


Journal club

SEEING IS BELIEVING

Developments in light microscopy, in particular in confocal fluorescence microscopy, have contributed tremendously to our understanding of intracellular membrane trafficking (notably endocytosis) during the past two decades. However, many key discoveries in cell biology would not have been possible without the ultra-high resolution of the transmission electron microscope. One famous example is the identification of the multivesicular body (MVB), which is now known to be a maturing endosome, and the recognition of its role in the transport of endocytosed membrane proteins to the lysosome for degradation.

Stanley Cohen and co-workers were intrigued by biochemical and fluorescence microscopy



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experiments that indicated that the binding of epidermal growth factor (EGF) to its receptor induced the internalization and lysosomal degradation of the receptor–ligand complex. To follow the pathway taken by EGF and its receptor in closer detail the authors conjugated EGF to ferritin — an iron-containing protein that is sufficiently large and electron-dense to be detected by a transmission electron microscope — and took electron micrographs of cells at various times after EGF-stimulated receptor internalization. They observed beautiful labelling of ferritin–EGF, initially at the plasma membrane and then in endocytic vesicles shortly after internalization. At later time points the conjugate was found in MVBs, but — here came the surprise — instead of being localized to the limiting membrane, ferritin–EGF was mainly associated with small vesicles inside MVBs called intraluminal vesicles.

It is now well established that the packaging of EGF receptors and many other membrane proteins into intraluminal vesicles makes them easier for the lysosome to digest, and this essential protein-sorting pathway has been further scrutinized by many researchers using sophisticated models. However, we must not forget how much our present understanding of the MVB pathway owes to early ultrastructural studies. As electron microscopists might say: a picture is worth a thousand words.

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ORIGINAL RESEARCH PAPER Haigler, H. T. et al. Direct visualization of the binding and internalization of a ferritin conjugate of epidermal growth factor in human carcinoma cells A-431. *J. Cell Biol.* **81**, 382–395 (1979)