From the low-density lipoprotein receptor–related protein 1 to neuropathic pain: a potentially novel target
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Abstract
This review describes the roles of the low-density lipoprotein receptor–related protein 1 (LRP-1) in inflammatory pathways, nerve degeneration and -regeneration and in neuropathic pain. Induction of LRP-1 is able to reduce the activation of the proinflammatory NFκB-mediated pathway and the mitogen-activated protein kinase (MAPK) c-Jun N-terminal kinase and p38 signaling pathways, in turn decreasing the production of inflammatory mediators. Low-density lipoprotein receptor-related protein 1 activation also decreases reactive astrogliosis and polarizes microglial cells and macrophages from a proinflammatory phenotype (M1) to an anti-inflammatory phenotype (M2), attenuating the neuroinflammatory environment. Low-density lipoprotein receptor-related protein 1 can also modulate the permeability of the blood–brain barrier and the blood–nerve barrier, thus regulating the infiltration of systemic insults and cells into the central and the peripheral nervous system, respectively. Furthermore, LRP-1 is involved in the maturation of oligodendrocytes and in the activation, migration, and repair phenotype of Schwann cells, therefore suggesting a major role in restoring the myelin sheaths upon injury. Low-density lipoprotein receptor-related protein 1 activation can indirectly decrease neurodegeneration and neuropathic pain by attenuation of the inflammatory environment. Moreover, LRP-1 agonists can directly promote neural cell survival and neurite sprouting, decrease cell death, and attenuate pain and neurological disorders by the inhibition of MAPK c-Jun N-terminal kinase and p38-pathway and activation of MAPK extracellular signal–regulated kinase pathway. In addition, activation of LRP-1 resulted in better outcomes for neuropathies such as Alzheimer disease, nerve injury, or diabetic peripheral neuropathy, attenuating neuropathic pain and improving cognitive functions. To summarize, LRP-1 plays an important role in the development of different experimental diseases of the nervous system, and it is emerging as a very interesting therapeutic target.

Keywords: LRP-1, NFκB, JNK, ERK, Inflammation, Neurodegeneration, Neuroregeneration, Neuropathic pain, Neuropathies

1. Introduction
Many recent studies focused on understanding the underlying determinants of pain in neuropathies. One of the main players in the development of neuropathic pain is the immune system. A disorder often associated with neuropathic pain is peripheral neuropathy or polyneuropathy. Polyneuropathy describes a group of diseases with multiple causes where degeneration affects the peripheral nervous system (PNS). Symptoms may involve the motor, sensory, and/or autonomic system and in approximately 50% of cases patients report pain independent of the etiology. From the myriad of causes leading to polyneuropathies, about 14% to 20% are immune-related such as chronic inflammatory demyelinating polyneuropathy. The immune system, nevertheless, has been found to be involved not only in immune-mediated neuropathies but to also play a critical role in nerve degeneration and regeneration, and pain in neuropathies of diverse origin. In polyneuropathies, the immune system initiates an inflammatory response to fight the disease. This response, although intended to clear damaged tissues and promote repair, can result in the production of neurotoxic compounds that may exacerbate nerve degeneration. Many studies have been conducted to understand the role of the immune system in neurodegeneration and neuroregeneration including patients with neuropathies and neuropathic pain.

Lately, studies have focused on 1 specific novel target: the low-density lipoprotein receptor–related protein 1 (LRP-1). It is known that LRP-1 is highly involved in many inflammatory processes and diseases, including cancer, kidney, lung, and heart diseases, or atherosclerosis. Evidence indicates that LRP-1...
is not only modulating inflammation, but it also has an effect on learning, memory, and cognition processes and is involved in neurological disorders such as Alzheimer disease and brain injury and in pain.

In this review, we will describe the involvement of LRP-1 in inflammation and its role in nerve degeneration and -regeneration and in neuropathic pain.

2. Low-density lipoprotein receptor-related protein 1 under physiological conditions

Low-density lipoprotein receptor-related protein 1, or cluster of differentiation (CD) 91, is a type I transmembrane endocytic receptor from the low-density lipoprotein (LDL) receptor family. The members of this family of receptors bind and endocytose a various number of ligands, leading to diverse biological functions. One of the first functions described was the internalization of apolipoprotein (ApoB or ApoE) containing lipoproteins to maintain cholesterol homeostasis. Low-density lipoprotein receptor-related protein 1, like all LDL receptor family proteins, presents different extracellular ligand-binding repeats, a transmembrane segment, and a cytoplasmic tail with an NPxY motif. From all the receptors that conform the LDL receptor family, LRP-1 in particular is the largest one, containing several ligand-binding repeats and more than 1 NPxY motif. This allows the recognition of the widest variety of ligands.

So far, many LRP-1 ligands have been identified including proteases, protease inhibitor complexes, extracellular matrix proteins, growth factors, toxins, and viral proteins (reviewed elsewhere). On binding, these ligands can activate or inhibit several signaling pathways. For the modulation of some of these pathways, LRP-1 may need the coupling of a coreceptor. These coreceptors may differ from one cell type to another, and although many of them remain to be identified, some have already been found, including tyrosine kinase (Trk) receptor and N-methyl-D-aspartate receptor (NMDA-R).

