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REVIEW

Endocytosis in proliferating, quiescent and terminally differentiated cells

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ABSTRACT

Endocytosis mediates nutrient uptake, receptor internalization and the regulation of cell signaling. It is also hijacked by many bacteria, viruses and toxins to mediate their cellular entry. Several endocytic routes exist in parallel, fulfilling different functions. Most studies on endocytosis have used transformed cells in culture. However, as the majority of cells in an adult body have exited the cell cycle, our understanding is biased towards proliferating cells. Here, we review the evidence for the different pathways of endocytosis not only in dividing, but also in quiescent, senescent and terminally differentiated cells. During mitosis, residual endocytosis is dedicated to the internalization of caveolae and specific receptors. In non-dividing cells, clathrin-mediated endocytosis (CME) functions, but the activity of alternative processes, such as caveolae, macropinocytosis and clathrin-independent routes, vary widely depending on cell types and functions. Endocytosis supports the quiescent state by either upregulating cell cycle arrest pathways or downregulating mitogen-induced signaling, thereby inhibiting cell proliferation. Endocytosis in terminally differentiated cells, such as skeletal muscles, adipocytes, kidney podocytes and neurons, supports tissue-specific functions. Finally, uptake is downregulated in senescent cells, making them insensitive to proliferative stimuli by growth factors. Future studies should reveal the molecular basis for the differences in activities between the different cell states.

KEY WORDS: Endocytosis, Clathrin-mediated endocytosis, Clathrin-independent endocytosis, Cell cycle, Mitosis, Quiescence, Terminally differentiated cells, Senescence

Introduction

Endocytosis is a ubiquitous cellular process that is essential for growth and survival. Extracellular macromolecules cannot be transported across the plasma membrane and must bind instead to cell surface transmembrane receptors and be internalized through endocytosis. Several parallel endocytic pathways (Box 1) mediate the uptake of nutrients and control cell surface receptor levels, plasma membrane turnover and cellular signaling, and are required for cell spreading, polarization and migration (Barbieri et al., 2016). Because of their importance and evolutionary conservation, endocytic pathways are hijacked by many pathogens (Gruenberg and Van Der Goot, 2006). Furthermore, mutations resulting in mis-regulated endocytosis cause diseases, such as cancer, neurodegeneration, atherosclerosis and lysosomal storage diseases (Doherty and McMahon, 2009; McMahon and Boucrot, 2011).

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During endocytosis, the folding of the plasma membrane generates membrane invaginations of various sizes and shapes, which contain the cargo to be internalized. Nascent vesicles are subsequently detached from the plasma membrane and traffic to their intracellular destinations. To date, there is evidence of three fundamental mechanisms generating endocytic carriers: (1) binding of cargo and localized membrane bending mediated by cytosolic adaptor proteins, (2) membrane bending induced by clustering of extracellular lipid or cargo [the so-called glycolipid-lectin (GL-Lect) hypothesis (reviewed in Johannes et al., 2016)], and (3) acute signal-induced membrane protrusions pushing outwards from the cell and folding back onto themselves (reviewed in Ferreira and Boucrot, 2018). The multiplicity of endocytic pathways is consistent with the myriad of cellular processes they serve. Throughout the cell cycle, cells grow and need nutrients to synthesize proteins, DNA and lipids, to undergo membrane remodeling during mitosis, and to leave the cell cycle and stop dividing to perform specialized functions (Box 2). There are ∼200 different cell types in an adult human body, each with specific needs linked to their physiological roles (Bianconi et al., 2013). Signaling mechanisms underlie biological functions and many are regulated by endocytosis, which connects the cell with its environment. In this Review, we survey the evidence for the occurence of endocytic pathways in dividing cells as well as in non-dividing cells, such as in quiescent, terminally differentiated and senescent cells. Clathrin-mediated endocytosis (CME) has been reported to be active in all cellular states, although at different levels of efficacy, and to mediate the uptake of different cargos. The study of clathrin-independent pathways in non-proliferating cells has been lagging behind that of CME, and thus it is not clear whether they function in every cell state.

