Endocytic receptor-mediated control of morphogen signaling

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Summary
Receptor-mediated endocytosis provides a mechanism by which cells take up signaling molecules from the extracellular space. Recent studies have shown that one class of endocytic receptors, the low-density lipoprotein receptor-related proteins (LRPs), is of particular relevance for embryonic development. In this Primer, we describe how LRPs constitute central pathways that modulate morphogen presentation to target tissues and cellular signal reception, and how LRP dysfunction leads to developmental disturbances in many species.

Key words: LDL receptor-related proteins, Endocytosis, Morphogens

Introduction
Receptor-mediated endocytosis is the main mechanism by which cells are able to specifically take up macromolecules from the extracellular space. It is a fundamental process known to all eukaryotic cells. Depending on the type of receptor, the fate of ligands may entail degradation in lysosomes, re-secretion or transcytosis (Box 1). Initially, endocytosis was recognized as a pathway that could provide cells with essential nutrients and regulate the concentration of metabolites in extracellular fluids (e.g. cholesterol in the circulation). However, endocytosis has more recently proved to be a versatile pathway that is vital to many cellular activities, including control of growth and differentiation, cell migration and synaptic transmission (reviewed by McMahon and Boucrot, 2011). As well as being important in the adult organism, receptor-mediated endocytosis has emerged as a central mechanism that can influence embryonic development. We owe this recognition largely to the identification of a unique class of endocytic receptors, termed low-density lipoprotein (LDL) receptor-related proteins (LRPs), that regulate many aspects of development in vertebrate and invertebrate species. In this Primer, we summarize recent data that uncovered the sophisticated molecular mechanisms by which LRPs modulate signal transduction pathways. These findings have not only advanced our knowledge about the functional properties of a distinct class of endocytic receptors in embryonic tissues, but have also changed our perception of regulatory concepts in development.

LRPs: endocytic receptors that control embryonic development
The LDL receptor gene family
Much of our insight into the functional organization of endocytic receptors stems from studies of the LDL receptor, a type-1 membrane protein expressed in all vertebrate cell types (Goldstein et al., 2001). It displays the typical arrangement of domains required for endocytosis (Fig. 1), namely an extracellular domain containing sites for ligand binding and for pH-dependent release of such ligands in endosomes (Rudenko et al., 2002). In addition, its cytoplasmic tail harbors interaction motifs for cytosolic adaptor proteins that guide shuttling of the receptor between the plasma membrane and endocytic compartments. The main function of the LDL receptor is the cellular uptake of cholesterol-rich low-density lipoproteins (LDLs; see Glossary, Box 2) from the circulation. The significance of this receptor for cholesterol homeostasis is underscored by the pathological features of patients with inheritable LDL receptor gene defects in familial hypercholesterolemia (FH; see Glossary, Box 2). FH results in the inability to clear LDL from the blood stream, leading to excessive levels of circulating cholesterol and premature death from coronary artery disease (Goldstein et al., 2001).

Through cloning efforts, it soon became apparent that the LDL receptor is not unique but is a member of a group of closely related endocytic receptors designated LDL receptor-related proteins, or LRPs. The modular structure of the extracellular domains of individual LRPs (Fig. 1) is conserved throughout evolution from nematodes to mammals. By contrast, their cytoplasmic domains share little sequence similarity, with the exception of a short amino acid motif (NPxY) that is required for clathrin-mediated endocytosis (Box 1). This finding suggested distinct functions performed by the various receptor species, a notion that was confirmed when animal models and humans with LRP gene defects were characterized.

LRP activities: insights from loss-of-function studies
The LDL receptor appeared to be dispensable for embryogenesis, as judged by the normal development of organisms lacking this receptor (Ishibashi et al., 1993; Goldstein et al., 2001). Thus, it came as a surprise when loss of expression of other family members had profound consequences on developmental processes in many phyla (Table 1). In some instances, linking developmental defects to impaired lipoprotein metabolism was obvious, as was the case with mutations in genes encoding vitellogenin (see Glossary, Box 2) receptors in egg-laying species. For example, loss of receptor activity in the C. elegans rme-2 mutant (Grant and Hirsh, 1999), in the Drosophila yolkless mutant (Schonbaum et al., 1995) and in the chicken restricted ovulator strain (Bujo et al., 1995) prevents the deposition of yolk (vitellogenesis), thereby causing female sterility.