In this review, we will focus mainly on the roles of apolipoprotein E (ApoE), α-2-macroglobulin (α2M), and tissue-type plasminogen activator (tPA), as ligands of LRP-1, because they have extensively shown to be involved in these interac-

3. Low-density lipoprotein receptor-related protein 1 in inflammation

In case of infection or injury, the phagocytic activities of LRP-1 contribute to the clearance of invading microorganisms or cellular debris. This is essential to prevent the development of an exacerbated inflammatory response and to maintain tissue homeostasis. However, LRP-1 is not only involved in inflammation through phagocytic activities. Studies show that LRP-1 can also regulate several proinflammatory pathways and thus the production of proinflammatory and anti-inflammatory cytokines, and the activation of immune cells.

3.1. Toll-like receptor–mediated pathways

One of the main proinflammatory pathways that are activated upon infection or injury is toll-like receptor (TLR) dependent. In particular, TLR4, as one of the main characterized pathways, is able to induce an inflammatory response through 2 possible cascades: the TIR-domain–containing adapter-inducing interferon-β (TRIF)-dependent cascade and the myeloid differentiation primary response gene 88 (MyD88)-dependent cascade.

The TRIF-dependent pathway, through the phosphorylation of TRIF, results in the phosphorylation and activation of the interferon regulatory factor 3 (IRF-3). Subsequently, a dimer is formed between 2 phosphorylated IRF-3, which is translocated to the nucleus, where it initiates the expression of IFN-β.

Studies have shown that in inflammatory conditions, TLR4 activation with lipopolysaccharides (LPS) can lead to the cleavage of LRP-1, resulting in the cytoplastic and the extracellular sLRP-1. Furthermore, activated microglia can likewise cause LRP-1 shedding from the plasma membrane.

On the other hand, the MyD88-dependent pathway leads to the activation of the interleukin-1 receptor associated kinase 1 (IRAK1). After the phosphorylation of IRAK1, tumor necrosis factor (TNF) receptor–associated factor 6 (TRAF6) is recruited and an IRAK1–TRAF6 complex is formed. This results in the phosphorylation of NFκB (nuclear factor kappa-light-chain-enhancer of activated B cells) and its translocation to the nucleus. As part of its regulatory process, IRAK-1 has been described as one of the main targets of the apolipoprotein E (ApoE), a major protein component of plasma lipoproteins. Since 1988, LRP-1 has been described as a receptor of ApoE, and on binding, this can activate several cell signaling pathways. Furthermore, because LRP-1 is an LDL receptor, it is involved in
the macrophage uptake of ApoE-containing very LDL. 62 There is evidence for the effect of ApoE in the proteolysis of the ApoE receptor 2 (apoEr2)/LRP-8, a close member of the LDL receptor family, with the release of its cytoplasmic tail. 37 Therefore, there is controversy whether it can induce LRP-1 shedding or activate the whole receptor to regulate signaling pathways. Although these mechanisms are not yet clear, studies probe that in vascular smooth muscle cells (VSMCs), ApoE interaction with LRP-1 can inhibit the phosphorylation of IRAK1 and the formation of the IRAK1-TRAF6 complex, thus repressing the translocation of NF-κB and the proinflammatory reaction (Fig. 1). 50 On the other hand, a deletion of LRP-1 in macrophages leads to an increased NFκB activation and an enhanced inflammation that is reduced after treatment with ApoE. 123

Furthermore, the translocation of NFκB results in the release of proinflammatory cytokines interleukin (IL)-1β, TNF-alpha (TNF-α), and IL-6. In a variety of cell types, including (VSMCs), 66 macrophages, 128 dendritic cells, 76 microglia, 10,11,124 Schwann cells, 30 and astrocytes, 60 LRP-1 shows a specific role in the regulation of proinflammatory cytokines and its inhibition or deletion induces an increased secretion of them, therefore confirming a major role of LRP-1 in the MyD88-dependent cascade.

### 3.2. Mitogen-activated protein kinase signaling pathways

Another important route where LRP-1 plays a role is in the c-Jun N-terminal kinase (JNK) pathway. JNK is one of well-characterized mitogen-activated protein kinase (MAPK) pathways. It allows the transduction of extracellular signals such as cytokines, growth factors, or danger signals to control a wide variety of cellular processes. These MAPK pathways are activated through a cascade of phosphorylation reactions. 37 Studies show that LRP-1 activation presents an inhibitory effect on JNK-mediated pathways. Although the mechanisms are still not clear, Pociavasek et al. proposed a model in microglial cells where shedding on LRP-1 by ApoE results in an interaction between the ICD and JNK-interacting proteins (JIP) that suppresses the activation of JNK and its translocation to the nucleus (Fig. 1). This can result in a regulation of the response of immune cells such as microglia and affect cell apoptosis. 55,63,86,87,121,124

One of the described roles of JNK is the induction of cell apoptosis. Studies show that LRP-1 might decrease the JNK-mediated apoptosis in different cells and thus be involved in neuronal cell survival. Likewise, the knock down or inhibition of LRP-1 results in the phosphorylation of JNK, 121 following an increment of several proinflammatory cytokines, including TNF-α and IL-18, and chemokines such as chemokine (C-C motif) ligand 2 (CCL2), chemokine (C-C motif) ligand 3 (CCL3), or chemokine (C-C motif) ligand 4 (CCL4). 128

Both JNK and NFκB pathways can be induced by many of the same stimuli. Furthermore, the 2 pathways are closely related because JNK can directly activate NFκB while NFκB limits JNK-dependent cell death.