Endocytosis in dividing cells

The vast majority of our understanding of endocytosis comes from studies on proliferating cell lines. During exponential growth *in vitro*, cells continuously progress through the cell cycle and divide every 15 to 30 h, depending on the cell type. Analyses have been almost exclusively focused on cells during interphase (which constitutes over 98% of the cells in proliferating cultures; see also Box 2). Thus, it is widely assumed that endocytosis rates are similar during G1, S and G2, even though there is evidence of differences in uptake for some cargos, depending on the cellular context (Snijder et al., 2009). For instance, cholera and Shiga toxins only enter cells during G1 and G2, respectively. This is because their cellular receptors, the glycosphingolipids monosialotetrahexosylganglioside (GM1) and globotriaosylceramide (Gb3), are only expressed at sufficiently high levels during these cell cycle phases (Majoul et al., 2002). Moreover, although CME is constitutively active (Bitsikas et al., 2014) at any given time, the activity of other pathways, such as macropinocytosis, clathrin-independent carrier/GPI-anchored proteins-enriched carriers (CLIC/GEEC) or fast endophilin-mediated endocytosis (FEME) (Box 1), varies depending on the cellular state. Indeed, cell migration,

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Box 1. Brief overview of the main endocytic pathways

Endocytic pathways are differentiated by the shape, size and kinetics of the carriers produced, the cargos internalized and the cytosolic proteins marking and regulating them. CME is constitutively active and is the best characterized process (Kaksonen and Roux, 2018). Many receptors, including transferrin receptor (TfR), mostly rely on CME to enter cells. Clathrin chains assemble into triskelia that, once recruited by AP2 or other adaptors, polymerize into a proteinaceous coat around the nascent vesicles. The GTPase dynamin then severs the neck of budding clathrin-coated pits (Kaksonen and Roux, 2018). Several CIE processes exist in parallel to CME and mediate the uptake of cargos that do not use CME selectively. These cargos include CD44, CD147, major histocompatibility (MHC) class I, interleukin-2 receptor (IL2R) and β1-adrenergic receptor or glycosylphosphatidylinositol (GPI)-anchored proteins, such as CD55, CD59 and CD90 (also called Thy-1) (Maldonado-Báez et al., 2013). They also regulate specific processes, such as the fast removal of cell surface receptors, and the response to receptor hyper-stimulation or stress hormones (the 'fight or flight' response) (Johannes et al., 2015; Ferreira and Boucrot, 2018). CIE processes include the CLIC/GEEC pathway, which generates endocytic carriers using the BAR domain proteins GRAF1, Irsp53 and PICK1, as well as local actin polymerization that is mediated by Arf1, its exchange factor GBF1 and Cdc42, but not dynamin (reviewed in Lundmark et al., 2008; Hinze and Boucrot, 2018). Initial membrane curvature in some CIE events is mediated by a mechanism termed the 'glycolipid-lectin (GL-Lect) hypothesis', whereby the clustering of extracellular cargo proteins or lipids mediated by galectin-3 or Shiga and cholera toxins drives an inwards-directed buckling of the membrane (reviewed in Johannes et al., 2016). FEME is not constitutive, but leads to a prompt formation of tubulo-vesicular endocytic carriers following the activation of several receptors by their cognate ligands (reviewed in Watanabe and Boucrot, 2017; Ferreira and Boucrot, 2018). Ultrafast endocytosis at the synapse shares features with FEME in that it also relies on dynamin, endophilin, actin and synaptojanin, but is at least one order of magnitude faster (reviewed in Gan and Watanabe, 2018; Watanabe and Boucrot, 2017). Following intense stimulations, macropinocytosis and ADBE in neurons lead to the formation of large (≥0.5 µm) carriers that take up substantial amounts of extracellular material and plasma membrane (Cousin, 2017; Mercer and Helenius, 2012). Finally, caveolae are cholesterol-rich membrane domains on the plasma membrane that invaginate and pinch off upon clustering of caveolin and cavin proteins (Parton et al., 2018).

