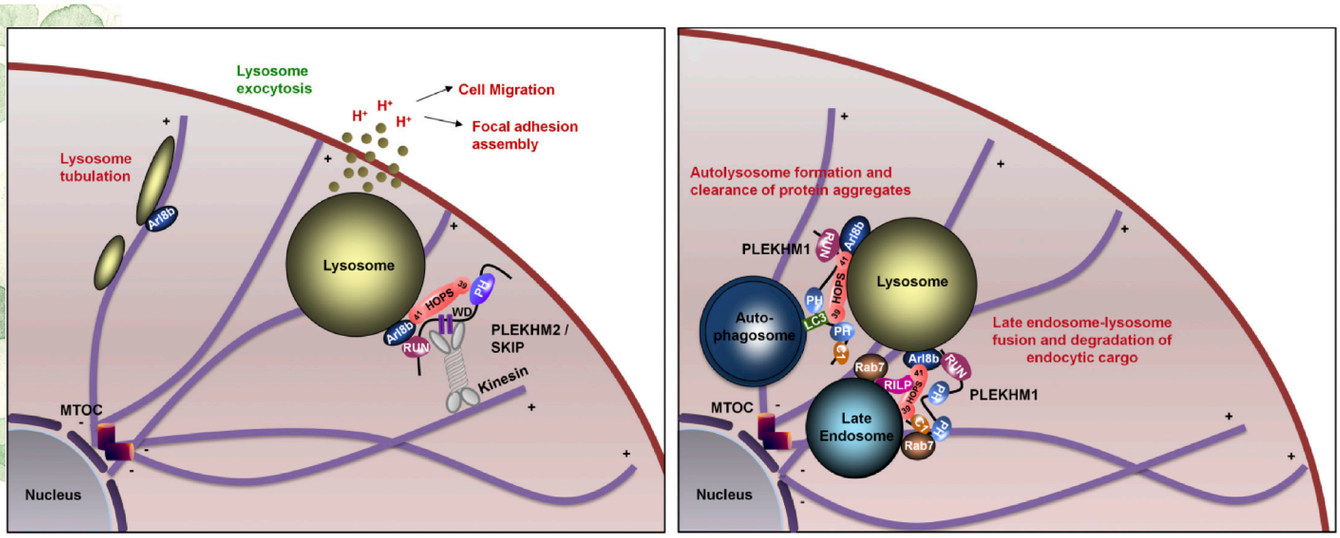

The interaction between SKIP and Arl8b may promote lysosome position and function at the cell periphery (left), whereas the interaction between PLEKHM1 and both Arl8b and Rab7 promotes the clustering and fusion of lysosomes, endosomes, and autophagosomes near the cell nucleus (right).
Credit: Marwaha et al., 2017.

HOW CELLS DIRECT LYSOSOMAL TRAFFIC

A protein called PLEKHM1 binds to the GTPases Rab7 and Arl8b to coordinate lysosomal transport and fusion with other organelles.

Lysosomes perform many different functions in the cell. For example, they can degrade cargo delivered via various pathways, including endocytosis and autophagy, and can be exocytosed to promote processes ranging from cell migration to membrane wound repair. To perform these different functions, lysosomes must move to different parts of the cell and fuse with different target membranes. Two small GTPases—Rab7 and Arl8b—regulate lysosome motility and fusion, but whether these GTPases coordinate their activities is unclear. In a recent JCB paper, a team of researchers led by Amit Tuli and Mahak Sharma have now discovered that a protein called PLEKHM1 orchestrates lysosome transport and fusion by binding to both Rab7 and Arl8b.

Rab7 mainly localizes to a pool of late endosomes and lysosomes that accumulate around the nucleus near the cell's microtubule-organizing center. This GTPase binds to several effector proteins, including PLEKHM1, that promote the dynein-mediated transport of late endosomes and lysosomes towards the minus ends of microtubules and recruit the HOPS complex that tethers lysosomes to endosomes and autophagosomes in preparation for membrane fusion. In contrast, Arl8b is enriched on lysosomes at the cell periphery, where it can bind to the HOPS complex directly and also recruit an effector protein called SKIP that promotes the kinesin-1–mediated transport of lysosomes towards the plus ends of microtubules.

Mahak Sharma, from the Indian Institute of Science Education and Research in Mohali, and Amit Tuli, from the Institute of Microbial Technology in Chandigarh, India, noticed that the Rab7 effector PLEKHM1 possesses an N-terminal RUN domain highly similar to the RUN domain that mediates SKIP's association with Arl8b. "This prompted us to investigate whether PLEKHM1 can interact with Arl8b as well as Rab7," Sharma explains.

"OUR FINDINGS SUGGEST THAT PLEKHM1 IS A DUAL EFFECTOR PROTEIN THAT BINDS TO BOTH RAB7 AND ARL8B TO ORCHESTRATE ASSEMBLY OF THE VESICLE FUSION MACHINERY, LEADING TO LYSOSOMAL DEGRADATION OF CARGO INTERNALIZED VIA ENDOCYTIC AND AUTOPHAGIC PATHWAYS."

Sure enough, the researchers, including co–first authors Rituraj Marwaha and Subhash Arya, determined that PLEKHM1 can bind to Arl8b via its N-terminal RUN domain and, because it binds to Rab7 via its C-terminal domain, it can physically link the two GTPases to each other in vivo.

Rab7 recruits PLEKHM1 to late endosomes, but the interaction between PLEKHM1 and Arl8b was necessary for PLEKHM1 to localize to lysosomes and for late endosomes and lysosomes to cluster together near the cell nucleus. Moreover, the PLEKHM1–Arl8b interaction was required for the recruitment of the HOPS tethering complex. Disrupting the PLEKHM1–Arl8b interaction therefore prevented lysosomes from fusing with, and degrading the contents of, endosomes and autophagosomes.

"Our findings suggest that PLEKHM1 is a dual effector protein that binds to both Rab7 and Arl8b to orchestrate assembly of the vesicle fusion machinery, leading to lysosomal degradation of cargo internalized via endocytic and autophagic pathways," says Tuli.

The researchers also found that PLEKHM1 controls lysosome positioning within the cell by competing with SKIP for binding to Arl8b. Overexpressing PLEKHM1 promoted the relocation of lysosomes to the perinuclear region of the cell, whereas depleting PLEKHM1 (or overexpressing SKIP) caused the organelles to accumulate at the cell periphery. "We speculate that while the Arl8b–PLEKHM1 interaction is required for cargo delivery to lysosomes, the interaction with SKIP might regulate the ascribed roles of lysosomes at the cell periphery, including exocytosis, cell migration, and plasma membrane repair," says Sharma.

Mutations in the *PLEKHM1* gene cause the rare genetic disorder osteopetrosis, in which the function of bone-resorbing osteoclast cells is impaired. "It will be important to elucidate whether the Arl8b–PLEKHM1 interaction is required for the bone-remodeling function of osteoclasts," Tuli says. ■

RESEARCHER DETAILS

Left to right: Amit Tuli, Rituraj Marwaha, Subhash B. Arya, and Mahak Sharma

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