### 3.3. MicroRNA regulation

The pathways described above can be regulated by a wide variety of compounds and routes. Part of this regulation is mediated by microRNAs (miRNAs). miRNAs are small...
endogenous RNA fragments that mainly participate in the posttranscriptional silencing of target genes. Because of their silencing activity, miRNAs are considered major regulators of inflammation and macrophage/microglia activation. Several miRNAs are involved in proinflammatory pathways such as miR-155, miR-146, miR-132, miR-9, and several more. Although there is controversy on the proinflammatory and anti-inflammatory roles of miR-155, there is evidence of its effect in enhancing inflammation and microglial activation through the regulation of NFκB-mediated pathway, while its inhibitor blocks NFκB nuclear translocation, therefore reducing the inflammatory response. Some of the proposed models to explain this regulation include the direct target of TAK1-binding protein 2 (TAB2), as a multifunctional signaling molecule involved in both NFκB and JNK activation. By contrast, another proposed model describes peroxisome proliferator–activated receptor α (PPARα), B-cell lymphoma 6 protein (BCL-6), and suppressor of cytokine signaling 1 (SOCS1) as some of the miR-155 direct targets to repress the activity of NFκB signaling. Both of these models agree that miR-155 posttranscriptional silencing results in a downregulated inhibition of NFκB- and JNK-mediated pathways and thus in an increased inflammatory response. Because many studies describe a positive correlation between miR-155 upregulation and NFκB activation, there have been some discrepancies on whether miR-155 is present upstream or downstream of NFκB. Some studies show that the activation of the NFκB-mediated pathway through different stimuli can also lead to an upregulation of miR-155. Cunha et al. postulated that this upregulated miR-155 can be transported in exosomes from microglial cells to adjacent cells to sustain the neuroinflammatory response. In myeloid cells, an inhibition or deletion of LRP-1 reflects an enhanced activation of NFκB, with an increased expression of TNF-α and miR-155. This miR-155 upregulation is detected several hours after the TNF-α increment, which is in agreement with its role as a secondary response downstream of the cytokine expression. Furthermore, inhibition of miR-155 induced a late reduction of the expression of TNF-α, CCL4, and IL-6. Therefore, LRP-1 inhibitors can increase the expression of TNF-α and miR-155, which in turn promotes the expression of proinflammatory mediators. This creates a positive feedback loop that may play a role in supporting chronic inflammation.

3.4. Soluble low-density lipoprotein receptor-related protein 1

In inflammatory conditions, LRP-1 can undergo proteolysis and release a soluble LRP-1 into the extracellular space. This proteolysis is mediated by a disintegrin and metalloproteinase (ADAM) 10 and 17 on activation. Shedding of LRP-1 has been seen after treatment with LPS and LRP-1 ligands, thus suggesting a role in inflammatory processes.
So far, high levels of sLRP-1 have been found in human plasma, brain tissue, and cerebrospinal fluid, as well as in the PNS.\textsuperscript{9,10,30,34,49,61} Furthermore, the levels in plasma were elevated in elderly patients and in patients with rheumatoid arthritis or systemic lupus erythematosus. Therefore, sLRP-1 may emerge as a novel inflammatory marker.

In models of peripheral nerve injury, sLRP-1 is secreted by Schwann cells in vitro and in vivo. Moreover, sLRP-1 can directly bind to the Schwann cell surface, block cell signaling pathways in response to TNF-\(\alpha\), and downregulate the expression of TNF-\(\alpha\) and IL-1\(\beta\). This would propose sLRP-1 as an anti-inflammatory molecule in accordance with the membrane-anchored LRP-1.\textsuperscript{10}

Because sLRP-1 contains the extracellular domain of the receptor, recent studies suggest that it may act as a binding protein for LRP-1 ligands and work as a competitive antagonist, blocking the membrane-anchored LRP-1.\textsuperscript{9,49} This would rise out controversy on whether sLRP-1 can have anti-inflammatory properties or act as a proinflammatory mediator. In agreement with this last model, Gorovoy et al. showed that sLRP-1 can induce an upregulation of the expression of TNF-\(\alpha\), CCL2, and IL-10 in macrophages.\textsuperscript{34} Furthermore, in vitro and in vivo models, microglial cells present higher expression of TNF-\(\alpha\), IL-1\(\beta\), and IL-6 on stimulation with sLRP-1, thus suggesting a proinflammatory modulation of the NFkB-mediated pathway.\textsuperscript{9,10}

4. Low-density lipoprotein receptor-related protein 1 modulates glial cell activation

Many of the recent studies involving LRP-1 and its shed form have been performed in gial cells (astrocytes, oligodendrocytes, or Schwann cells), immune cells from the nervous system (microglia and macrophages), and neuropathic models, such as nerve injury, white matter injury, or Alzheimer disease.

The expression of LRP-1 has been described throughout the central nervous system (CNS) in different neuronal cell types and oligodendrocytes. Although this might explain its involvement in the neurodegeneration and pain taking place in neuropathic models, LRP-1 expression in astrocytes, microglia, or macrophages might be mediating the neuroinflammatory environment developing upon neuropathic injury.

4.1. Microglia

Microglial cells are the innate immune cells of the CNS. In the context of injury, disease, or inflammation, microglial cells can get activated to initiate an inflammatory response to fight the disease. This response, intended to clear cellular debris and promote repair, is necessary for the recovery process of neurons but may also lead to an exacerbated neuroinflammation.

