve.[97] By using an expression array approach followed by validation experiments, we showed that Schwann cells express increased levels of CCL2 when these cells are treated with activated α_2M. This LRP1-mediated response differentiated Schwann cells from macrophages and suggested that Schwann cell LRP1 may be involved in generating early signals for macrophage recruitment after nerve injury. Interestingly, in this *in vitro* study, tumor necrosis factor α and CCL3 were both decreased in expression in response to activated α_2M, suggesting that the activity of Schwann cell LRP1 may be more accurately characterized as regulating inflammation in the injured nerve, as opposed to simply promoting it.

The potent activity of Schwann cell LRP1 as a regulator of inflammation, tissue damage, and repair in the injured peripheral nerve emerged when LRP1 was deleted in Schwann cells by activating *Cre* under the control of the myelin P0 promoter in mice in which the *LRP1* gene is flanked by LoxP sites.[95] P0 is expressed by myelinating and nonmyelinating Schwann cells. Quickly after nerve injury, mice with LRP1-deficient Schwann cells demonstrated greatly increased nerve deterioration, with extensive edema, loss of myelin, and increased inflammatory cell infiltrates. Histological evidence of exacerbated nerve injury was accompanied by functional evidence. Mice with LRP1-deficient Schwann cells demonstrated sustained loss of motor and sensory function. Tactile allodynia was increased in magnitude and persistent after this test of pain sensation normalized in control mice. Compromise to the processes that occur in the early stages after nerve injury was associated with permanent sequelae. Nerve regeneration 20 days

after nerve injury was substantially attenuated in the mice with LRP1-deficient Schwann cells.[95]

LRP1 gene deletion in Schwann cells highlighted the important role these cells play in preventing the development and maintenance of chronic neuropathic pain. The mechanisms that lead to total collapse of regulated injury repair in nerves in which LRP1 is deleted in Schwann cells remain incompletely understood. We know that LRP1-deficient Schwann cells survive in decreasing numbers under stressful conditions[86,94,95]; however, other processes are also most likely operational. In wild-type nerves, injury may increase expression of the LRP1 ligand, MMP9, by as much as 100-fold, which is important because MMP9 serves as a chemoattractant for macrophages in PNS injury.[98] It is reasonable to hypothesize that LRP1 functions to clear MMP9 from the peripheral nerve, thereby serving to attenuate inflammation. The LRP1 ligand, tissue-type plasminogen activator, plays a protective role in sciatic nerve injury.[99] Finally, although it is not clear at this time to what extent LRP1 shedding occurs in the injured peripheral nerve, when shed LRP1 interacts with Schwann cells, it counteracts the effects of tumor necrosis factor α and IL-1β locally and in the spinal dorsal horn, providing a potentially potent mechanism for regulation of neuroinflammation and chronic neuropathic pain after nerve injury.[50]

Neuropathic pain is a difficult and chronic disorder, affecting millions of patients worldwide with limited therapeutic options.[100] The activities of Schwann cell LRP1 that we have described support a model in which interventions that regulate Schwann cell physiology in PNS injury may prevent or treat chronic pain. The extent to which LRP1 signaling is activated in PNS injury remains unclear. An opportunity exists to supplement the injured nerve with targeted LRP1 ligands that activate cell signaling.[43,45] Whether such agents promote regeneration, facilitate favorable cycling of neuroinflammation, and prevent chronic neuropathic pain is under investigation.

Conclusions

The ability of LRP1 to couple endocytosis and phagocytosis with cell signaling provides the cell with a unique means to respond to its microenvironment. Specificity in the function of LRP1, regarding cell type, coreceptor expression, the cellular microenvironment, and even the assortment of ligands that are present, appears to be the rule. In diverse forms of pathology, LRP1 has emerged as a regulator of the response to injury and inflammation. Multiple mechanisms appear to be conserved in different tissues and in different forms of pathology. These include the ability of LRP1 to facilitate removal of potentially autoantigenic injury products and to regulate signaling pathways that control expression of cytokines, chemokines, and other inflammatory mediators. In atherosclerosis, cancer, and injury to the nervous system, LRP1 regulates inflammatory cell recruitment and, likely, their survival and persistence. Considerable opportunity exists to exploit LRP1 activity for therapeutics development. However, numerous challenges remain to understand the function of this receptor and other receptors in this exciting gene family, at the molecular level and in the pathophysiology of disease.

Acknowledgments

We thank the numerous scientists who worked as members of our research groups and helped shape our models regarding the function of LRP1, in particular Drs. Alban Gaultier (University of Virginia, Charlottesville, VA) and Elisabetta Mantuano (University of California, San Diego, CA); Dr. Dudley Strickland (University of Maryland, College Park, MD) for providing LRP1 polyclonal antibody R2629; Dr. Steven Brown for assisting in the preparation of the molecular model showing docking of an LRP1 ligand; and Dr. Richard Klemke for assisting in the preparation of Figure 2.

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