Box 2. Cell cycle exit

Proliferating cells progress through interphase (G1, S and G2) and divide during mitosis (Harashima et al., 2013), which is divided in five successive steps: prophase, metaphase, anaphase, telophase and cytokinesis. Because of different lengths of time spent by mammalian cells at each stage, an asynchronous population has typically >98% of cells in interphase (~40–50% of cells in G1, ~20–30% in S and ~10–20% in G2) and 0.5–2% of cells undergoing mitosis (Cameron and Greulich, 1963; Hahn et al., 2009). Continuous proliferation is not physiologically sustainable, and most cells in an adult multicellular organism exit the cell cycle temporarily (quiescence) or irreversibly (terminal differentiation and senescence).

Cellular quiescence (also called G0) is the reversible exit from the cell cycle that is induced upon contact inhibition, mitogen withdrawal or cell isolation in suspension (Coller et al., 2006). Quiescent cells are resistant to differentiation and show increased survival (Coller et al., 2006; Cheung and Rando, 2013; Legesses-Miller et al., 2012). Cell cycle exit is regulated by retinoblastoma proteins (Rb), which repress E2F-mediated transcription of cell cycle-progressing genes (Frolov and Dyson, 2004). Quiescent cells display reduced Akt (Segrelles et al., 2014; Wei et al., 2016) and increased PTEN phosphatase activity (Yue et al., 2017), which, in turn, suppress mTOR signaling (Gan and DePinho, 2009). Low mTOR activity protects quiescent cells from senescence and mediates the recycling of proteins and damaged organelles by autophagy, which is essential for long-term survival (García-Prat et al., 2016; Ho et al., 2017). Cell cycle-inhibiting genes, including p21 (CDKN1A), p27 (CDKN1B) and p53, are elevated in G0 cells (Coller et al., 2006; Itahana et al., 2002; Liu et al., 2007; Liu et al., 2009), whereas senescence-inducing p16 (CDKN2A) is suppressed (Leontieva et al., 2010; Sousa-Victor et al., 2014).

Cellular senescence is a growth arrest mechanism that exists to prevent the replication of old or damaged cells (Muñoz-Espín and Serrano, 2014). Irreversible DNA damage, severe oxidative stress or telomere attrition induce senescence (Fumagalli et al., 2012), which is characterized by apoptosis resistance and hypo-responsiveness towards growth factors and other external stimuli (Matsuda et al., 1992; Seshadri and Campisi, 1990). Dependent on the trigger, senescence is either induced by the upregulation of the p53–$p21^{CIP1}$ axis or by the activation of the $p16^{Ink4a}$–Rb pathway (Campisi, 2005; von Muhlinen et al., 2018). In contrast to quiescent cells, which are also characterized by high p53 activity, senescent cells retain a high mTOR activity and cellular growth (Leontieva et al., 2010; Leontieva et al., 2011).

Finally, terminally differentiated cells, also called post-mitotic, are derived from pluripotent progenitors and are highly specialized cells that have permanently lost the capacity to replicate. There is no universal marker known for these cells, they are instead identified by markers that are specific to their differentiation lineage (Buttitta and Edgar, 2007).

cell surface receptor activation and intracellular signaling and changes in membrane tension all stimulate clathrin-independent endocytosis (CIE) (Lundmark et al., 2008; Boucrot et al., 2015; Holst et al., 2017).