For this purpose, microglia are able to polarize between phenotype M1 (proinflammatory) and M2 (anti-inflammatory). A proper regulation between these 2 phenotypes is essential to promote neuroregeneration and restore the physiological conditions of the tissue. In cases of an excessive neuroinflammation that may lead to the death of healthy cells, the polarization of M1 microglial cells into an M2 phenotype might be considered as a novel treatment for neuropathies.\textsuperscript{18,114,121}

There is evidence to suggest that the activation of microglia into the proinflammatory M1 phenotype can happen as a result of the stimulation of TLR4 with one of its agonists, such as LPS.\textsuperscript{9,10,18,80,121,124} Because the activation of LRP-1 has an anti-inflammatory effect on the NFkB-mediated pathway, it is reasonable to think that LRP-1 activation would reduce the microglial activation. Furthermore, not only LRP-1 is able to reduce the polarization into the proinflammatory phenotype, but it can reverse it into the M2 anti-inflammatory microglia, therefore reducing the neuroinflammatory environment (Fig. 2).\textsuperscript{85,114,121}

Moreover, ApoE is mainly expressed in astrocytes and microglia in the CNS, where it has anti-inflammatory properties.\textsuperscript{85,86-87,124,126} The interaction between LRP-1 and ApoE can explain its involvement in the activation of these cell populations specifically. Because this interaction can induce the shedding of LRP-1, the released sLRP-1 can inhibit the JNK-mediated pathway as well, as it has been described in microglial cells. This suggests that LRP-1 might modulate the neuroinflammation in microglia and the polarization into an anti-inflammatory phenotype through more than 1 pathway.\textsuperscript{85-87,124}

In addition, the LRP-1-mediated polarization of microglial cells into the M2 anti-inflammatory phenotype has been seen to attenuate white matter injury, improve axonal growth, neurological function, learning, and memory capacities, and reduce pain.\textsuperscript{10,30,40,36,85}

4.2. Astrocytes

Another cell type that is extensively distributed throughout the nervous system are astrocytes. Astrocytes are ubiquitous to the entire CNS and play an essential role in regulating the blood–brain barrier (BBB), providing nutrients to neurons, maintaining the balance of extracellular ions and neurotransmitters, and sustaining synapse formation. In neurodegenerative diseases, astrocytes can be activated to regulate the inflammatory response and coordinate the injury repair. One of the main features of this activation is the overexpression of the glial fibrillary acidic protein and vimentin and the release of proinflammatory cytokines. Like an inflammatory environment, an exacerbated activation of astrocytes can be detrimental to neuropathies and its attenuation can improve synaptic and axonal regeneration.\textsuperscript{77}

Some studies suggest that this activation, denominated reactive astrogliosis, might happen as a result of a crosstalk with activated microglia and the production of proinflammatory cytokines, among them TNF-\(\alpha\) and IL-18.\textsuperscript{78} Hence, an inhibition of the NFkB inflammatory pathway and the microglial activation through LRP-1 would likely diminish the reactive astrogliosis in the lesion region (Fig. 2). This has been described recently in different neuropathic models, such as Alzheimer disease. In 1992, Wolf et al. and, in 2007, Wilhelmsen et al. found low or no expression of LRP-1 in astrocytes specifically, suggesting that the microglia crosstalk might be necessary to regulate astrogliosis through LRP-1.\textsuperscript{115,116} This has been disproved later by different studies showing its abundant expression in astrocytes.\textsuperscript{4,60,130}

Some recent groups also described LRP-1 deficiency exclusively in astrocytes, as well as in cellular and conditional knock-out mouse models. In Alzheimer disease, astrocytes are involved in A\(\beta\) clearance and therefore in the development of the pathology.\textsuperscript{40,60,115,119,130} Low-density lipoprotein receptor-related protein 1 deficiency in astrocytes leads to increased A\(\beta\) depositions, and therefore, its activation might be a new strategy to combat Alzheimer disease, among other neuropathies.

4.3. Blood–brain barrier

One of the essential roles of astrocytes is the maintenance of the BBB. The BBB is the vasculature located in the CNS specifically. It constitutes a barrier between the blood and the CNS, and it regulates the movement of molecules and cells to protect the CNS from toxins, pathogens, or systemic inflammation. The BBB is essential for a proper synaptic and neuronal function.\textsuperscript{20}
different neuropathies such as Alzheimer disease, Parkinson disease, Huntington disease, amyotrophic lateral sclerosis, or multiple sclerosis, a disruption of the BBB leads to an enhanced neuronal injury, synaptic dysfunction, loss of neuronal connectivity, and neurodegeneration.108

The BBB is sheathed by mural cells and astrocyte end-feet. Astrocytes are therefore important effectors on the integrity of the BBB. Studies suggest that BBB regulation by LRP-1 is mediated by one of its ligands: the tissue-type plasminogen activator (tPA). tPA levels are increased in neuropathic models, and tPA has been described to cause LRP-1 shedding in perivascular astrocytes.88,127

Furthermore, immature macrophages (monocytes) can be recruited to the site of injury from the vasculature and differentiate into distinct populations of macrophages.15,135 Movement of macrophages must be recruited to the injured site, to clear cellular and myelin debris, modulate Schwann cells, and create a regenerative environment. This recruitment happens in response to chemoattractant ligands such as CCL2, CCL3, or CCL4.15,102,135 Studies show that LRP-1 can act through the NfkB pathway to inhibit the inflammatory response mediated by macrophages (Fig. 2).18,34,67,82,120,123

