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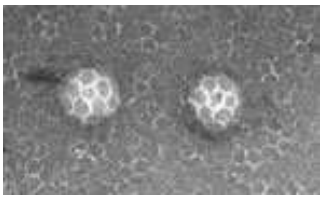
The bubble's bend

Vivienne Baillie Gerritsen

Bubbles are not reserved to the likes of champagne or beer. Our cells also sprout bubbles – or vesicles. Vesicles are formed by means of two cellular processes: exocytosis and endocytosis. The point of such bubbles in living organisms is to relieve the plasma membrane of a number of constituents. Be it to down regulate a pathway – by removing a given receptor from the plasma membrane for example – or to transport molecules from one side of a cell to another. One species of vesicle – the clathrin-coated vesicles – are particularly important in vesicle trafficking in endocytosis and in exocytosis. And in the process of endocytosis, one protein – epsin – has a major role in the initial steps of membrane budding.

A horde of proteins are involved in clathrin-mediated endocytosis: receptors, accessory factors, the clathrin adaptor protein AP2 and clathrin. In the process of endocytosis, patches are observed on the surface of the cell's membrane. Such patches form when specific molecules cluster. Clathrin is one such molecule. Clathrin molecules form a spherical scaffolding and accompany the membrane as it moves inwards, thus forming a spherical shell: the clathrin-coated vesicle. Epsin acts as cement by binding not only to clathrin – and in doing so promoting its assembly – but also to the plasma membrane. Yet this is not epsin's major asset.



Clathrin-mediated vesicle formation.

Courtesy of Harvey McMahon
MRC Laboratory of Molecular Biology

Epsin – an accessory factor – was discovered in 1988 by virtue of its binding to a second accessory factor: Eps15. As a result, it became the 'Eps15 interacting protein', or epsin for short. The N-terminal domain – known as the ENTH domain (from epsin NH2 terminal homology domain) – is a neat, compact bundle of alpha helices, one of which changes its orientation depending on whether epsin is bound to its ligand or not. The C-terminal portion of epsin binds to Eps15, its central portion binds both to clathrin adaptor protein AP2 and clathrin itself, and the ENTH domain binds to phosphatidyl inositols, with a clear preference for phosphatidylinositol-4,5-bisposphates or PtdIns(4,5)P_2. And this is the ligand upon which epsin will act to initiate cell budding.

We have all had fun stretching part of the torn rubber remnants of a balloon between our thumbs to suck out a mini-balloon. Such playful invagination is very much what happens in the process of cell endocytosis. By sucking a bubble out of the rubber, we were applying stress to make it bend and curve into a small sphere. Cell endocytosis puts bending stress on the plasma membrane and rearranges its underlying structure – first to form a budding vesicle and then to form the vesicle in its entirety. In the formation of clathrin-coated vesicles, epsin rearranges the underlying structure of the plasma membrane so that it curves spontaneously. How?

When epsin spots a patch of PtdIns(4,5)P_2 within a lipid layer, it inserts part of its N-terminal ENTH domain into the plasma membrane, by way of a short alpha helix with a particularity. Indeed, epsin is a soluble protein yet it presents hydrophobic residues on its outer

surface. When this amphipathic helix encounters a membrane enriched in PtdIns(4,5)P_2, it folds back onto the other neatly bundled helices and forms a pocket into which the PtdIns(4,5)P_2 head can fit. Such movement disrupts the organisation of the lipid layer causing it to adopt a different arrangement. The effect is not dissimilar to that caused by a large man who – despite a tight squeeze – decides to seat himself on an already crowded bench, making all the others shift a little on either side of him for comfort. This shift in location causes the membrane to curve as the lipids rearrange in the membrane. Why? Epsin insertion into the lipid layer creates chemical asymmetry in the plasma membrane as a whole, i.e. a difference arises between the interfacial tension and the internal surface pressure of the membrane, the result of which is the curving of the membrane.

So epsin not only stimulates clathrin assembly and serves as an initial scaffolding onto which the clathrin cage could grow, but it also causes the membrane to camber, thanks to its ENTH domain. The popularity of the ENTH domain is growing fast. As research progresses, this specific domain is showing signs of recruiting and bridging vesicle coat components other than clathrin, and could well have a role not only in forming the container in which cargo is transported but also in transporting the cargo itself.

Cross-references to Swiss-Prot

Epsin 1, *Homo sapiens* (Human) : Q9Y6I3
Epsin 1, *Rattus norvegicus* (Rat) : O88339

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