The level of endocytosis during mitosis has been a topic of contention. The premise was that most cellular processes, other than microtubule spindle and cortical actin-driven cell rounding, cease during cell division. Indeed, transcription, translation and several other cellular functions slow down considerably during mitosis (Conrad, 1963; Fan and Penman, 1970; Gottesfeld and Forbes, 1997; Orthwein et al., 2014). Some membrane flows also decrease during mitosis; for example, the Golgi disassembles, thus blocking protein secretion (Lucocq and Warren, 1987; Wei and Seemann, 2009), and endosomal recycling is strongly decreased, particularly during metaphase (Boucrot and Kirchhausen, 2007; Sager et al., 1984; Tacheva-Grigorova et al., 2013; Warren et al., 1984).

Endocytosis of typical CME cargos, such as transferrin (Tf) or low-density lipoprotein (LDL), is strongly reduced during mitosis (Pypaert et al., 1987; Fielding et al., 2012; Boucrot and Kirchhausen, 2007; Tacheva-Grigorova et al., 2013). The proposed mechanism for the inhibition of CME is the unavailability of actin to overcome the elevated plasma membrane tension in mitotic cells as free G-actin is recruited into cortical actin (Kaur et al., 2014). However, G-actin availability is unlikely to be rate limiting, as robust actin polymerization can be triggered in mitotic cells (Moulding et al., 2007; Santos et al., 2013). Instead, the strong reduction of Tf uptake is due to the low abundance of its receptor TfR at the cell surface of mitotic cells (Fig. 1Ai), as it becomes trapped inside cells when endosomal recycling shuts down (Sager et al., 1984; Warren et al., 1984; Boucrot and Kirchhausen, 2007; Tacheva-Grigorova et al., 2013). Clathrin-coated pits and vesicles continue to form during mitosis with the same characteristics (lifetimes and maximum intensities reached by the core adaptor AP2), although at lower rates than during metaphase (Tacheva-Grigorova et al., 2013; Aguet et al., 2016) (Fig. 1B). This is consistent with the decrease in plasma membrane area during that phase of mitosis (Boucrot and Kirchhausen, 2007; Aguet et al., 2016). However, such endocytic activity is only preserved in unperturbed cells, whereas CME is inhibited upon the chemical synchronization that is commonly used to stall cells in metaphase (e.g. use of nocodazole, RO-3306 or S-Trityl-L-cysteine) (Fielding