While in the CNS, injured neurons exhibit an abnormal growth and retraction bulbs as a sign of regeneration failure; in the PNS, severed axons can successfully regenerate back to their original targets and heal.13 For this regeneration to take place, macrophages must be recruited to the injured site, to clear cellular and myelin debris, modulate Schwann cells, and create a regenerative environment. This recruitment happens in response to chemoattractant ligands such as CCL2, CCL3, or CCL4.15,102,135 Studies show that LRP-1 can act through the NfkB pathway to inhibit the inflammatory response mediated by macrophages (Fig. 2).18,34,67,82,120,123

On the other hand, some later studies since 2012 show that an interaction between LRP-1 and ApoE4 can suppress the BBB breakdown caused by a cyclophilin A (CypA)-NfkB-mediated pathway. Low-density lipoprotein receptor-related protein 1 deficiency in several neuropathies would have thus an impact on the integrity of the BBB (Fig. 2).7,26,84,132 The integrity of the BBB is an important feature in the clearance of toxins or molecules such as Aβ deposits from the brain or in the infiltration of peripheral myeloid cells. This can exacerbate the inflammatory environment taking place in the CNS and aggravate the neuropathy.

4.4. Macrophages

In the PNS, as well as in the rest of the body, the main innate immune cells are the macrophages. These cells, much like the microglial cells, can polarize between a proinflammatory phenotype (M1) and an anti-inflammatory phenotype (M2). A proper regulation of this polarization is necessary to control the inflammatory environment taking place in the PNS and promote neuroregeneration.15,102,135

Figure 2. LRP-1 modulates glial cells upon injury: In the CNS: The interaction between LRP-1 and ApoE can induce the polarization of microglia M1 (proinflammatory) into M2 (anti-inflammatory) and reduce the reactive astrogliosis. LRP-1 binding with ApoE can prevent BBB breakdown, whereas LRP-1 and tPA promotes it. LRP-1 is involved in the maturation of oligodendrocytes, although the process is yet unclear. In the PNS: The interaction between LRP-1 and ApoE can induce the polarization of macrophages M1 (proinflammatory) into M2 (anti-inflammatory). LRP-1 interaction with tPA promotes BNB breakdown. LRP-1 in Schwann cells is involved in nerve sprouting and abnormal regeneration. This might be deleterious for the axons. LRP-1 interaction with ApoE or tPA through NMDA-R promotes the migration of Schwann cells to the injury site. Binding of LRP-1 and tPA promotes the Schwann cell repairing phenotype to promote regeneration. Images from https://smart.servier.com/, under the Creative Common Attribution 3.0 Unported Licence. ApoE, apolipoprotein E; BBB, blood–brain barrier; BNB, blood–nerve barrier; CNS, central nervous system; LDL, low-density lipoprotein; LRP-1, LDL receptor–related protein 1; NMDA-R, N-methyl-D-aspartate receptor; OPCs, oligodendrocyte progenitor cells; PNS, peripheral nervous system; tPA, tissue-type plasminogen activator.
5. Low-density lipoprotein receptor-related protein 1 in myelination

Axons, both in the CNS and in the PNS, require to be surrounded by a myelin sheath for rapid and efficient nerve conduction. This myelin is produced by oligodendrocytes in the CNS and by Schwann cells in the PNS. In neuropathy, a degradation of the myelin sheath and apoptosis of oligodendrocytes or Schwann cells can release myelin vesicles, can impair a proper synopsis, and can cause neuropathic pain. These myelin vesicles can be recognized by different cells and receptors and can initiate an inflammatory response and accelerate the progression of the disease.32

5.1. Oligodendrocytes

Although LRP-1 is abundantly expressed in Schwann cells and in oligodendrocyte progenitor cells (OPCs), it seems like mature oligodendrocytes lack this specific receptor.3 Furthermore, LRP-1 mediates the differentiation of neural stem/progenitor cells into the different neural and glial populations in the CNS. Although its deletion seems to promote the differentiation into astrocytes, it also reduces oligodendrocytes and neuron maturation. Thus, LRP-1 is essential for the differentiation of OPCs into oligodendrocytes (Fig. 2).57,96 In addition, in cases of injury, the differentiation of OPCs into myelin-producing oligodendrocytes is necessary for the remyelination of denuded axons. Therefore, LRP-1 seems to be essential not only in the developing brain but also in the adult brain to repair lesions.57

This theory has been challenged by a recent study, in which the removal of LRP-1 in OPCs specifically resulted in better outcomes in animal models of demyelination. The authors showed that the deletion of LRP-1 had no influence on the differentiation of the OPCs into oligodendrocytes but improved myelin repair by modulation of the inflammatory environment.28 There could be many reasons to explain the contradictory results of these studies, and further research should be performed to determine the role of LRP-1 in OPCs and oligodendrocytes.

