Axopodial spikes (left) owe their shape to an array of microtubules (right).

Soon after microtubules were first described by electron microscopy, several investigators began suggesting that they were structural elements (Byers and Porter, 1964) because they were localized to sites where cells were changing their shape. In 1967, Lewis Tilney and Keith Porter, then at Harvard University, provided direct experimental evidence that microtubule polymerization was important for the development and maintenance of cell shape.

Earlier work by Inoué (1952) had shown that when cells are exposed to cold temperatures the mitotic spindle—later shown to be composed of microtubules—disappears. Working with the protozoan Actinosphaerium nucleofilum, which has needle-like extensions (axopodia) consisting of a well-defined system of microtubules, Tilney and Porter reasoned that “if the microtubules are instrumental in the maintenance of these slender protoplasmic extensions, then low temperature, which, as previously stated, should cause the breakdown of the microtubules, ought secondarily to cause retraction of the axopodia.”

Their results supported this hypothesis. Cold treatment of A. nucleofilum cells caused the microtubules to disassemble and the axopodia to withdraw; after returning the cells to room temperature for a few minutes, the microtubules started to reassemble and the axopodia reformed (Tilney and Porter, 1967). The authors concluded that “microtubules are intimately involved not only with the maintenance of the axopodia but also with their growth.” Experiments performed at about the same time showed that treatment of A. nucleofilum cells with agents that cause microtubule depolymerization—mainly, hydrostatic pressure and colchicine treatment—gave similar results (Tilney et al., 1966; Tilney, 1968). Importantly, later work by Tilney and Gibbins (1969) established that microtubules also help change cell structure in higher organisms. The authors treated embryos of the purple sea urchin Arbacia punctulata with colchicine and hydrostatic pressure at different stages of development. Disassembly of the microtubules with these treatments prevented the characteristic cell shape changes in, and thus differentiation of, the mesenchyme of the developing embryo. LB

Since the small vesicles, which Farquhar refers to as “Golgi vesicles,” carry lytic enzymes, the authors concluded

How to make a lysosome

Coated vesicles had been described as early as 1961. These small membranous structures were characterized by a highly organized layer of material on the cytoplasmic surface, “but no one knew their function,” says Marilyn Farquhar, whose lab at the time had become interested in how the Golgi complex helped produce enzymes.

Roth and Porter (1964) had provided evidence that coated vesicles have specialized functions in the cellular uptake of proteins. But for Friend and Farquhar (1967), the simple idea of uptake was not enough. They helped cement the idea that cellular trafficking involved an intersecting set of cellular highways.

They demonstrated that cells contain different types of coated vesicles, and that these vesicles are not only involved in protein uptake but also in the transport of lysosomal enzymes. The two pathways converged in multivesicular bodies (now known as endosomes), explaining how proteins could be endocytosed and then processed by cellular enzymes. The processing, we now know, takes places only after endosomes have either matured into or sent vesicles to lysosomes.

The 1967 paper “was quite unique for its time,” says Farquhar, because the group used three labels: soluble horseradish peroxidase as a tracer for protein uptake; thiamine pyrophosphatase as a Golgi marker; and acid phosphatase as a lysosomal enzyme marker. Using this method her group was able to distinguish among different types of vesicles and follow their direction of movement during protein uptake.

One type of coated vesicle, which was larger in diameter, formed at the cell surface by pinocytic invagination of the apical cell membrane. It moved toward and fused with multivesicular bodies, thereby serving to transport endocytosed protein inside the cell. The other type of coated vesicle, smaller in size, seemed to originate from the Golgi cisternae and serve, at least in part, to transport the enzyme acid phosphatase and possibly other acid hydrolases from their site of packaging in the Golgi to multivesicular bodies, thus uniting the endocytosed and lytic proteins.

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