Lysosome positioning and mTOR activity in Lowe syndrome

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Abstract:

Lowe syndrome is a rare, developmental disorder caused by mutations in the phosphatase, OCRL. A study in this issue of *EMBO Reports* shows that OCRL is required for microtubule nucleation and that mutations in this protein lead to an inability to activate mTORC1 signaling and consequent cell proliferation in the presence of nutrients. These defects are the result of impaired microtubule-dependent lysosomal trafficking to the cell periphery and are independent of OCRL phosphatase activity.

Lowe syndrome is a rare, X-linked, developmental, multisystem disease characterized by congenital cataracts, central hypotonia, intellectual disability and renal Fanconi syndrome (Bökenkamp and Ludwig, 2016). It is caused by mutations in *OCRL* (Lowe oculocerebrorenal syndrome protein), an inositol polyphosphate 5-phosphatase that dephosphorylates the phospholipid $PI(4,5)P_2$ to PI(4)P (Attree et al., 1992).

Since phospholipids are involved in a myriad of cellular pathways, the implications of defects in the phosphatase function of OCRL for Lowe syndrome pathology has been extensively studied. For example, OCRL deficiency leads to the accumulation of $PI(4,5)P_2$ on early endosomes, leading to dysregulation of the actin cytoskeleton (Bökenkamp and Ludwig, 2016). This was found to affect recycling of receptors, such as megalin, which mediates protein reabsorption in the kidney (Vicinanza et al., 2011). However, disease-causing mutations have been found in both the phosphatase and the non-catalytic ASH-RhoGAP domains of OCRL. Interestingly, an analysis of the phosphatase activity found no difference from controls in fibroblasts obtained from patients with Lowe syndrome, nor any difference in fibroblasts from patients harbouring missense mutations, or mutations resulting in premature truncations of OCRL (Hichri et al., 2011). While OCRL-depleted cells exhibit an increase in $PI(4,5)P_2$ levels, causing vesicular trafficking defects and resulting in defective receptor-

mediated endocytosis (Erdmann et al., 2007), the contribution of non-catalytic OCRL mutations to Lowe syndrome remains elusive.

In a recent study, Wang et al. (2021) describe a mechanism by which non-catalytic OCRL mutations contribute to Lowe syndrome independently of the OCRL phosphatase function. This work reveals a lysosomal positioning defect and abrogated mTORC1 signaling in cells obtained from patients with Lowe syndrome, cells from OCRL-knockout mice and from a humanized Lowe syndrome mouse model.

Lysosomes are highly dynamic organelles that can move rapidly throughout the cell. Their distribution is tightly linked to their roles in cellular functions. Therefore, alterations in lysosomal positioning contribute to a variety of diseases, including neurodegeneration, cancer, and lysosomal storage diseases (Cabukusta and Neefjes, 2018). Additionally, lysosome positioning defects have been linked to major features of Lowe syndrome, such as intellectual disability and growth retardation (Crino, 2011). Lysosomal motility is intimately linked to mTORC1 activity and nutrient availability (Korolchuk et al., 2011). mTORC1 is a master growth regulator that becomes activated in response to nutrients. Nutrient-rich conditions cause migration of lysosomes to the periphery enabling mTORC1 activation, while upon starvation, lysosomes move to the perinuclear region and cluster at the microtubule organizing center (MTOC), which inhibits mTORC1 activity (Korolchuk et al., 2011). Defects in lysosomal positioning and mTOR dysfunction cause many disorders including developmental and degenerative neurological diseases (Sabatini, 2017).

Interestingly, Wang et al (2021) reveal that OCRL-deficient cells exhibit persistent perinuclear lysosomal localization. Unlike in control cells, lysosomal positioning does not change as a response to nutrient replenishment after starvation in OCRL-deficient cells. In control cells, the presence of nutrients leads to recruitment and activation of mTORC1 on the surface of peripherally-localised (Korolchuk et al., 2011). However, in OCRL-deficient cells mTOR activity remains low and fails to return to normal levels after nutrient replenishment and this could be attributed to a failure of the lysosomes to move peripherally in the cells from their perinuclear locations, even though mTOR was associated with these lysosomes. Consistent with the roles of mTOR in cell growth, cell proliferation was impaired in Lowe patient cells and this was rescued by an mTORC1-activating compound.

The impaired lysosome movement in OCRL-deficient cells was attributed to microtubule defects, as these cells have non-radial microtubule arrays, a phenomenon resulting from abnormal microtubule nucleation, and the microtubules were not normally anchored to the centrosome, consistent with abnormal function of the microtubule organising centre (MTOC). By performing biochemical studies and confocal imaging, OCRL was found to be localised to the centrosome via its ASH domain, where it recruits the microtubule anchoring factor SSX2IP to the centrosome through its RhoGAP domain. The recruitment of SSX2IP is important for the formation of the MTOC, which is nucleated at the centrosome. These mechanisms can explain how OCRL deficiency results in defective MTOC microtubule nucleation and impaired microtubule-based lysosome movement, resulting in mTORC1 inactivation and abnormal nutrient sensing. OCRL-deficient cells did not exhibit any changes in PI(4,5)P2 levels in the centrosomes, suggesting that the non-phosphatase function of

OCRL is important for centrosomal regulation. Importantly, centrosome-targeted SSX2IP restored microtubule anchoring and mTORC1 activity and rescued lysosome mobility defects and nutrient sensing in Lowe patient cells.

