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Fast and ultrafast endocytosis

Shigeki Watanabe[1,2] and Emmanuel Boucrot[3,4]

Clathrin-mediated endocytosis (CME) is the main endocytic pathway supporting housekeeping functions in cells. However, CME may be too slow to internalize proteins from the cell surface during certain physiological processes such as reaction to stress hormones ('fight-or-flight' reaction), chemotaxis or compensatory endocytosis following exocytosis of synaptic vesicles or hormone-containing vesicles. These processes take place on a millisecond to second timescale and thus require very rapid cellular reaction to prevent overstimulation or exhaustion of the response. There are several fast endocytic processes identified so far: macropinocytosis, activity-dependent bulk endocytosis (ABDE), fast-endophilin-mediated endocytosis (FEME), kiss-and-run and ultrafast endocytosis. All are clathrin-independent and are not constitutively active but may use different molecular mechanisms to rapidly remove receptors and proteins from the cell surface. Here, we review our current understanding of fast and ultrafast endocytosis, their functions, and molecular mechanisms.

Addresses
[1] Department of Cell Biology, John Hopkins University School of Medicine, 725 N. Wolfe Street, Baltimore, MD21205, USA
[2] Solomon H. Snyder Department of Neuroscience, John Hopkins University School of Medicine, 725 N. Wolfe Street, Baltimore, MD21205, USA
[3] Institute of Structural and Molecular Biology, Division of Biosciences, University College London, London WC1E 6BT, UK
[4] Institute of Structural and Molecular Biology, Department of Biological Sciences, Birkbeck College, London WC1E 7HX, UK

Corresponding authors: Watanabe, Shigeki (shigeki.watanabe@jhmi.edu), Boucrot, Emmanuel (e.boucrot@ucl.ac.uk)

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Introduction

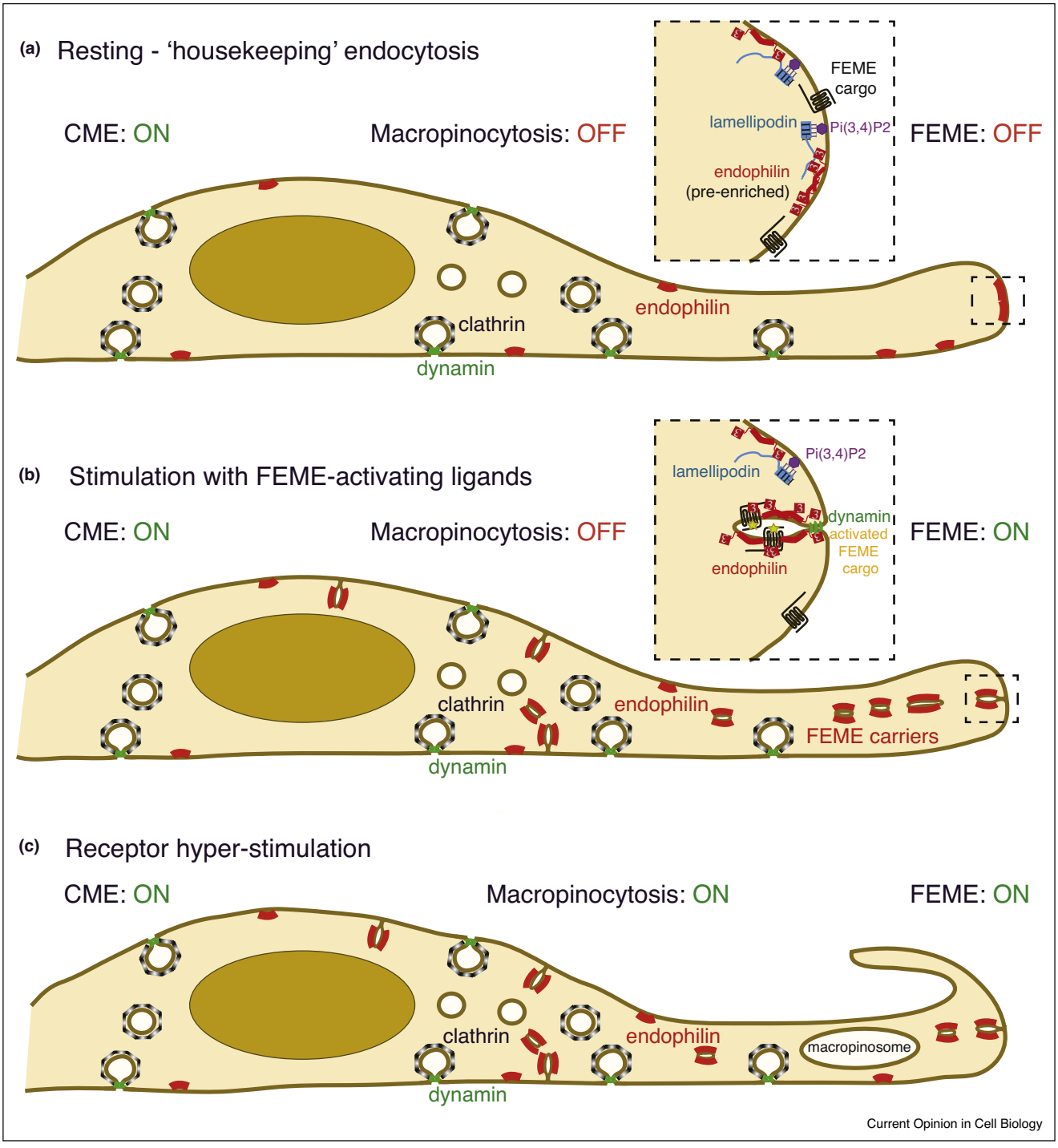
Endocytosis is essential for all eukaryotic cells to internalize macromolecules and proteins such as receptors, channels and transporters from plasma membrane. Endocytosis controls the levels of receptors at the cell surface and thereby regulates their signaling [1]. It also mediates synaptic vesicle recycling to support the rapid recovery of vesicle pools following synaptic transmission [2•,3]. Internalized receptors (also referred to as endocytic 'cargoes') are sorted in endosomes for recycling back to the plasma membrane to sustain signaling or for degradation in lysosomes to induce long-term desensitization of the cell [4,5]. Many viruses and bacterial toxins exploit endocytosis to gain access into eukaryotic cells and infect or poison cells [6,7]. There are several pathways of endocytosis, defined by their distinct morphological features or by their requirement of key cytosolic components. Clathrin-mediated endocytosis (hereafter, CME) is the best characterized endocytic pathway and supports the uptake of a wide range of cell surface proteins [1,8]. In CME, cargo receptors are sorted by adaptor proteins that bridge them to clathrin triskelia. Clathrin then polymerizes into 'soccer ball' looking coats during the formation of endocytic pits [8]. All other endocytic pathways are referred to as clathrin-independent endocytosis (CIE) [1,9•]. Each CIE pathway is typically named after its morphology (coat-less invaginations emanating from the plasma membrane), cytosolic proteins markers or cargoes (such as viruses, IL2Rβ, MHC class I, CD44 or Shiga toxin [10–15]). However, some CIE do not appear to have specific cargoes or markers and can only be identified by morphology (macropinocytosis).