For other receptors, the interpretation of phenotypes had been complicated by the fact that, in contrast to the LDL receptor, LRPs bind not only lipoproteins but also a multitude of different macromolecules, including proteases, vitamin carriers and signaling factors. Based on the respective phenotypes in gain- and loss-of-function models, these LRPs may be categorized into two groups: those affecting early patterning and those with later embryonic functions. Exemplifying early patterning defects, arrow/Lrp6 mutations in fruit fly, frog and mouse result in axial
truncation and abnormal head and limb structures, phenocopies of defects in Wnt signaling pathways (Pinson et al., 2000; Tamai et al., 2000; Wehrli et al., 2000). Furthermore, inactivation of Lrp1b, a receptor expressed in the neural tube, in mice causes early embryonic lethality, although the mechanism underlying this phenotype has not yet been elucidated (Dietrich et al., 2010). LRPs that affect later stages of development include LRP4, a receptor expressed in limb, kidney and reproductive tract, and LRP5. Loss of LRP4 in mice results in abnormal limb development, renal agenesis and defects in neuromuscular junction (NMJ; see Glossary, Box 2) formation (Johnson et al., 2005; Simon-Chazottes et al., 2006; Weatherbee et al., 2006). Abnormal distal limb development and kidney malformations are also seen in humans with LRP4 defects (Cenani-Lenz syndrome) (Li et al., 2010). LRP5 mutations affect retinal development and bone formation in humans and in animal models, with high- and low-bone mass traits associated with gain- or loss-of-function mutations, respectively (Table 1). These phenotypes were also traced to abnormal Wnt signaling (Boyd et al., 2002). Finally, two receptor pathways were shown to be crucial for development of the central nervous system. Loss of the related very low density lipoprotein (VLDL; CD320 – Mouse Genome Informatics) receptor (VLDLR) and LRP8 (also known as apolipoprotein receptor-2) in mice causes abnormal layering of neurons in the cortex and cerebellum (Trommsdorff et al., 1999). Patients with VLDL receptor deficiency suffer from cerebellar hyperplasia and ataxia (see Glossary, Box 2) (Boycott et al., 2005; Ozcelik et al., 2008). Absence of LRP2 (also known as megalin), a receptor expressed in the neuroepithelium, in mice results in forebrain patterning defects defined as holoprosencephaly (see Glossary, Box 2) (Willnow et al., 1996). Related phenotypes are seen in patients with Donnai-Barrow syndrome (Rosenfeld et al., 2010), an autosomal recessive disorder caused by familial LRP2 deficiency. Defects in several morphogen pathways, including the sonic hedgehog (SHH) pathway, have been implicated in LRP2-deficiency phenotypes (Spoelgen et al., 2005; Christ et al., 2012).

**Mechanisms of LRP-mediated control of development**

What sounded like a plethora of unrelated functions performed by a group of multifunctional endocytic receptors, later turned out to be phenotypic consequences of a single unifying mechanism: the control of morphogen presentation to target tissues. Below, we describe the molecular mechanisms by which LRPs regulate embryonic development. These mechanisms include control of morphogen gradient formation, determination of local concentrations in the target field, as well as modulation of the cellular competence for signal reception.
LRPs control the graded concentration of morphogens