In conclusion, this study provides a new mechanism contributing to pathology in Lowe syndrome, which is independent of OCRL phosphatase function. Defective OCRL results in an impaired ability of cells to activate mTORC1 in the presence of nutrients that is due to defective microtubule-dependent trafficking of lysosomes to the cell periphery. The impaired nutrient sensing to mTORC1 results in reduced proliferation of Lowe syndrome cells and the rescue of this phenotype with mTORC1 activation raises the possibility of therapeutic approaches via this pathway.

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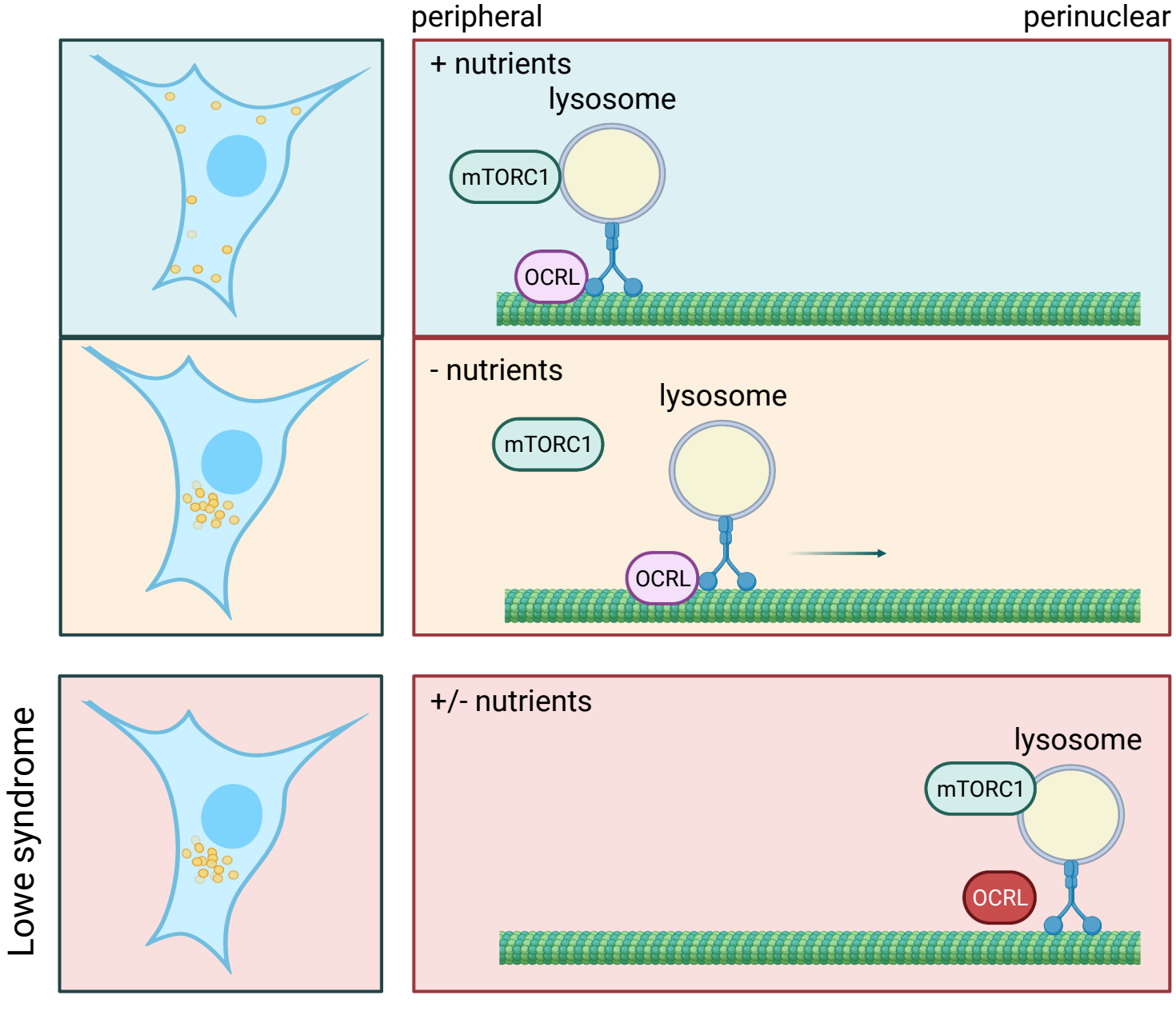
Conflict of Interests

DCR is a consultant for Aladdin Healthcare Technologies SE, Drishti Doscoveries and Nido Biosciences. None of the other authors have any potential competing interests.

FIGURE LEGEND:

Figure 1. Schematic of lysosomal positioning upon nutrient starvation and Lowe syndrome

Upon nutrient starvation, lysosomes in the cell periphery are transported along the microtubules to the perinuclear region of the cell in an OCRL-dependent fashion. As a response to reduced levels of nutrients, mTORC1 also dissociates from lysosomes and is inactivated. In Lowe syndrome, OCRL deficiency impairs lysosome trafficking and results in decreased mTORC1 sensitivity to nutrient. Lysosome positioning in the cell is shown on the left panel.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