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Review

Endocytosis and signalling: A meeting with mathematics

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ABSTRACT

Although endocytosis has traditionally been understood as a signal attenuation mechanism, an emerging view considers endocytosis as an integral part of signal propagation and processing. On the short time scale, trafficking of endocytic vesicles contributes to signal propagation from the surface to distant targets, with bi-directional communication between signalling and trafficking. Mathematical modelling helps combine the mechanistic, molecular knowledge with rigorous analysis of the complex output dynamics of endocytosis in time and space. Simulations reveal novel roles for endocytosis, including the control of cell polarity, enhancing the spatial signal propagation, and controlling the signal magnitudes, kinetics, and synchronization with stimulus dynamics.

1. Introduction

Endocytosis is a main process by which cells transport extracellular and plasma membrane bound entities into the cell interior. Although there are many intricate endocytic mechanisms (Bareford and Swaan, 2007; Benmerah and Lamaze, 2007; Jones, 2007; Rizzoli and Jahn, 2007), the formation of endocytic vesicles can be illustrated in terms of two simple component processes (Figure 1). First, a part of the plasma membrane invaginates, and, second, it pinches off. The internalized endocytic vesicle, now within the cell and separate from the cell membrane, has in its lumen what was previously extracellular material, and has on its cytosolic surface what was previously cell membrane bound and cytosolic. After internalization, cellular trafficking machinery transports the vesicle and its cargo to the appropriate cellular locations through a network of specialized organelles, including early endosomes, recycling endosomes, late endosomes, multivesicular bodies, and lysosomes (Hicke and Dunn, 2003; Sorkin and Goh, 2009; Williams and Urbe, 2007).

While the central importance of endocytosis in cell biology cannot be understated, of particular interest in this review is the role of endocytosis in signal transduction. Traditionally, endocytosis was regarded as a simple signal attenuation mechanism, as it removes signals from the extracellular space and receptors from the cell surface. These processes not only terminate signalling, but also desensitize the cell and prepare it for subsequent signals. Numerous recent studies, however, have brought about a more complex view: endocytosis and trafficking play a central role in signal propagation and specificity by regulating both the dynamics and localization of signalling (Di Fiore and De Camilli, 2001; Kholodenko, 2002; Polo and Di Fiore, 2006; Sorkin and Von Zastrow, 2002; von Zastrow and Sorkin, 2007; Disanza et al., 2009). For example, the small G-protein Ras, whose constitutive activation drives a number of human malignancies, can be activated by receptor tyrosine kinases

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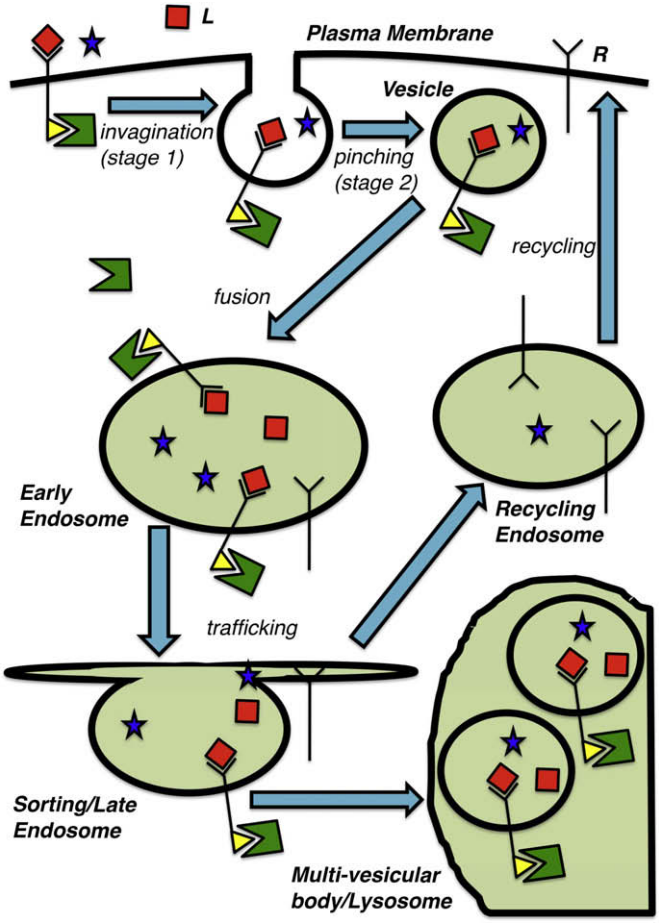

Figure 1 – A general, simlified scheme of endocytic and trafficking processes. A small area of the plasma membrane invaginates (stage 1), and then it is pinched off into a vesicle (stage 2). The vesicle lumen contains previously extracellular material (including ligands *L* (shown by red) bound to the receptor (*R*) extracellular domains), while the vesicle surface that faces the cytoplasm contains the material, previously exposed into cytosol (including the cytoplasmic receptor tails (shown by yellow) with bound adaptor or target proteins (shown by green)). The internalized vesicle fuses with larger, early endosomes. The internalized material is then trafficked to tubulovesicular sorting endosomes. From here, material can either be taken to recycling endosomes and thus back to the cell surface, or be re-internalized, creating a multi-vesicular body destined for lysosomal degradation.

not only at the cell membrane, but also on the membranes of various endosomal structures (Haugh et al., 1999a; Jiang and Sorkin, 2002; Li et al., 2005). In some cases, such as vascular endothelial growth factor (VEGF)-induced extracellular regulated kinase (ERK) activation, full signal propagation depends upon endocytosis (Lampugnani et al., 2006). In fact, for some signals that emanate at the cell surface, endocytosis may be the only way to reach distant cellular locations, such as the nucleus. Indeed, signal deactivation during diffusion in the cytoplasm can cause precipitous signalling gradients and very low signal magnitudes near the target (Brown and Kholodenko, 1999; Kholodenko, 2003). Such gradients of protein active forms have been observed for the small GTPase Ran (Kalab et al., 2002), phosphorylated stathmin oncoprotein 18 (Niethammer et al., 2004), and the yeast MAPK Fus3 (Maeder et al., 2007). Endosomal trafficking is even more crucial for signal propagation over distances greater than ~10–100 μm, when diffusion is unsatisfactorily slow. Such situations arise in signal propagation from the plasma membrane to the nucleus in large cells, e.g., *Xenopus* oocytes (~1 mm), or in transport of nerve growth factor (NGF) survival signals from distal axon terminals to the soma (1 cm–1 m). For the long distance transport, molecular motor driven trafficking of endosomes or protein complexes not only accelerates signal propagation relative to diffusion, but association of signals with specific proteins can also help protect signals from deactivation (Howe and Mobley, 2004; Perlson et al., 2005, 2006). In terms of localization, some MAPK cascade scaffolds are preferentially localized to either plasma or endosomal membranes, which could lead to different signalling outcomes depending on where the signal originates (Hancock, 2003; Kolch, 2005). Furthermore, the access to membrane bound substrates that are critical for signalling, such as phosphoinositols, can be regulated via endocytosis and trafficking (Haugh, 2002; Haugh et al., 1999b).

Not only does endocytosis control signalling, but signalling also regulates endocytosis, acting in a bi-directional manner (von Zastrow and Sorkin, 2007; Pyrzynska et al., 2009). The classical epidermal growth factor (EGF) receptor signalling system, for example, regulates endocytosis in several ways. First, EGF binding to its receptor (EGFR) causes a rapid increase