The graded activity of morphogens is crucial for establishing region-specific responses in target tissues and for patterning the embryo. A prevailing concept states that passive diffusion of a morphogen from a local source to a target field establishes a long-range gradient, with diffusion parameters being largely determined by the biophysical properties of the secreted factor. In addition, specific mechanisms modulate the rate at which morphogens travel, including attachment to transport vehicles (e.g. lipoproteins), trapping by cell-surface binding sites (e.g. heparan sulfate proteoglycans) and active transport (planar transcytosis). There are several excellent reviews on this topic (Zhu and Scott, 2004; Rogers and Schier, 2011). Here, we will discuss how endocytic receptors modulate gradient formation by restricting morphogen spreading or, in the converse situation, by promoting cellular release (Entchev et al., 2000). The formation of Dpp gradients is promoted by association of Dpp with a vitellogenin-like protein called Crossveinless d (Chen et al., 2012). Remarkably, the association of Wg and Hh with lipophorins, another class of lipoproteins in the fly, is also crucial for formation of the respective gradients, as RNAi knockdown of lipophorin expression impairs morphogen spread in the wing imaginal disc (Panáková et al., 2005). Taken together, these findings indicate that lipoproteins act as vehicles for movement of morphogens, and that, in some instances, this movement involves receptor-mediated transcytosis through the

Box 2. Glossary

Ataxia. Impaired coordination of muscle movement due to neurological dysfunctions.


Familial hypercholesterolemia (FH). Pathological increase in the level of cholesterol in the circulation.

Holoprosencephaly. Fusion of the forebrain hemispheres.

Imaginal discs. Clusters of embryonic cells that form various parts of the exoskeleton structures of the fly during the pupal stage.

Cortical lamination. Formation of the cortical layers in the brain by distinct neuronal subtypes.

Low-density lipoproteins (LDLs). Macromolecular lipid-protein complexes that transport cholesterol and other types of lipids in the circulation.

Metabolic syndrome. Condition characterized by a combination of cardiovascular and metabolic disturbances, including hyperlipidemia, high blood pressure, obesity and diabetes.

Myoblasts. Progenitor cells that give rise to muscle cells.

Neuromuscular junction (NMJ). A specialized synapse that mediates communication between a motoneuron and a muscle fiber.

Smith-Lemli-Opitz syndrome. Inborn error in the 7-dehydrocholesterol reductase gene resulting in lack of cholesterol biosynthesis, cleft palate and holoprosencephaly.

