OCRL is a PI(4,5)P2 5-phosphatase that is defective in Lowe syndrome, a rare X-linked disorder characterized by renal Fanconi syndrome, congenital cataracts, and psychomotor impairment. OCRL has been shown to control endocytic uptake and recycling, endosome-to-Golgi transport, early phagocytic steps, cytokinesis, and cilium formation. However, many gaps remain in our understanding of the mechanisms linking OCRL mutations to the manifestations of Lowe syndrome. In an attempt to fill these gaps we adopted an unbiased approach to uncover how cells suffer from/react to the loss of OCRL by analyzing the changes in gene expression caused by the depletion of OCRL. Unexpectedly, one of the gene classes most significantly up-regulated by OCRL depletion was that of lysosomal genes. Prompted by these results we investigated the role of OCRL in lysosomal function. We found that, while at steady state, as reported, OCRL associates with clathrin-coated vesicles, early endosomes, and the Golgi complex, it translocates to lysosomes under conditions demanding high degradation efficiency (such as autophagy). Interestingly, the lysosomal translocation of OCRL is insensitive to the activity state of mTORC1 (a lysosomal based signaling complex) but is controlled by Toll Like Receptor 9 signaling from autolysosomes and is mediated by AP2 and clathrin, two binding partners of OCRL. By confining in time and space the lysosomal PI45P2 pool, OCRL safeguards the activity of mucolipin1 (MCOLN1), the lysosomal calcium channel required for autophagosome-lysosome fusion. The elevation of lysosomal PI(4,5)P2 caused by OCRL depletion/mutation impairs MCOLN1 activity and lysosomal calcium release, hampering the autophagic flux through lysosomes and leading to accumulation of autophagosomes. Importantly, boosting the activity of MCOLN1 with selective agonists rescues lysosomal function in kidney cells from Lowe syndrome patients, thus identifying MCOLN1 as a possible drug target. In conclusion, we have uncovered a lysosomal “cargo-load response” that is mediated by TLR9 signaling and that enhances the degradative flux through lysosomes.