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Mechanisms by which LRP1 Maintains Arterial Integrity: Keeping Your Vascular Smooth Muscle Happy and Healthy

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LDL Receptor-related Protein-1 (LRP1) was cloned and identified as a probable apolipoprotein-E receptor by Herz et al.[1] Strickland et al[2] then reported that LRP1 functions as the receptor for the activated form of the proteinase inhibitor, α_2-macroglobulin. Subsequent work by numerous laboratories defined the first novel paradigm regarding LRP1, which is its ability to function as an endocytic receptor for as many as one hundred diverse ligands, in each case, satisfying the criteria of receptor specificity and saturability. Rapid endocytosis and efficient LRP1 recycling allow transport of associated cargo to lysosomes for degradation; clearance of proteins from the cellular microenvironment was the first recognized pathway by which LRP1 may regulate cell biology and tissue physiology.[3] Because LRP1 internalizes multiprotein complexes, which may include other membrane proteins active in cell-signaling, LRP1 regulates cell-signaling indirectly, by altering the composition of the plasma membrane proteome.[4] LRP1 also regulates cell-signaling directly, by binding cell-signaling adapter and scaffold proteins after it is phosphorylated at specific residues in its cytoplasmic tail and by interaction with receptors such as the N-methyl-D-aspartate receptor, Trk receptors, and $p75^{NTR}$.[5–7] A second novel paradigm regarding the function of LRP1 is its ability to activate distinct and sometimes opposing signaling responses upon binding different ligands.[8] This unique LRP1 activity may allow LRP1 to function as a radar system for the cell, sensing changes in the cellular microenvironment and directing context-appropriate cellular responses. LRP1 has been implicated in phagocytosis, efferocytosis, and antigen presentation.[9–11] Finally, membrane-anchored LRP1 is a substrate for transmembrane proteinases that release a soluble form of the receptor, which may be biologically activity in immunity.[12,13] These various activities of LRP1 are summarized in the accompanying Figure The challenge now is to understand how the activities of LRP1 are integrated at the cellular and tissue levels to regulate physiology and various forms of pathology.

In this issue of *ATVB*, Au et al.[14] describe novel mechanisms by which LRP1 may regulate vascular smooth muscle contractility and the phenotype of vascular smooth muscle cells (VSMCs). The focus of this study is highly justified because of genome-wide association studies, which have identified single nucleotide polymorphisms in the *LRP1* gene that are associated with abdominal aortic aneurysm development in humans.[15,16] Mice in which

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Disclosures

None

LRP1 is deleted conditionally in VSMCs also develop aneurysms in the context of a diverse array of structural abnormalities in arteries.[17,18]

During development and in response to various cues in the cellular microenvironment, VSMCs undergo substantial changes in differentiation, gene expression, and phenotype.[19] To measure contractility of LRP1-deficient and control VSMCs under isometric conditions, Au et al.[14] performed aortic ring contraction assays using segments of descending thoracic aorta. Responses to a number of agonists were either attenuated or completely absent; however, calyculin A triggered increased responses in aortic rings from mice with LRP1-deficient VSMCs, arguing against a generalized loss of contractile machinery as the responsible mechanism. To explore this finding, the investigators undertook a discovery approach, using proteomics to identify over 200 proteins that are regulated when LRP1 is deficient in VSMCs. Many of the identified proteins express activities related to VSMC contractility and the function of the cytoskeleton. $\alpha_2\delta-1$, a chaperone for voltage-gated Ca^{2+} channels, bound directly to LRP1, suggesting a novel mechanism by which LRP1 may regulate these channels. LRP1 deficiency in VSMCs also resulted in abnormal function of Ryanodine Receptors, which are instrumental in controlling calcium release from the sarcoplasmic reticulum.

A strength of this paper is the utilization of two distinct mouse model systems for deleting *LRP1* in VSMCs. In the first model system, Cre recombinase is active during development whereas in the second, Cre recombinase is expressed as a fusion protein, which may be activated in adult mice treated with Tamoxifen. The combination of systems allowed the investigators to probe for genetic compensation following *LRP1* deletion, which is particularly important given that there are receptors in the LDL Receptor gene family with overlapping activities.[5] A second strength of this paper is replication of key results using aortic rings and primary cultures of VSMCs.