Vitellogenins. Glycolipoproteins in egg-laying species that deliver nutritional lipids (yolk) to the embryo prior to egg deposition.
<table>
<thead>
<tr>
<th>Receptor</th>
<th>Organism</th>
<th>Type of mutant</th>
<th>Phenotype/disease</th>
<th>References</th>
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<tbody>
<tr>
<td>RME-2</td>
<td>C. elegans</td>
<td>Loss of function (spontaneous mutant)</td>
<td>Impaired yolk deposition, reduced embryonic viability</td>
<td>(Grant and Hirsh, 1999)</td>
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<td>VLDL receptor</td>
<td>Mouse</td>
<td>Loss of function (targeted gene disruption)</td>
<td>Dysplastic cerebellum, abnormal cortical layering, absent rostral migratory stream</td>
<td>(Trommsdorff et al., 1999; Andrade et al., 2007; Hack et al., 2007)</td>
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<tr>
<td>Arrow</td>
<td>Mouse</td>
<td>Loss of function (spontaneous mutant)</td>
<td>Impaired vitellogenesis, female sterility</td>
<td>(Bujo et al., 1995)</td>
</tr>
<tr>
<td>Human</td>
<td>Loss of function (familial, autosomal recessive)</td>
<td>Cerebellar hypoplasia, ataxia, mental retardation</td>
<td>(Boycott et al., 2005; Ozcelik et al., 2008)</td>
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<td>LRP8 (APOER2)</td>
<td>Mouse</td>
<td>Loss of function (targeted gene disruption)</td>
<td>Dysplastic hippocampus and cerebellum, impaired retinal synaptic connectivity</td>
<td>(Trommsdorff et al., 1999; Trotter et al., 2011)</td>
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<td>LRP5</td>
<td>Mouse</td>
<td>Loss of function (targeted gene disruption)</td>
<td>Low bone mass, hypercholesterolemia, impaired insulin secretion, impaired retinal vascularization, impaired mammary development</td>
<td>(Kato et al., 2002; Fujino et al., 2003; Lindvall et al., 2006; Ye et al., 2009)</td>
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<tr>
<td>Human</td>
<td>Loss of function (familial, autosomal recessive)</td>
<td>Osteoporosis-Pseudoglioma Syndrome (reduced bone mass, persistent embryonic eye vascularization)</td>
<td>(Gong et al., 2001)</td>
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<tr>
<td>Human</td>
<td>Gain of function (familial, autosomal dominant)</td>
<td>High-bone-mass trait</td>
<td>(Little et al., 2002)</td>
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<tr>
<td>Human</td>
<td>Mutations (familial, autosomal recessive)</td>
<td>Familial exudative vitreoretinopathy</td>
<td>(Toomes et al., 2004)</td>
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<tr>
<td>LRP6</td>
<td>Mouse</td>
<td>Loss of function (targeted gene disruption)</td>
<td>Abnormal pattering of body axis, neural tube and limb defects, orofacial abnormalities, cardiac neural crest and outflow tract defects, hypoplasia of neocortex, ocular coloboma, neuroretinal patterning defect</td>
<td>(Pinson et al., 2000; Zhou et al., 2006; Zhou et al., 2008; Song et al., 2009; Song et al., 2010)</td>
</tr>
<tr>
<td>Arrow</td>
<td>Drosophila</td>
<td>Gain of function (spontaneous nucleotide substitution)</td>
<td>Protection against diet-induced obesity (Neural tube defect)</td>
<td>(Liu et al., 2012)</td>
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<tr>
<td>LRP6</td>
<td>Crooked tail mouse</td>
<td>Loss of function (ENU mutagenesis, spontaneous mutant, targeted disruption)</td>
<td>Impaired limb formation, renal agenesis, impaired orofacial development, neuromuscular junction defects</td>
<td>(Johnston et al., 2005; Simon-Chazottes et al., 2006; Weatherbee et al., 2006; Zhou et al., 2006; Kim et al., 2008; Zhang et al., 2008; Karner et al., 2010; Ohazama et al., 2010)</td>
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<td>LRP4</td>
<td>Mouse</td>
<td>Loss of function (spontaneous mutant)</td>
<td>Impaired limb formation, renal agenesis, impaired orofacial development, neuromuscular junction defects</td>
<td>(Wehrli et al., 2000)</td>
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<td>Cattle</td>
<td>Loss of function (spontaneous mutant)</td>
<td>Mulefoot disease (syndactyly)</td>
<td>(Duchesne et al., 2006; Johnson et al., 2006; Drögemüller et al., 2007)</td>
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<td>Human</td>
<td>Loss of function (familial, autosomal recessive)</td>
<td>Cenani-Lenz syndrome (limb and kidney malformations)</td>
<td>(Li et al., 2010)</td>
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<td>Yolkless</td>
<td>Drosophila</td>
<td>Loss of function (X-ray-induced mutant)</td>
<td>Impaired vitellogenesis, female sterility</td>
<td>(DiMario and Mahowald, 1987)</td>
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<td>LRP1</td>
<td>Mouse</td>
<td>Loss of function (targeted gene disruption)</td>
<td>Embryonic lethality, impaired formation of liver</td>
<td>(Herz et al., 1992; Roebroek et al., 2006)</td>
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<td>LRP1B</td>
<td>Mouse</td>
<td>Loss of function (targeted gene disruption)</td>
<td>Early embryonic lethality</td>
<td>(Dietrich et al., 2010)</td>
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<td>Human</td>
<td>Loss of function (sporadic)</td>
<td>Esophageal squamous cell carcinoma, non-small-cell lung cancer</td>
<td>(Liu et al., 2000; Sonoda et al., 2004)</td>
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<td>LRP2</td>
<td>Mouse</td>
<td>Loss of function (targeted gene disruption)</td>
<td>Defects in development of forebrain, spinal cord and optic nerve, impaired maturation of reproductive organs, renal dysfunction</td>
<td>(Wilnow et al., 1996; Hammes et al., 2005; Spoelgen et al., 2005; Wicher and Aldskogius, 2008; Ortega et al., 2012)</td>
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<tr>
<td>Zebrfish (bugeye)</td>
<td>Mouse</td>
<td>Loss of function (ENU mutagenesis)</td>
<td>Glaucoma, myopia, pronephric tubular clearance defects</td>
<td>(Kur et al., 2011; Veth et al., 2011)</td>
</tr>
<tr>
<td>Human</td>
<td>Loss of function (familial, autosomal recessive)</td>
<td>Donnai-Barrow Syndrome (proteinuria, brain malformation, diaphragmatic hernia, microform of HPE)</td>
<td>(Kantarci et al., 2007; Rosenfeld et al., 2010)</td>
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target field. Although it is tempting to speculate that LRPs might be involved in vesicular transport of lipoprotein-bound morphogens, this hypothesis has not yet been proven. The ability of LRP2/Megalin to control the spread of Yellow, another secreted factor, in the imaginal disc might, however, serve as an explanatory model (Fig. 2A). Yellow is a secreted factor that regulates synthesis of black melanin, a pigment deposited in defined layers of the Drosophila wing. LRP2/Megalin-mediated endocytosis restricts Yellow to distinct layers of the cuticle and controls spatial melanization (Riedel et al., 2011).