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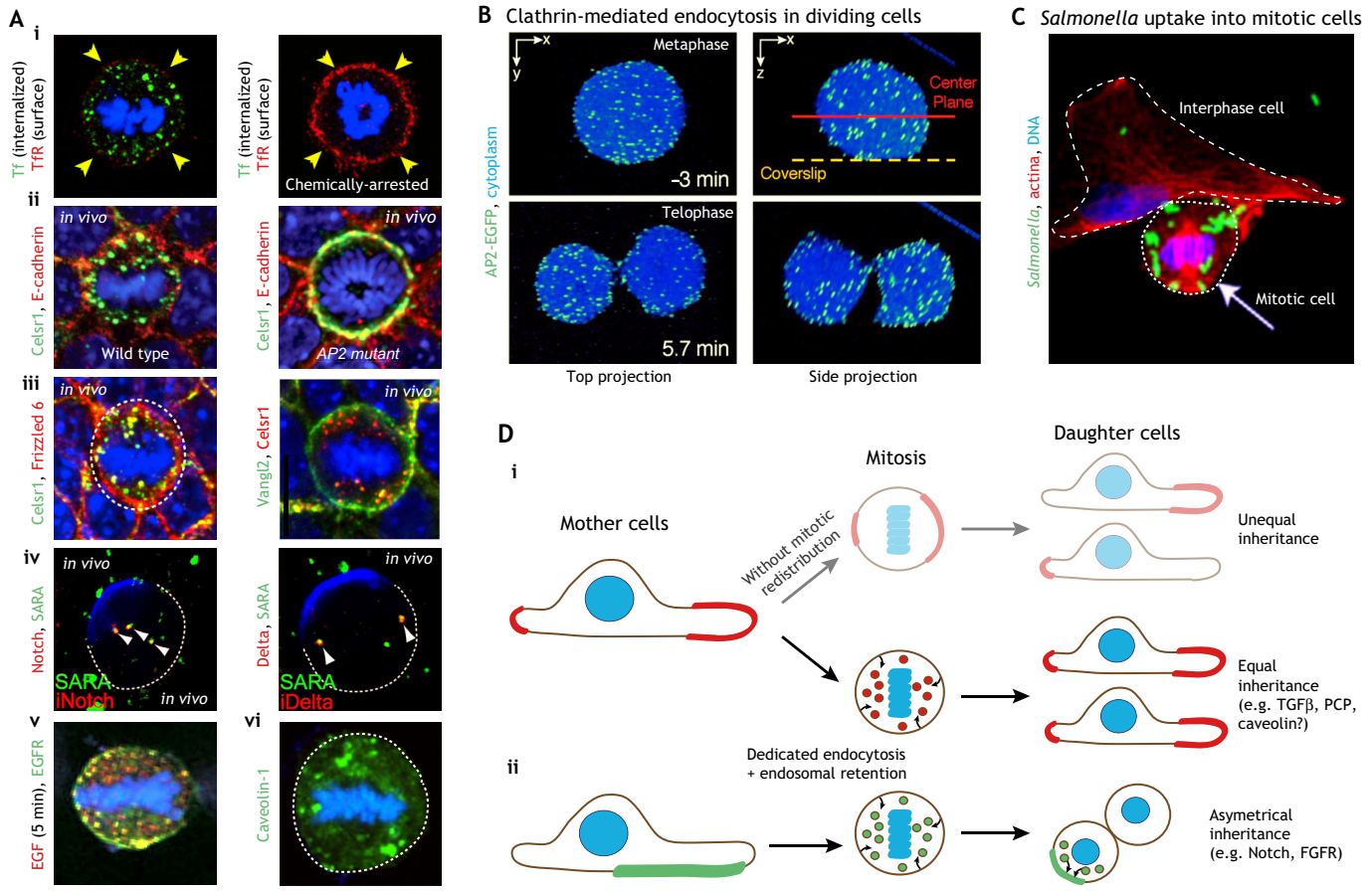

Fig. 1. Endocytosis in dividing cells. (A) Examples of endocytosis of endogenous cargos during mitosis. (i) Left, transferrin uptake (Tf, green) occurs in unperturbed mitotic BSC-1 cells, although at a much lower level than in interphase. This is because the amount of Tf receptor available at the cell surface (TfR, red) is strongly reduced because the receptor is trapped in endosomes (not labeled) of mitotic cells. Right, Transferrin uptake (green) is blocked in nocodazole-arrested metaphase BSC-1 cells (chemical synchronization is a common method to enrich mitotic cells), despite ample cell surface TfR (red). This is because chemical synchronization induces the disappearance of clathrin-coated pits. Arrowheads point to the plasma membrane. Modified from Tacheva-Grigorova et al. (2013), where it was published under a Creative Commons Attribution License (CC BY 3.0). (ii, iii) Planar cell polarity (PCP) pathway receptors Celsr1 (ii), Frizzled 6 (iii, left) and Vangl2 (iii, right) are actively endocytosed in mouse mitotic cells *in vivo*. A Celsr1 receptor bearing a mutation in its cytoplasmic tail (abrogating its interaction with AP2, '*AP2 mutant*') is not internalized (ii, right). Panel ii is modifed from Devenport et al., 2011 with permission from Springer Nature. Panel iii is modfied from Heck and Devenport, 2017 with permission from Elsevier. (iv) Notch (red, left) and its ligand Delta (red, right) (arrowheads) are both internalized in dividing fly stem cells *in vivo* and accumulate into endosomes (SARA, green). Modified from Coumailleau et al. (2009) with permission from Springer Nature. (v) Both EGF (red) and EGFR (green) are internalized in a clathrin-independent manner in mitotic COS-7 cells. Modified from Liu et al. (2011) with permission from Wiley. (vi) Most of the caveolin-1 is internalized in mitotic BSC-1 cells and accumulates into endosomes. Modified from Boucrot et al. (2011). (B) CME in dividing cells. Active clathrin-coated pits (labeled with gene-edited AP2–EGFP, green) can be seen over the surface of the same cell during metaphase (upper panels) and telophase (lower panels). The cell cytoplasm is shown in blue. Modified with permission of the American Society for Cell Biology, from Aguet et al. (2016); permission conveyed through the Copyright Clearance Center. Time (minutes) is relative to anaphase onset. (C) Efficient uptake of *Salmonella* into mitotic cells. *Salmonella* (green) internalizes more efficiently into mitotic cells (arrow) than into interphase cells. Modified from Santos et al. (2013). (D) Model for the roles of endocytosis during cell division in the inheritance of transmembrane cell surface proteins. (i) Without mitotic redistribution, receptors that are polarized in the mother cells (e.g. PCP complex, TGFβ and caveolin-1) would be inherited unequally between the two daughter cells, causing loss of polarity (upper pathway). Dedicated endocytosis during mitosis coupled with a shutdown of endosomal recycling causes receptors to accumulate in endosomes (lower pathway). The symmetrical partitioning of the endosomes between the two daughter cells mediates the equal inheritance of the proteins. (ii) Targeting of mitotic endosomes containing receptors (e.g. Notch and FGFR) into one of the daughter cells during asymmetrical division drives the maintenance of the stemness and the differentiation of the other cell during organ development. White dashed lines show the cell boundaries.

