The Lowe syndrome protein OCRL1 is involved in primary cilia assembly.

Coon BG, Hernandez V, Madhivanan K, Mukherjee D, Hanna CB, Barinaga-Rementeria Ramirez I, Lowe M, Beales PL, Aguilar RC.

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Abstract

Lowe syndrome (LS) is a devastating, X-linked genetic disease characterized by the presence of congenital cataracts, profound learning disabilities and renal dysfunction. Unfortunately, children affected with LS often die early of health complications including renal failure. Although this syndrome was first described in the early 1950s and the affected gene, OCRL1, was identified more than 17 years ago, the mechanism by which Ocrl1 defects lead to LS's symptoms remains unknown. Here we show that LS display characteristics of a ciliopathy. Specifically, we found that patients' cells have defects in the assembly of primary cilia and this phenotype was reproduced in cell lines by knock-down of Ocrl1. Importantly, this defect could be rescued by re-introduction of WT Ocrl1 in both patient and Ocrl1 knock-down cells. In addition, a zebrafish animal model of LS exhibited cilia defects and multiple morphological and anatomical abnormalities typically seen in ciliopathies. Mechanistically, we show that Ocrl1 is involved in protein trafficking to the primary cilia in an Rab8-and IPIP27/Ses-dependent manner. Taking into consideration the relevance of the signaling pathways hosted by the primary cilium, our results suggest hitherto unrecognized mechanisms by which Ocrl1 deficiency may contribute to the phenotypic characteristics of LS. This conceptual change in our understanding of the disease etiology may provide an alternative avenue for the development of therapies.

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Additional Information

Paradigm Shift in Lowe Syndrome: Primary Cilia and Therapeutic Prospects

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The Oculo-Cerebro-Renal syndrome of Lowe (OCRL) or Lowe Syndrome (LS) is a lethal, genetic disease characterized by the presence of congenital cataracts, mental retardation and kidney dysfunction. Unfortunately, children affected by LS die at an early age, largely due to renal failure. Although this disorder (associated with abnormal function of the lipid phosphatase Ocrl1) was first described almost 60 years ago, *no specific treatment is available to LS patients*. This unacceptable situation is mainly due to lack of understanding of the mechanism by which Ocrl1 deficiencies lead to this disease.

We have recently taken an important step towards filling this gap by establishing that LS is not an isolated disease but it is related to the heterogeneous group of ciliopathies. Specifically, we discovered that, similar to ciliopathies, LS patient fibroblasts cannot efficiently assemble primary cilia (Ref. 1). Importantly, this defect could be rescued by re-introduction of WT Ocrl1 and emulated by Ocrl1 depletion (Fig. 1 and Ref.1). The primary cilium is a sensing organelle that plays a crucial role in cell regulation particularly during development. From a mechanistic

point of view, we discovered that LS cells display deficiencies in vesicle trafficking to the primary cilium, which are likely to impair cilia assembly (Ref.1). Interestingly, similar to LS, ciliopathy patients display symptoms affecting the brain, eyes and kidney.

These findings are very important because they change the status of LS from an isolated disease to member of a broad pathology group. This innovative view is likely to have a major impact in the field and ultimately on the patients' well-being. Specifically, breakthroughs in terms of mechanistic insights or novel therapeutic approaches, arising in the field of ciliopathies could be immediately capitalized upon by LS researchers (and vice versa).

Indeed, we predict that drugs capable of counteracting cellular defects in ciliopathies should be beneficial for LS patients as well. Therefore, *we are currently testing on LS patient's cells the effect of agents proven to suppress cellular deficiencies in certain ciliopathies*.

In summary, these discoveries lay the foundation for synergistic interactions between investigators working on different developmental diseases (Lowe and ciliopathy syndromes) who have unified goal of finding therapeutic approaches to alleviate patient suffering.

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References

1. Coon BG, Hernandez V, Madhivanan K, Mukherjee D, Hanna CB, Barinaga-Rementeria Ramirez I, Lowe M, Beales PL, Aguilar RC. 2012. *The Lowe syndrome protein OCRL1 is involved in primary cilia assembly.* Hum Mol Genet. 21(8):1835-47.

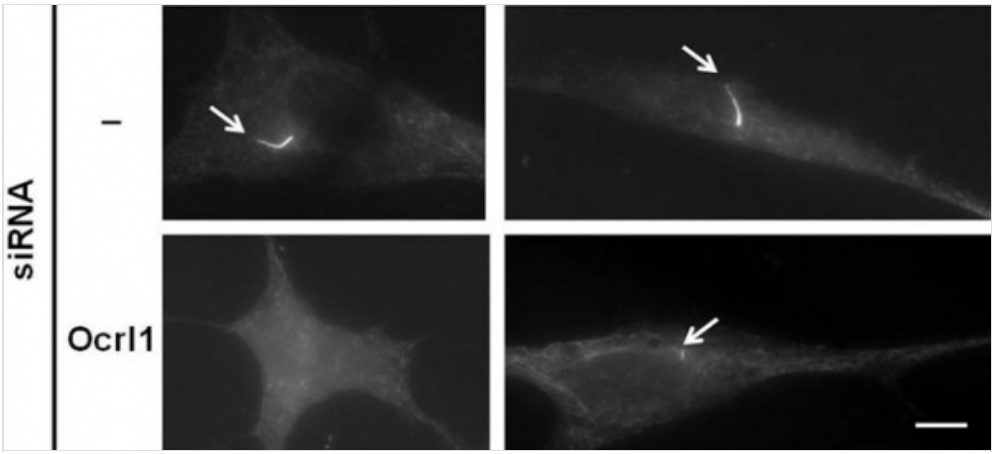

Fig. 1. Ocrl1 Knock-down Impairs Primary Cilia Assembly. NIH3T3 cells were treated or not with Ocrl1-specific siRNA and subjected to immunofluorescence with an anti-acetylated tubulin antibody as indicated before (ref. 1). Arrows indicate the position of primary cilia (2 examples of each treatment is shown). Scale bar: 10microns.

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