LRPs control the local concentration of morphogens

Within the target field, the microenvironment of growth factors and morphogens is a crucial determinant of the tissue response to extracellular cues. Endocytic receptors are also involved in control of local morphogen concentration, as exemplified by LRP2, LRP4 and C. elegans (Ce) LRP-1 and LRP-2. In mammals, LRP2 is expressed in ependymal cells lining the lateral ventricles of the brain (Gajera et al., 2010). In the subventricular zone (SVZ), a neurogenic niche in the adult forebrain, competing signals provided by SHH and BMP regulate the rate of neural stem cell proliferation (reviewed by Kriegstein and Alvarez-Buylla, 2009). Loss of LRP2 in mice results in a decrease in size of the neural stem cell population in the SVZ and a decline in proliferative capacity that coincides with an increase in BMP2 and BMP4 expression and activity (Gajera et al., 2010). Because LRP2 mediates cellular uptake and degradation of BMP4 (Spool et al., 2005), a role for this endocytic pathway in balancing proliferative and non-proliferative cell fates through BMP has been proposed (Fig. 2B). Similarly, during murine tooth development, the binding of BMP to the secreted antagonist Wise (SOSTDC1 – Mouse Genome Informatics) results in sequestration of BMP by LRP4, thus antagonizing BMP receptor signaling (Ohazuma et al., 2008) (Fig. 2B). Unexpectedly, LRPs even promote secretion of morphogens, as documented for Ce-LRPs and egg-laying defective 17 (EGL-17), a fibroblast growth factor-like protein in nematodes. Ce-LRP1 and Ce-LRP2 (Fig. 1) are C. elegans homologs of vertebrate LRP1 and LRP2, respectively, that are expressed in cells of the developing worm vulva and gonads. They bind newly synthesized EGL-17 in the secretory pathway of producing cells enabling cellular release of this factor. Secreted EGL-17 then serves as an attractive cue for myoblasts (see Glossary, Box 2) that migrate into the gonad center to generate uterine and vulva musculature (Kamikura and Cooper, 2003). Furthermore, Ce-LRP1/2-dependent secretion of EGL-17 requires the activity of Ce-disabled-1 (Ce-DAB-1), a receptor-specific adaptor found in nematodes (Kamikura and Cooper, 2003) and mammals (Dab2) (Morris et al., 2002).

LRPs modulate cellular morphogen signal reception

As well as controlling the graded and local concentrations of morphogens, endocytosis also modulates signal reception by target cells. Such cell-intrinsic functions were recognized early on, when it was shown that binding of a signaling molecule (e.g. epidermal growth factor) to its receptor induces internalization and lysosomal catabolism of the ligand and sometimes even the receptor. Obviously, this mechanism can serve to terminate signaling (reviewed by McMahon and Boucrot, 2011); however, endocytic receptors can be even more sophisticated in controlling cellular signal reception, as we describe below. For simplicity, we focus on proximal events at the cell surface whereby exposure or removal of endocytic receptors, or clearance of ligands, controls the presentation of morphogens to target cells. Concerning the respective downstream signal transduction mechanisms, the reader is referred to detailed reviews on these pathways elsewhere (He et al., 2004; Herz and Chen, 2006; Niehrs and Shen, 2010; Clevers and Nusse, 2012).