On the other hand, in models of multiple sclerosis, phagocytosis of degraded myelin vesicles by fibroblasts, astrocytes, and microglia is mediated by LRP-1. Although the regulatory process is not fully clear, the myelin basic protein can directly interact with LRP-1, emerging as one of its novel ligands.32

5.2. Schwann cells

Like in the CNS, peripheral nerves are surrounded by a myelin sheath produced by Schwann cells. The myelinization is essential for a proper synopsis and transmission of the impulse.97

Under physiological conditions, the low basal expression of LRP-1 in Schwann cells seems to be essential to maintain a proper myelination and nerve function.11 Deletion of LRP-1 specifically in Schwann cells leads to neurite outgrowth and accelerated regeneration. This results in abnormalities in axon myelination and Remak bundle structure, resulting in mechanical allodynia and neuropathic pain.81,85 Furthermore, LRP-1 activation in Schwann cells can induce neurite sprouting and axonal receptivity to myelination by the TrkC receptor and protein kinase B (Akt), and extracellular signal-regulated kinase (ERK) activation (Fig. 2).122 These effects have been described both with and without a nerve injury, suggesting a role in neuropathic regeneration as well.89,128

In peripheral neuropathies or nerve damage, Schwann cells migrate to the site of lesion and change their phenotype into repair Schwann cells to promote nerve regeneration.29,46,68 The expression of genes involved in actin remodeling and lamellipodia formation are necessary for Schwann cell migration to the injury. The interaction of LRP-1 with one of its ligands results in the phosphorylation of Akt and ERK and in the following expression of these genes.58 For some ligands, such as α2-macroglobulin (α2M) and tPA, the interaction of LRP-1 with the coreceptor NMDA-R is required to trigger cell signaling response.70 A deletion of LRP-1 can therefore improve local cell adhesion and diminish the migration to the lesion site (Fig. 2).59

On injury, the Schwann cell repair phenotype is essential to promote regeneration of the nerves. Studies suggest that the recognition of tPA by LRP-1 induces this repair phenotype through the phosphorylation of c-Jun (JNK-mediated pathway). They propose that LRP-1 may act as an injury detection receptor in the PNS, binding to proteins released in the earliest stages of the degeneration, to induce the Schwann cell repair phenotype and a neuroregeneration cascade (Fig. 2).29 This might explain why the deletion of LRP-1 in Schwann cells results in an abnormal response to nerve injury.

After peripheral nerve injury or a proinflammatory stimulus such as TNF-α, the levels of LRP-1 can increase in Schwann cells, whereas they decrease in the damaged axons. Furthermore, it was first described in Schwann cells that TNF-α, acting through the TNF-α receptor II (TNFRII), can modulate the expression of LRP-1. In addition, LRP-1 promotes Schwann cell survival after stimulation with TNF-α. Interestingly, in immature Schwann cells, that are known to die upon nerve injury, LRP-1 expression was not increased, suggesting that its upregulation might be necessary for their survival. This was confirmed when an inhibition of LRP-1 resulted in an increased Schwann cell death.11 Because of Schwann cell and axon interactions, a deletion of LRP-1 leads to accelerated nerve degeneration and reduced remyelination, which results in mechanical allodynia and loss of motor function.81

In peripheral nerve injury, Schwann cells have been described to induce LRP-1 shedding into the soluble extracellular sLRP-1 and the cytoplasmic iLRP-1 fragment. Soluble LRP-1, in peripheral nerves locally and in Schwann cell cultures, can attenuate some MAPK-mediated pathways and decrease the expression of TNF-α and IL-1β. In the studied model, it also reduced neuropathic pain.30

6. Low-density lipoprotein receptor-related protein 1 in neurodegeneration and pain

The immune system plays a key role in the development of nervous system diseases, both in the CNS and in the PNS. Evidence shows that there is a strong correlation between the inflammation and the neurodegeneration taken place in these diseases.

6.1. Neurodegeneration through inflammatory mediators

Neurodegeneration is the process of neuronal sickness that will eventually result in neural cell death, caused by necrosis or apoptosis. A necrosis process is induced by an increment of the reactive oxygen species (ROS) and excitotoxins in the cell that lead to mitochondrial and nuclear swelling, chromatin dissolution, and eventually cell membrane degeneration. Apoptosis, or programmed cell death, is caused by the activation of a cascade of biochemical reactions that induce proteases. These proteases, or caspasases, disrupt cell integrity, cause intracellular acidification, and generate ROS.66,77,133
The cascade leading to apoptosis can be induced and regulated by many different molecules or stimuli (e.g., TNF-α). In cases of neuropathy or nerve injury, the presence of antigens released by the damaged tissue, also called damage-associated molecular patterns, can activate TLR-mediated pathways in cells nearby. This activation, as we have seen before, can lead to the production of proinflammatory cytokines such as TNF-α, IL-1β, and IL-6 through NFκB and the generation of ROS. Toll-like receptors are present in most cell types of the CNS and the PNS, and thus, their activation results in a polarization of the microglia into the proinflammatory phenotype (M1) and a reactive astroglisis in the CNS, and an activation of proinflammatory macrophages in the PNS. The activation of these cell types sustains the immune response to repair the injury and can promote the development of an exacerbated inflammatory response that results in neural cell degeneration. In the PNS in particular, the activation of TLRs leads to the production of chemokines, but it also induces the expression of different proapoptotic genes. P38, on the other hand, is essential for macrophage infiltration after sciatic nerve injury. Extracellular signal–regulated kinase is a central signaling pathway controlling Schwann cell plasticity and also exhibits an essential role for macrophage infiltration after sciatic nerve injury.

One of the mechanisms of neural cell apoptosis is the activation of the TNF-α receptor (TNFR) by TNF-α, which recruits the TNFR-associated domain protein (TRADD) and Fas-associated death domain (FADD), triggering the activation of caspase 8 and 10, and the protease cascade leading to apoptosis. Furthermore, TNFR can recruit TNFR-associated factor 1 (TRAF1) and TRAF2 to activate the NFκB-mediated pathway, therefore creating a detrimental proinflammatory loop. In addition, TNF-α modulates synapses by regulating the glutamate receptor trafficking under physiological conditions. In neuropathy, high levels of TNF-α can result in an accumulation of glutamate, which shows high excitotoxicity for the neurons, and can lead to cell death. Furthermore, studies show that the activation of TNFR can lead to the phosphorylation and activation of JNK and p38, leading to the induction of a proapoptotic cascade (Fig. 3).

