Nature Reviews Nephrology | Published online 18 Jul 2016; doi:10.1038/nrneph.2016.110

LOWE SYNDROME

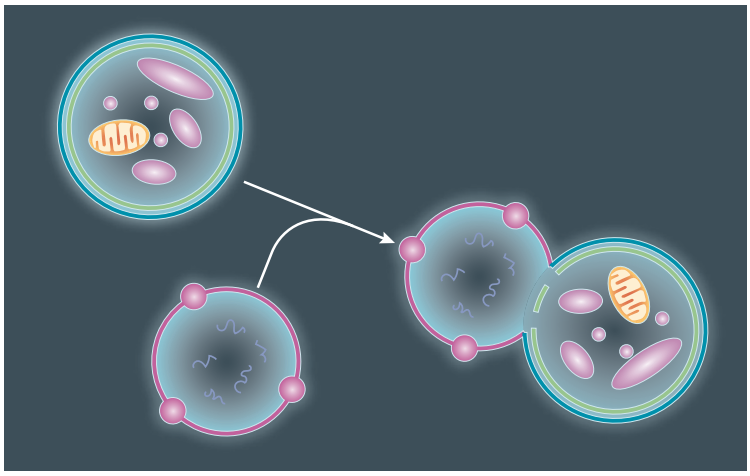
Dysregulation of autophagosome–lysosome fusion in Lowe syndrome

Lowe syndrome is a rare X-linked genetic disorder that affects the eyes, brain and kidneys, and is caused by mutations in the lipid phosphatase OCRL. Despite advances in our understanding of OCRL function, the mechanism by which loss of OCRL leads to clinical manifestations of disease is unclear. Researchers have now uncovered an unexpected role for OCRL in regulating the response of lysosomes to the autophagic cargo, whereby loss of OCRL leads to lysosome dysfunction and autophagosome accumulation. "Our findings demonstrate the physiological relevance of the lysosomal role of OCRL and suggest that impaired autophagic flux might have a role in the progression of kidney dysfunction in Lowe syndrome," say researchers Leopoldo Staiano and Antonella De Matteis.

To study the mechanisms by which OCRL inhibition leads to proximal tubule dysfunction, De Matteis and colleagues first assessed changes in gene expression induced by loss of OCRL in human proximal tubule cells. "We were surprised to find that lysosomal genes were among those most responsive to OCRL depletion, leading us to investigate the role of OCRL at lysosomes, a compartment in which OCRL was not known to reside, at least under unperturbed conditions," says De Matteis.

The researchers found that OCRL translocates to lysosomes in response to the fusion of autophagosomes with lysosomes and under the control of clathrin and AP2. Autophagosome–lysosome fusion induced a local increase in the OCRL substrate $PI(4,5)P_2$. In investigating signalling pathways that mediate the lysosomal response to autophagosome fusion, De Matteis and colleagues found that upon autophagy induction and autophagosome–lysosome fusion, mitochondrial DNA is delivered by the autophagosomes into the lysosomes, activating lysosomal TLR9. Activation of TLR9 induced the recruitment of enzymes responsible for $PI(4,5)P_2$ synthesis, whereas depletion of TLR9 or mitochondrial DNA blunted the response to autophagosome–lysosome fusion, attenuating the generation of $PI(4,5)P_2$ and the recruitment of AP2, clathrin and OCRL. Depletion of TLR9 also led to the formation of enlarged lysosomes and an accumulation of autophagosomes with impaired autophagosome–lysosome fusion, suggesting that this pathway is required for lysosomal homeostasis and autophagic flux. "Our data confirmed the presence and the activity of TLR9 in kidney proximal tubular cells but highlighted a new and unexpected role for this receptor," explains Staiano. "Our findings also corroborate recent evidence pointing towards a central role of lysosomes as sensing and signalling platforms and not just degradative end points of the endocytic pathway." In investigating the downstream targets of $PI(4,5)P_2$, the researchers focused on the lysosomal calcium channel mucolipin 1, which is required for autophagosome–lysosome fusion and is inhibited by $PI(4,5)P_2$. Depletion of OCRL led to increased levels of $PI(4,5)P_2$ and decreased mucolipin 1-dependent calcium release. In line with these findings, they also observed an accumulation of autophagosomes in cells depleted of OCRL and also in the kidneys of patients with Lowe syndrome. "We highlight the need for an extremely precise control of $PI(4,5)P_2$ in the lysosome," says De Matteis. "Finally, we were able to partially restore the autophagic flux by boosting the activity of mucolipin 1 with synthetic agonists, thus identifying mucolipin 1 as a candidate target for pharmacological intervention in patients with Lowe syndrome."

> "Our findings demonstrate the physiological relevance of the lysosomal role of OCRL"



NPG

Susan J. Allison

ORIGINAL ARTICLE De Leo, M.G. *et al.* Autophagosome-lysosome fusion triggers a lysosomal response mediated by TLR9 and controlled by OCRL. *Nat. Cell Biol.* http://dx.doi.org/10.1038/ncb3386