ENDOCYTOSIS

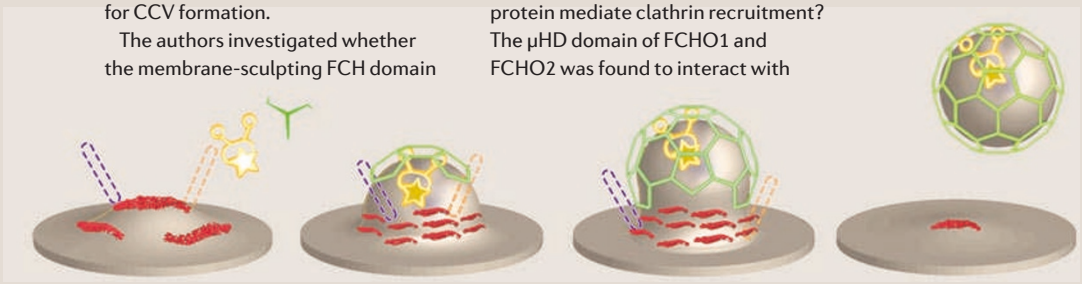
Curvature proteins direct traffic

The internalization of molecules by clathrin-mediated endocytosis is crucial for several cellular processes. Clathrin-coated vesicles (CCVs) are proposed to assemble through the binding of adaptor protein complex 2 (AP2) and the coat protein clathrin to cargo proteins destined for internalization, but it has been unclear how the site of CCV formation is determined. In a study published in *Science*, Henne *et al.* provide evidence that a family of proteins that coordinate membrane curvature is responsible for marking the initial sites of internalization and recruiting the endocytic machinery for CCV formation.

The authors investigated whether the membrane-sculpting FCH domain only protein 1 (FCHO1) and FCHO2 participate in the early stages of CCV invagination. Cryo-immunoelectron microscopy and live-cell imaging showed that FCHO1 and FCHO2 localize to clathrin-coated pits (CCPs) and that their recruitment precedes that of AP2 and clathrin, suggesting that these proteins define the localization of CCPs and act as CCP nucleators. In support of this, overexpression or knockdown of FCHO1 and FCHO2 altered the nucleation rate of CCPs, as determined by the number of new CCPs per unit area per second.

How does a membrane-sculpting protein mediate clathrin recruitment? The μHD domain of FCHO1 and FCHO2 was found to interact with two components of the vesicular trafficking machinery, epidermal growth factor receptor substrate 15 (EPS15) and intersectin 1, which led to the recruitment of AP2 and clathrin to initiate CCP maturation. FCHO proteins also contain an F-BAR-x domain that recognizes, and contributes to, curvature of the membrane. Mutating FCHO2 in this region resulted in delayed and aberrant CCP formation, and these mutants were unable to rescue CCP formation following RNA interference of FCHO1 and FCHO2.

Together, these results reveal a new piece of the CCP assembly puzzle and suggest a model in which the membrane-sculpting properties of FCHO proteins, in addition to their interactions with CCP accessory proteins, are essential for directing CCP formation and maturation.



FCH domain only protein 1 (FCHO1) and FCHO2 (red) are recruited to sites of clathrin-coated vesicle budding, and define where clathrin (green) and the adaptor protein complex 2 (yellow) will associate and vesicles will bud. Image courtesy of H. McMahon, MRC Laboratory of Molecular Biology, Cambridge, UK.

Mhairi Skinner, Consulting Editor, NCI–Nature Pathway Interaction Database

ORIGINAL RESEARCH PAPER Henne, W. M. *et al.* FCHo proteins are nucleators of clathrin-mediated endocytosis. *Science* **328**, 1281–1284 (2010)
FURTHER READING Traub, L. M. Tickets to ride: selecting cargo for clathrin-regulated internalization. *Nature Rev. Mol. Cell Biol.* **10**, 583–596 (2009)