The study of orphan diseases, defined by the US Food and Drug Administration as any condition that affects <200,000 people nationwide, has been crucial not only in our understanding of disease pathophysiology and gene discovery but also in therapeutic development. Individuals with orphan conditions have played an active role not only in improving care of their own condition but often in improving the care of individuals with more common conditions by participating in clinical trials, donating biospecimens, and even through advocacy. Nowhere has this been more evident recently than in the field of lipidology, where the study of orphan conditions such as homozygous familial hypercholesterolemia, a rare condition generally caused by biallelic mutations in \( \text{LDLR} \), or lysosomal acid lipase deficiency has led to the Food and Drug Administration approval of specifically targeted therapies (lomitapide, mipomersen and the PCSK9 inhibitor evolocumab for the former, and sebelipase alfa for the latter).  

**Standards of Evidence and Mechanistic Inference in Autosomal Recessive Hypercholesterolemia**

James R. Priest, Joshua W. Knowles

Autosomal recessive hypercholesterolemia (ARH) is another such orphan disease. Fellin et al have beautifully reviewed the fascinating story describing the identification of ARH families around the globe and the worldwide quest to map the causal gene. The identification of a low-density lipoprotein receptor (LDLR)-chaperone protein, later named LRaRap1 (LDLRAP1), was critical to our mechanistic understanding of LDL metabolism. On binding LDL to LDLR, LDLRAP1 is recruited to clathrin-coated pits and promotes internalization of the LDL/LDLR complex, coupling this to the endocytic machinery (Figure 1). Interestingly, LDLRAP1 seems to be necessary in certain cell types (polarized cells such as hepatocytes and lymphoblasts) but dispensable to LDLR uptake in other cells (fibroblasts).

Clinically, ARH can be devastating to the adults and children who are affected. Although heterozygotes are unaffected, those with biallelic mutations in \( \text{LDLRAP1} \) have severe elevations in LDL-cholesterol (LDL-C) concentrations (often >400 mg/dL) and high likelihood of coronary heart disease before the age of 30 years. Clinically, ARH most closely resembles forms of homozygous familial hypercholesterolemia, where there is a minimal residual LDLR activity (so-called receptor defective as opposed to homozygous familial hypercholesterolemia caused by biallelic null mutations). Treatment options are suboptimal because therapies that work by increasing LDLR levels (eg, statins or bile acid–binding resins) are only modestly effective and often patients require LDL-apheresis.

Potentially motivated by the fact that the PCSK9 inhibitor evolocumab has a modest but significant effect in reducing LDL-C levels in receptor defective (but not receptor null) patients with homozygous familial hypercholesterolemia, as well as by the fact that endogenous PCSK9 levels are high in patients with ARH, Theodrez et al used primary lymphocytes from 28 individuals with genetically characterized disease for in vitro studies to characterize the cellular expression of LDLR and LDL-C uptake. As expected, the authors documented a higher level of cell surface LDLR expression (because of the inability to internalize the LDLR complex) and consequent lower level of LDL-C uptake in cells from individuals with ARH compared with controls (Figures 2 and 3), differences that were magnified by statin treatment. With the addition of recombinant PCSK9 (effectively reducing LDLR levels), LDL-C uptake was markedly reduced in control cells and (to a lesser extent) in ARH cells, a phenomenon that was rescued by the application of alirocumab. One caveat is that lymphocytes are, of course, a limited surrogate for hepatocytes and have many different properties related to lipid metabolism.

Overall, the in vitro studies suggest that PCSK9 inhibitors will likely not be a game changer for patients with ARH, which is not surprising given our understanding of the disease mechanism. After all, if the LDL/LDLR complex cannot be effectively internalized, it matters less how much LDLR is on the cell surface. This supposition was reinforced by the
modest effect PCSK9 inhibitors seemed to have clinically on patients with ARH (with an n=3, the max LDL-C reduction was 11% and in 2 of the patients, including one previously published treated with evolocumab, there was essentially no LDL-C lowering observed7).

In orphan lipid disorders, performing large primary prevention trials is an unrealistic goal. As a community, the question is: what standards of evidence are necessary to conduct and interpret small trials or simply to treat the patient in our clinic? The assembly of a cohort of 28 ARH patients with biospecimens in and of itself is a laudable accomplishment and positions the authors to test other emerging therapies for ARH. The era of precision medicine in hyperlipidemias will be rooted in our fundamental scientific understanding of a heterogeneous group of disorders, and this study has advanced that knowledge.

**Disclosures**

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**References**


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