et al., 2012; Tacheva-Grigorova et al., 2013; Aguet et al., 2016). In such cells, Tf uptake is inhibited despite high levels of TfR at the surface (Fig. 1Ai), because clathrin-coated pits no longer form (Tacheva-Grigorova et al., 2013). The usefulness of such residual CME has been questioned, but there are now several studies that provide direct evidence of uptake of endogenous cargos into dividing cells both *in vitro* and *in vivo* (Fig. 1Aii–iv) (Bökel et al., 2006; Coumailleau et al., 2009; Devenport et al., 2011; Cota and Davidson, 2015; Heck and Devenport, 2017; Shrestha et al., 2015).

In the absence of its typical cargos, residual CME during mitosis is dedicated to the internalization of specific receptors, namely the receptor for the TGF-β receptor-type morphogen decapentaplegic (Dpp), fibroblast growth factor receptor (FGFR), the Notch receptor, and the planar cell polarity (PCP) complex components Celsr1, Frizzled 6 and Vangl2, as shown in fly experiments (Fig. 1Aii–iv) (Bökel et al., 2006; Coumailleau et al., 2009; Devenport et al., 2011; Cota and Davidson, 2015; Heck and Devenport, 2017). Interestingly, some CIE events also occur during mitosis, such as the clathrin-independent uptake of epidermal growth factor receptor (EGFR) (Liu

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et al., 2011) (Fig. 1Av), and even the very efficient entry of *Salmonella* into mitotic cells (Fig. 1C), which occurs via an actin-driven process akin to macropinocytosis (Santos et al., 2013).

A function for the dedicated endocytosis of receptors into endosomes during mitosis is to mediate their equal or asymmetrical partitioning between the two daughter cells (Fig. 1D). Experiments in flies, for Dpp, and, in mouse, for the PCP complex, show that these proteins are polarized at the surface before cell division but yet need to be inherited equally to sustain tissue polarity (Fig. 1D). Indeed, blocking their uptake during mitosis *in vivo* induced a defective partitioning between daughter cells, thereby severely compromising tissue polarity (Bökel et al., 2006; Heck and Devenport, 2017). By contrast, the biased partitioning of Notch and its ligand Delta as well as of FGFR during mitosis of fly and *Ciona intestinalis* stem cells mediates the asymmetrical fate of the daughter cells during organ development and polarization: the cell keeping the receptors has a different fate than the other cells (Cota and Davidson, 2015; Coumailleau et al., 2009; Derivery et al., 2015). This is mediated by endocytosis of the receptors during cell division, followed by active targeting of the endosomes containing them (Fig. 1D). Later, during cytokinesis, endocytosis occurs at the forming cleavage furrow and supports the membrane fluxes that are required for changes in membrane shape during the abscission that separates the two daughter cells (reviewed in Frémont and Echard, 2018).