Compared to CME, our understanding of CIE is lagged likely because (i) these pathways are typically not constitutive and only activated upon specific stimuli, (ii) molecular players may not be specific to the CIE pathways and (iii) some CIE events might be too fast to be recorded by classical methods used to study endocytosis. This review focuses on recent advances revealing fast and ultrafast clathrin-independent endocytosis occurring upon activation of discrete receptors and at synapses.

The need for fast endocytosis

Clathrin-mediated endocytosis is the dominant endocytic route to support housekeeping functions in cells (Figure 1a) [8,16•]. However, some physiological processes require very rapid and scalable cellular response and need to be swiftly controlled to prevent exhaustion of the response. These processes include reaction to stress hormones ('fight-or-flight' reaction), membrane flux during directed cell migration (chemotaxis) or compensatory endocytosis following exocytosis of synaptic vesicles or hormone-containing vesicles. Additionally, signaling arising from some receptors needs to be tightly regulated to avoid overstimulation. For example, epidermal growth factor receptor (EGFR) is internalized almost exclusively

Figure 1



Fast endocytic mechanisms in non-neuronal cells. **(a)** Clathrin-mediated endocytosis is active ('CME: ON') and the main endocytic pathway functioning in resting, non-stimulated cells. Endocytosis by CME in resting cells support many housekeeping functions. Fast endophilin-mediated endocytosis is non active ('FEME: OFF') but endophilin is pre-enriched on specific zones of the plasma membrane. **(b)** Activation of several receptors (including β1-adrenergic receptor, EGFR and IL-2R) by their cognate ligands activate FEME and induce their rapid uptake ('FEME: ON'). CME is active in such cells. **(c)** Hyper-stimulation of cells with many receptors, including EGFR, trigger macropinocytosis and the rapid uptake of large portions of the plasma membrane and indiscriminate internalization of receptors ('Macropinocytosis: ON'). CME is still active in such cells. FEME might be active if the receptors activated also stimulate it.