In the most basic scenario, an LRP can act as a surface binding site for a signaling molecule and interacts with an effector to transmit this signal into the cell. This concept is exemplified by LRP4 (also known as multiple epidermal growth factor-type repeat containing protein-7) at the NMJ. Formation of the NMJ during development requires the neurally derived ligand agrin and muscle-specific receptor tyrosine kinase (MusK). Defects in NMJ formation result in defective innervation of muscle tissue, a phenotype seen in Lrp4-null mice (Weatherbee et al., 2006). Recent studies from several
Development of the mammalian brain, as shown in mice that lack either receptor, or both (Trommsdorff et al., 1999). During cortical lamination (see Glossary, Box 2), newborn neurons migrate from the proliferative zone to their final destination in the neocortex, generating a stereotypical pattern of different neuronal subtypes. Their migration is guided by a gradient of reelin, a signaling molecule that provides positional cues. Reelin acts by binding to VLDLR and LRP8 at the neuronal cell surface, resulting in clustering of the adaptor DAB1, which binds to the receptor tails. Subsequent phosphorylation of DAB1 by members of the Src family of kinases (SFKs) initiates a cytosolic kinase cascade, ultimately resulting in rearrangement of the cytoskeleton and control of migration (reviewed by Herz and Chen, 2006). Recruitment of SFKs into this signaling complex requires ephrin B, a transmembrane protein that also binds reelin (Sentürk et al., 2011). Reelin signaling through VLDLR and LRP8 does not necessitate endocytosis. However, phosphorylated DAB1 becomes ubiquitinylated, a modification that may cause internalization of receptor-DAB1 complexes thereby ‘turning down’ reelin signals (Bock et al., 2004).

LRP5 and LRP6 are LRPs that form signaling complexes, with their function being tightly controlled by endocytosis. Studies by many groups have elucidated in detail how LRP5 and LRP6 act as co-receptors for the Wnt receptor Frizzled, forming a composite receptor complex for canonical Wnt signaling. Best described for LRP6 in *Xenopus*, binding of Wnt ligands to this co-receptor complex induces phosphorylation of the intracellular domain of LRP6 by casein kinase 1γ, resulting in association of LRP6-Frizzled with the negative regulator Axin (Fig. 4A) (Davison et al., 2005; Zeng et al., 2005; Bilic et al., 2007). Sequestration of Axin, in turn, stabilizes the intracellular Wnt signaling machinery, ultimately resulting in induction of transcription factors of the TCF/LEF family (reviewed by He et al., 2004; Niehrs and Shen, 2010; Clevers and Nusse, 2012). Expression of LRP6 at the cell surface is controlled by the secreted Wnt inhibitor Dickkopf (Dkk) (Bafico et al., 2001; Mao et al., 2001). Dkk links LRP6 to Kremen, a transmembrane protein that induces rapid endocytosis of LRP6 molecules to antagonize Wnt signaling (Mao et al., 2002; Ahn et al., 2011). The Arrow/LRP6 pathway described above is implicated in early patterning of the body plan in *Drosophila*, *Xenopus* and mouse. LRP5 operates by a similar mechanism, but its role in WNT signaling in mammals seems to be more restricted (e.g. to bone and retina formation) as judged from phenotypes of mouse models and patients with *LRP5* mutations (Table 1).