Caveolae are also actively internalized during cell division (Boucrot et al., 2011). They enter cells during the mitotic roundup until metaphase (Fig. 1Avi) and return to the cell surface after anaphase and during cytokinesis, perhaps to ensure equal inheritance between the two daughter cells (Fig. 1D). These fluxes mirror that of the receptors internalized during mitosis, which enter cells but fail to return to the cell surface because of the shutdown in endosomal recycling until the subsequent onset of anaphase (Boucrot and Kirchhausen, 2007; Tacheva-Grigorova et al., 2013). Interestingly, mitotic Polo-like kinase 1 (Plk1) has been found to be critical for the uptake of the PCP receptor Celsr1 and its retention into endosomes in mouse cells, providing a link between mitosis progression and the regulation of membrane trafficking (Shrestha et al., 2015). Thus, endocytosis in proliferating cells switches from mediating the uptake of a large number of cargos during interphase to being dedicated to the internalization of specific receptors that must be redistributed equally or asymmetrically between the two daughter cells. This also illustrates that endocytosis varies depending on the cellular state, and thus, it is logical that non-dividing cells, such as quiescent, senescent and terminally differentiated cells, have different endocytic needs and mechanisms from proliferating ones, as the following sections will review.

Endocytosis in quiescent cells

Cellular quiescence (also named ‘G0’ stage of the cell cycle) is the state in which cells are not dividing but retain the ability to resume proliferation upon stimulation (Box 2). Many cells in an adult body, including endothelial cells, mature hepatocytes and dormant tissue stem cells, reside in a quiescent state. They can re-enter the cell cycle upon exposure to external stimuli, such as injury, or to maintain tissue homeostasis. Quiescent cells exhibit varying metabolic activity, but display reduced protein synthesis and cellular growth (Cho and Hwang, 2012; Lemons et al., 2010; Shapiro, 1981; Yusuf and Fruman, 2003) (Box 2). Endocytic mechanisms during this cellular state are still poorly understood, but evidence exists that endocytosis supports cell-type-specific functions. Such functions include clearance of the blood from harmful substances (e.g. LDL in liver), uptake of nutrients, such as iron and cholesterol (which can be stored), formation of a primary cilium, cell polarization and control of cell–cell junctions (Goto et al., 2017; Lin et al., 2015; Nunez et al., 1996; Zanoni et al., 2018). Trans-endocytosis (also called transcytosis) is also a feature of some quiescent cells, and mediates the transport of ligands and receptors across epithelial and endothelial barriers (reviewed in Rodriguez-Boulan et al., 2005). Finally, endocytosis maintains the quiescent state by either downregulating mitogen-induced signaling (Koo et al., 2012; Nakayama et al., 2013), or upregulating cell cycle arrest pathways (Pedersen et al., 2016). It also mediates the cellular uptake of extracellular proteins, which can then be degraded and the amino acids used to sustain survival during proliferative quiescence (Muranen et al., 2017).