IL-1β is constitutively expressed at low levels in the healthy brain and plays important roles in synaptic plasticity/pruning and memory formation/consolidation. IL-1β is recognized by the IL-1 receptor (IL-1R), and it can activate the NFκB-mediated pathway, MAPK P38, and JNK-mediated pathways, and the extracellular signal–regulated protein 1/2 (ERK1/2) pathway. Among all the responses induced by these pathways in the cells, the activation of NFκB and JNK pathways in particular promotes a second overexpression of TNF-α, IL-1β, IL-6, and several chemokines, which creates a proinflammatory loop and enhances the neuroinflammatory (and neurotoxic) environment. Although there is no evidence of a direct effect of IL-1β on neural cell death, studies show that high levels of IL-1β are strongly related with brain injury and neurodegeneration. Another possible explanation of the impact of TNF-α and IL-1β on neuronal death is the activation of the MAPK JNK and p38 pathways. It is described that in the JNK-mediated pathway, the activation and translocation of JNK to the nucleus does not only induce the expression of several proinflammatory cytokines and chemokines, but it also induces the expression of different proapoptotic genes. P38, on the other hand, is described to regulate senescence, apoptosis, and cell death regulators. The cell fate toward death or survival in this case depends on the cell type and stimulus and can be highly related to the levels of neurotrophic growth factors (NGFs). This evidence suggests that the regulation of JNK and p38 MAPK pathways might be essential to modulate the degeneration and death of neurons.

Moreover, many studies show that IL-6 can both induce and protect from cell death. This might depend on the tissue and the regulatory mechanism taken place. The pathways by which IL-6 might act in the nervous system are not completely understood yet. Interestingly, some very recent studies show that upon brain injury, a reduction of IL-6 prevented neuronal cell death, therefore suggesting a clear link between IL-6 and neurodegeneration.

Many of the recent studies involving LRP-1 and its shed form have been developed in glial cells, immune cells, or in neuropathic models, such as nerve injury or Alzheimer disease, suggesting a role of LRP-1 in the development of the neuroinflammation and the neurodegeneration. As we have seen before, LRP-1 is directly related to the activation of immune cells, and it can inhibit several proinflammatory pathways (e.g., NFκB- or JNK-mediated pathways). This implies a repression of the expression of TNF-α, IL-1β, and IL-6 and therefore in the cell death that these proinflammatory mediators can give rise to. Therefore, LRP-1 can indirectly modulate the neurodegeneration taken place in different neuropathies by the regulation of the neuroinflammatory environment (Fig. 3).

6.2. Neurodegeneration through low-density lipoprotein receptor-related protein 1

Furthermore, many studies suggest that LRP-1 not only modulates the inflammatory environment taking place upon neuropathic injury but also mediates synaptic and neuronal loss, memory and learning capacities, and neuropathic pain.

One of the pathways by which LRP-1 might directly mediate neuronal cell death is through ApoE. ApoE is present in the nervous system and is expressed by many different cell types, including astrocytes and microglia. Under physiological conditions, ApoE mediates processes such as synapse formation, neurite outgrowth, and synaptic plasticity, and it is one of the main risk factors for Alzheimer disease. As detailed above, ApoE can interact with LRP-1 to inhibit the JNK-dependent pathway. Because this pathway will not only induce the expression of proinflammatory molecules but also neural cell death, the downregulation of JNK by LRP-1 interaction with ApoE can protect from neurodegeneration (Fig. 3).

Furthermore, studies show that LRP-1 is able to regulate another pathway that we have not discussed deeply so far but that is highly involved in cell survival and neuroregeneration: The ERK (MAPK) pathway. Studies show that LRP-1 can couple with Trk receptors (A and C) and activate them upon binding some of its agonists (e.g., alpha-2-macroglobulin or matrix metalloproteinase 9). The transactivation of Trk by LRP-1 seems to be mediated by the Src family kinase activation. This can lead to the activation of Akt and ERK pathways, resulting in neurite growth and axonal sprouting and regeneration (Fig. 3). The activation of this pathway in Schwann cells promoted the migration of the Schwann cells towards the injury site, therefore promoting nerve regeneration upon PNS injury. Moreover, because the Trk receptors can bind to NGF, the neuronal regeneration and sprouting seems to be dependent on the levels of NGF in the tissue. Neurotrophic growth factor arrest by a growth factor carrier can thus antagonize neurite outgrowth.

A downregulation of the ERK signaling pathway is directly related to symptoms of depression. This suggests that the
modulation of these signaling pathways by LRP-1 might be involved not only in neurodegeneration but also in synapsis, neurological capacities, or neuropathic pain.