Looking forward, the study by Au et al,[14] defining changes in VSMCs using LRP1 “loss of function” model systems, sets the stage for future work examining how various LRP1 ligands may regulate VSMC physiology. Is there specificity in the response of VSMCs to different LRP1 ligands, as has been defined in cells such as PC12 cells?[8] How are the results of Au et al.[14] relevant to the role of VSMCs in atherogenesis? Finally, and perhaps most importantly, is LRP1 a therapeutic target for vascular disease?

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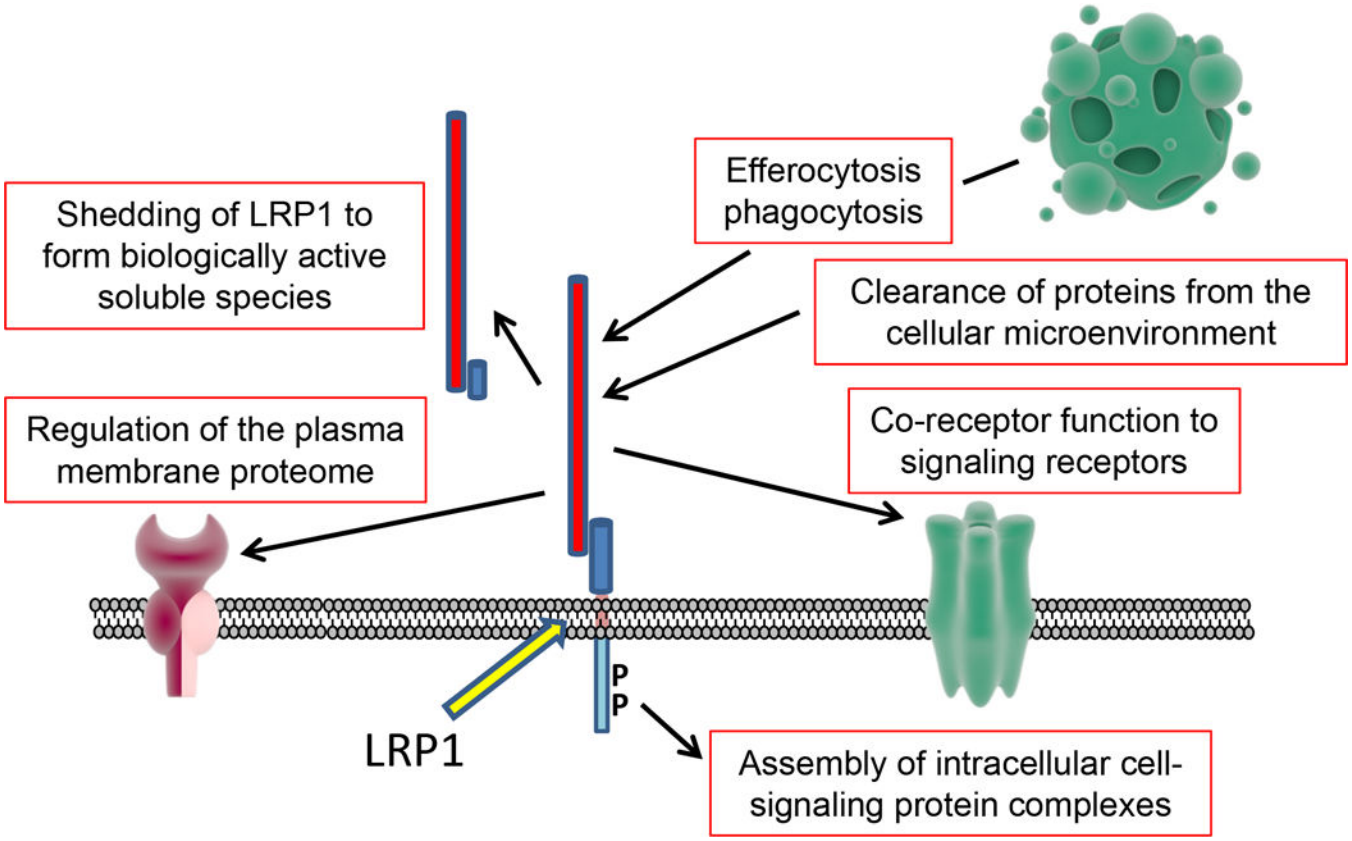

Figure.

LRP1 regulates cell physiology by diverse mechanisms shown here. In vascular smooth muscle cells, LRP1 deficiency regulates expression of numerous proteins and causes changes in cell physiology that impact contractility.