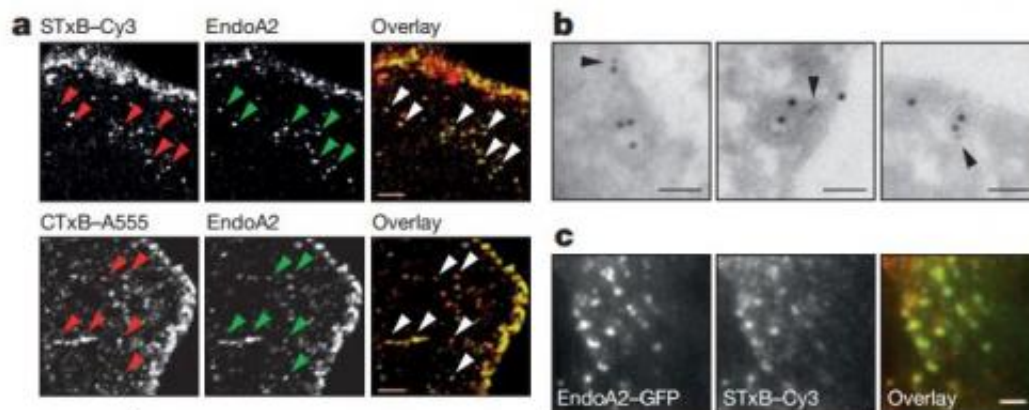


# Studies show a pathway for imported proteins through cell membrane that can be hijacked by toxins

December 18 2014, by Bob Yirka



EndoA2 localization to endocytic pathways. Credit: *Nature* (2014)  
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(Phys.org)—Two teams of researchers have been looking into the ways that toxins can fool cell membranes into gaining access, thereby allowing for human ailments such as cholera. One team describes a pathway that is independent of the clathrin protein while the second team shows that such a pathway can be hijacked by toxins such as the bacteria responsible for cholera. Both teams have published their findings in the journal *Nature*.

One of the ways our bodies try to keep us healthy is by maintaining a

[plasma membrane](#) around every one of our cells—the membrane's job is to keep out [harmful substances](#) while allowing those that are beneficial to pass through—no easy feat. One of the ways the membrane does this job is through a protein called clathrin—the process by which it does so, under normal conditions, is called clathrin-mediated endocytosis (CME). In this new effort, one team has found that there is a clathrin independent process whereby proteins are allowed to enter cells—they've named it fast endophilin-mediated endocytosis (FEME), while the other team has found that some bacteria are able to take advantage of this process to create channels to get inside cells and cause problems.

FEME, the first team found, appears to be triggered by membrane-bound receptor proteins or by [bacterial toxins](#). The molecules in the protein appear to be converted to a form that is able to attract the endophilin protein which causes the membrane to invaginate into tubules which eventually form into vesicles containing proteins or worse toxins. The second team found that the process involves endophylin, dynamin and actin proteins, in ways that allow the channel to come into existence, suggesting that some bacteria may even drive the process.

These findings by the two teams suggest there are pathways into our cells that scientists still don't understand and also provide avenues for additional studies in a variety of ways—such as looking into how bacteria are able to recruit endophilin in either FEME or CME and whether there are substances that might prevent it from happening in the first, place, bolstering the [cell membrane](#) defenses that are trying to keep us healthy.

**More information:** Endophilin-A2 functions in membrane scission in clathrin-independent endocytosis, *Nature* (2014) [DOI: 10.1038/nature14064](#)

## Abstract

During endocytosis, energy is invested to narrow the necks of cargo-containing plasma membrane invaginations to radii at which the opposing segments spontaneously coalesce, thereby leading to the detachment by scission of endocytic uptake carriers. In the clathrin pathway, dynamin uses mechanical energy from GTP hydrolysis to this effect, assisted by the BIN/amphiphysin/Rvs (BAR) domain-containing protein endophilin. Clathrin-independent endocytic events are often less reliant on dynamin, and whether in these cases BAR domain proteins such as endophilin contribute to scission has remained unexplored. Here we show, in human and other mammalian cell lines, that endophilin-A2 (endoA2) specifically and functionally associates with very early uptake structures that are induced by the bacterial Shiga and cholera toxins, which are both clathrin-independent endocytic cargoes. In controlled in vitro systems, endoA2 reshapes membranes before scission.

Furthermore, we demonstrate that endoA2, dynamin and actin contribute in parallel to the scission of Shiga-toxin-induced tubules. Our results establish a novel function of endoA2 in clathrin-independent endocytosis. They document that distinct scission factors operate in an additive manner, and predict that specificity within a given uptake process arises from defined combinations of universal modules. Our findings highlight a previously unnoticed link between membrane scaffolding by endoA2 and pulling-force-driven dynamic scission.

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