6.3. Neuropathic pain

Pain, or nociception, happens in the body in response to noxious stimulus that may cause damage. Under physiological conditions, this stimulus is recognized by nociceptors, where it activates ion channels, generating action potentials that are transmitted as a pain signal to the spinal cord. Neuropathic pain is pain caused by a lesion or disease of the somatosensory nervous system. This takes place in the PNS upon injury of nerve fibers. This injury can lead to axonal degeneration and alterations in ion channels, resulting in aberrant firing and deficient signal transmission.\(^7\),\(^7\)

There is strong evidence for the impact of a neuroinflammatory environment in the development of neuropathic pain. Proinflammatory mediators released by immune and glial cells can activate nociceptive neurons and contribute to pain hypersensitivity. One example would be the close connection between high levels of TNF-\(\alpha\) or IL-6 and painful neuropathies.\(^3\),\(^6\),\(^9\),\(^4\),\(^11\)

The activation of microglia upon inflammation is also involved in emotional and memory-related aspects of chronic pain, whereas its inhibition attenuates pain. In the spinal cord, the activation of microglial cells into the proinflammatory phenotype can as well increase pain hypersensitivity. The mechanism by which reactive (M1) microglia can promote neuropathic pain is mediated by the activation of the p38 MAPK pathway.\(^1\),\(^2\),\(^4\),\(^4\),\(^8\) As mentioned above, the p38 pathway can be activated by TNF-\(\alpha\) and IL-1\(\beta\). Moreover, in the PNS, a peripheral inflammation can activate p38 in the somas of nociceptors that lead to an NGF-induced increase of the transient receptor potential cation channel V1 (TRPV1) in the peripheral terminals, inducing heat hypersensitivity.\(^4\)

Furthermore, the activation of microglia can release brain-derived neurotrophic factor as a communication signal with neurons. Brain-derived neurotrophic factor triggers a collapse of the anion gradient in neurons through binding with TrkB, resulting in neuropathic pain.\(^1\)

In addition to p38, ERK MAPK pathway activation has also been described in early stages of neuropathic pain. Nevertheless,
some evidence suggests that both pathways might be activated in different microglial populations.46 Because ERK is involved in cell survival and regeneration, it is reasonable that it is activated in anti-inflammatory (M2) microglia to compensate the activation of p38, as an autoregulatory mechanism of neuropathic pain and neurodegeneration.

Furthermore, there is evidence that LRP-1 and NMDA-R coupling can induce calcium influx5,41 and modulate synaptic plasticity, neuroprotection, and neurotoxicity7,73,195 and therefore may be involved in the development of pain.96,94

As seen before, activation of LRP-1 by one of its ligands is able to polarize microglial cells from M1 proinflammatory into M2 anti-inflammatory, upregulate the ERK MAPK pathway, and down-regulate NFκB and JNK pathways. This would decrease the expression of the released proinflammatory mediators (eg, TNF-α, IL-1β, brain-derived neurotrophic factor, and NGF), therefore downregulating the p38 signaling pathway and attenuating neuropathic pain.10,30,81

7. Low-density lipoprotein receptor-related protein 1, a novel therapeutic target

Some research groups up to this day have studied how targeting LRP-1 can have beneficial effects over several neuropathies. As said above, LRP-1 cannot only reduce the neuroinflammatory environment upon nerve injury or neuropathy, but it can also protect from nerve degeneration, promote axonal regeneration, and attenuate neuropathic pain. Furthermore, in many neuropathies, there are often neurological symptoms such as impaired memory, learning, or cognition capacities.39

In models of CNS injury, activation of LRP-1 is required for OPC differentiation for myelin repair, and during white matter repair, and it is necessary for axonal regeneration.28,57,75,85 In addition, activation of microglia by treatment with LPS in mice lead to cognitive dysfunction that was exacerbated when suppressing LRP-1.121 Furthermore, in Alzheimer disease, several studies show that LRP-1 activation decreases the accumulation of Aβ depositions, and its downregulation promotes synaptic and neuronal loss, resulting in cognitive impairment.40,60,64,84,130

In mouse models of peripheral nerve injury, the soluble form of LRP-1 (sLRP-1) has been found biologically active and can attenuate neuropathic pain.30 Low-density lipoprotein receptor-related protein 1 deficiency in Schwann cells also leads to mechanical allodynia and impaired motor function, what might sustain PNS injury and chronic pain.81,89 Furthermore, activation of LRP-1 was necessary for sensory neuronal survival, development and regeneration after injury, and neurite sprouting.34,122,128 In diabetic peripheral neuropathy, LRP-1 levels correlated with nerve conduction studies and therefore might be involved in the pathogenesis of the disease.83

Several studies have investigated the treatment of axonal injury, both in the CNS and in the PNS, with different LRP-1 ligands. In these models, enhanced axonal sprouting and regeneration was achieved with improved cognitive dysfunction. These results show promise in the consolidation of LRP-1 ligands as new therapeutic compounds in the treatment of diverse neuropathies. Nevertheless, because a different ligand was used in each study, such as ApoE,85 α2M,128 urokinase-type plasminogen activator (uPA),12 or metallotheonineins/metalloproteinases,34,129 further research has to be performed to understand this complex LRP-1 receptor system and reach to a conclusion regarding the potential therapeutic capacities of its ligands.121

In summary, in different neurological diseases affecting the CNS and the PNS, LRP-1 plays an important role in the progression of the pathology. Low-density lipoprotein receptor-related protein 1 inhibition can maintain and promote a neuroinflammatory environment, neurodegeneration, neuroregeneration, development of neuropathic pain, and, in turn, impairment of several cognitive functions. Low-density lipoprotein receptor-related protein 1 is recently emerging as one very interesting therapeutic target to improve the outcome of a variety of neuropathies, and its future perspectives encourage much more research yet to come.

Disclosures

The authors have no conflicts of interest to declare.

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