As well as controlling signaling through FGF, BMP and WNT ligands, two LRPs have also been shown to modulate HH-dependent pathways. Thus, the cellular uptake of SHH by LRP1 (Capurro et al., 2012) and LRP2 (McCarthy et al., 2002; Morales et al., 2006) has been recognized. Lately, the significance of this interaction for embryonic development has been uncovered for LRP2. This receptor is expressed in the neuroepithelium, which gives rise to various parts of the central nervous system. Lack of LRP2 expression results in abnormal dorsoventral patterning of the neural tube, causing severe forebrain malformations in mouse models and patients (Willnow et al., 1996; Spoelgen et al., 2005; Kantarci et al., 2007). The underlying defect was traced to an inability of SHH to establish its signaling domain in the forebrain organizer region of the ventral rostral neural tube despite proper expression of HH signaling components, including the receptor patched 1 (PTCH1) and the effector smoothened (SMO) (Christ et al., 2012). Now, detailed studies have revealed how LRP2 acts as an auxiliary surface binding site for SHH in neuroepithelial cells

**Fig. 3.** LRP5s regulate signaling at the cell surface. (A) Formation of the neuromuscular junction is regulated by LRP4, which self-associates to form a binding site for agrin at the surface of myotubes. The binding of agrin to LRP4 then promotes interaction of LRP4 with muscle-specific kinase (MusK), resulting in activation of the kinase. MusK then triggers events required to form the postsynaptic apparatus on muscle cells, including the clustering of acetylcholine receptors (AChRs). (B) The migration of newborn neurons in the developing mammalian cortex is controlled by LRP8 and the VLDL receptor (VLDLR). Reelin binds to complexes of LRP8 and VLDLR and to ephrin B at the neuronal cell surface. The subsequent recruitment of Src family kinases (SFKs) by ephrin B results in phosphorylation of DAB1 clustered at the receptor tails, initiating a cascade of cytosolic kinase reactions that ultimately result in rearrangement of the cytoskeleton and control of cell migration.
Fig. 4. LRPs modulate signal reception through endocytosis. (A) In *Xenopus*, Wnt ligands induce canonical signaling by binding to a coreceptor complex of LRPS and Fz, causing phosphorylation-dependent binding of Axin to the LRP6 tail. This sequester of Axin stabilizes components of the intracellular Wnt signaling pathway, resulting in induction of target genes through TCF/LEF transcription factors. Dickkopf (Dkk) antagonizes Wnt signals by coupling LRPS to Kremen for endocytic removal from the cell surface. (B) Cells in the ventral neuroepithelium of the developing mammalian forebrain express a co-receptor complex composed of LRPS and patched 1. In the absence of the ligand SHH, patched 1 inhibits the effector smoothened. (C) Binding of SHH to patched 1 induces uptake of receptor-ligand complexes and releases the patched 1-mediated block of smoothened, resulting in target gene induction through GLI transcription factors. The internalized SHH is recycled by LRPS, which is likely to increase local morphogen concentration further.

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**Competing interests statement**

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**References**


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**Conclusion**

Beginning with the identification of a group of alleged lipoprotein receptors, recent years witnessed the elucidation of LRPs as morphogen-binding proteins important in the control of embryonic development. Still, the relevance of these endocytic receptors is not limited to morphogen signal reception. Rather, studies have also firmly established the significance of several of these receptors in control of cellular and systemic lipoprotein metabolism. Thus, impaired energy homeostasis and dyslipidemia have been documented in mouse models with deficiencies in the genes encoding LRPS1, VLDLR, LRPS5 and LRPS6 (Table 1). Missense mutations in LRPS6 cause metabolic syndrome (see Glossary, Box 2) in an autosomal dominant inheritable trait in humans (Table 1). Furthermore, impaired cholesterol biosynthesis, as in patients with Smith-Lemli-Opitz syndrome (see Glossary, Box 2), causes holoprosencephaly (HPE), arguing for a mechanistic link between cholesterol metabolism and developmental pathways. Perhaps control of lipid homeostasis and morphogen signaling are just two unrelated functions performed by receptors with dual functionality? More exciting is the idea that both biological concepts have more in common than previously anticipated. Perhaps metabolism and energy homeostasis modulates morphogen signaling in embryonic and adult organisms, or, in the converse situation, morphogens have previously unrecognized functions in control of metabolism. Clearly, LRPs would be perfectly equipped to integrate both tasks.


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