From gene manager to traffic cop

“Nuclear” protein keeps endosomes rolling.

A protein that tweaks gene expression moonlights in the cytoplasm, Xu et al. show (1). The protein, which is part of a histone-modifying complex in the nucleus, regulates endosome trafficking in the cytoplasm and might influence when cells crawl and when they stay put.

Histone lysine methyltransferase complexes affix methyl groups to lysines in the H3 and H4 histones. Depending on the circumstances, the additions can turn gene activity up or down (2). Researchers are learning that a growing number of other proteins—including the tumor-fighter p53—also accrue methyl groups. “That’s a clue that methyltransferases might do something else,” says senior author Dzwokai “Zach” Ma. However, says Ma, the team was surprised that the something else entailed intracellular transport.

Xu et al. got their first inkling of this alternative function while performing a yeast two-hybrid screen to uncover rat brain cell proteins that latch onto a potassium channel. The experiment turned up mDpy-30, a component of several histone methyltransferase complexes (3). Whether mDpy-30 and the channel also interact in vivo—and why—is unknown. But the finding spurred the team to further investigate mDpy-30.

The protein was prevalent not only in the nucleus, the researchers found, but also in the trans-Golgi network, suggesting a role in membrane trafficking. To clarify that role, the researchers tracked the protein CIMPR, which ushers newly made enzymes from the trans-Golgi network to the lysosomes. Some CIMPR normally shuttles between the plasma membrane and Golgi apparatus in early, recycling, and late endosomes. When the team trimmed mDpy-30 levels with RNAi, CIMPR amassed at protrusions that cells extend when beginning to crawl. However, depletion of mDpy-30 didn’t alter trafficking of two other proteins that ride in early and recycling endosomes, suggesting that mDpy-30’s job involves the late endosomes.

Further evidence that mDpy-30 takes part in late endosome transport came when the team followed a labeled version of CIMPR from the cell surface to a site where late endosomes gather near the Golgi apparatus. Within 15 minutes, CIMPR had made the trip in about 80% of cells. When mDpy-30 levels were down, however, CIMPR reached this location in only one-half to one-third as many cells within the same period. Instead, the protein detoured to the protrusions and built up there.

The team also took a closer look at what happens at the protrusions by testing for Rab GTPases that characterize specific kinds of endosomes. The extensions teemed with Rab4 and Rab11, both of which mark recycling endosomes, but not with Rab5 linked to other types of endosomes. Together, the findings suggest that disrupting mDpy-30 stalls transport to the Golgi apparatus in late endosomes, leading to a pile-up of recycling endosomes near the membrane.

That leaves two big questions to answer. The first is how mDpy-30 influences intracellular transportation. One possibility is that it teams up with its histone-methylating partners at the Golgi, forming complexes that modify traffic regulating proteins. The team found that knocking down two of these partners, Ash2L and RbBP5, had the same effect on CIMPR distribution as depletion of mDpy-30.

However, the researchers couldn’t find evidence that Ash2L and RbBP5 gather at the trans-Golgi network, so the complexes’ direct participation in trafficking remains in doubt. Another option, Ma says, is that both pools of mDpy-30—nuclear and Golgi—participate. The cytoplasmic pool might direct traffic, for example, while the nuclear pool manages expression of gene products involved in endosomal transport. If that’s the case, Ma says, researchers also need to explain how the two pools of mDpy-30 integrate their actions.

The second big mystery concerns the function of mDpy-30’s traffic control. “We suspect that one physiological consequence of this event is to control adhesion and migration,” says Ma. Formation of cell protrusions is the first step toward migration and previous studies have implicated CIMPR, Rab4, and Rab11 in cell movement (4, 5). So mDpy-30 might regulate cell movement by adjusting the membrane levels or surface distribution of key migratory molecules.

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