Many quiescent cells develop a primary cilium, which senses the availability of extracellular nutrients and growth factors (reviewed in Goto et al., 2017). The ciliary pocket at the base of the cilium is a site of active endocytosis, characterized by an abundance of clathrin-coated pits and vesicles (Ghossoub et al., 2016; Molla-Herman et al., 2010). Endocytosis at the ciliary pocket controls ciliary Sonic Hedgehog (Shh) and TGF-β signaling (Fig. 2i), potentially supporting the non-proliferative state of quiescent cells (Pedersen et al., 2016). Most quiescent cells are part of tissues and form junctional cell–cell contacts on their basolateral membranes [adherens junctions (AJs) composed of cadherins, tight junctions (TJs) formed by claudins, occludins and ZO proteins, and gap

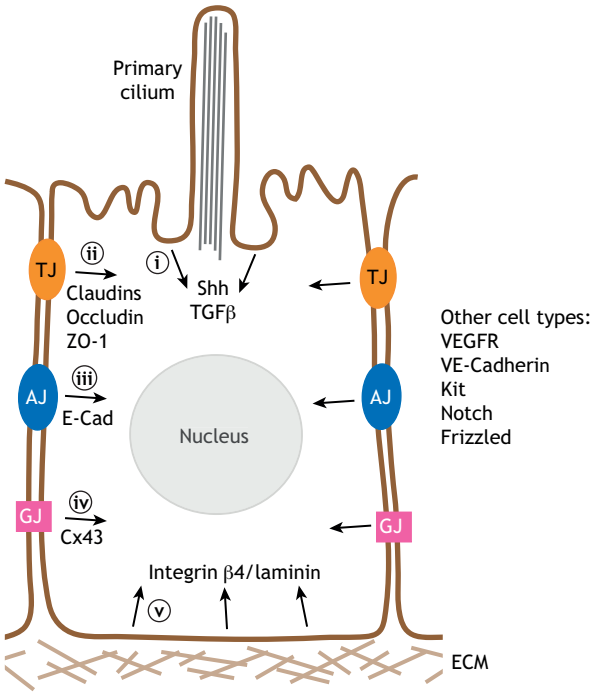

Fig. 2. Endocytosis in quiescent cells. Illustrated here are examples of cargos that are internalized in quiescent epithelial cells. (i) At the ciliary pocket, Sonic Hedgehog (Shh) and TGFβ are both internalized by CME. (ii) At TJs, endocytosis of claudins, occludin and ZO-1 (also known as TJP1) is key to TJ maintenance. (iii) E-cadherins (E-Cad) mediate the interactions between cells through the formation of AJs; they are internalized by CME when in their free form and perhaps through a modified mechanism when clustered into AJs. (iv) At GJs, connexin 43 (Cx43) enters cells upon GJ disassembly. (v) Integrin β4 and its ligand laminin from the ECM are endocytosed and degraded into quiescent cells to provide amino acids and support their metabolism. Other receptors, such as VEGFR, VE-cadherin, Kit, Notch and Frizzled are internalized into other quiescent cell types, such as endothelial or stem cells.

junctions (GJs) comprising connexins (Radeva and Waschke, 2018)]. Endocytosis of endothelial (E)- and vascular endothelial (VE)-cadherin is required for the formation and maintenance of mature AJs in quiescent epithelial and endothelial cells (Fig. 2iii) (de Beco et al., 2009; Nanes et al., 2012).

Mechanistically, E-cadherin uptake at AJs requires the endocytic proteins CIP4, also known as TRIP10) and dynamin 2 (hereafter called dynamin), as well as local actin polymerization that is mediated by Cdc42, Arf6, N-WASP and Arp2/3 (Druso et al., 2016; Georgiou et al., 2008; Leibfried et al., 2008; Palacios et al., 2002). The precise endocytic pathway is still unclear, but these are molecular factors that act both in CME and in FEME (Chan Wah Hak et al., 2018; Taylor et al., 2011). Furthermore, it is unclear whether the mechanism of uptake of free cadherins is similar to that of those clustered at AJs. Cadherins have a conserved binding motif for the core CME adaptor AP2 in their cytoplasmic domains, but it is obstructed upon binding to β-catenin and p120 catenin in AJs (Miyashita and Ozawa, 2007; Nanes et al., 2012). Thus, CME might mediate the uptake of free but not AJ-clustered cadherins. Alternatively, the uptake might be independent of AP2, as is seen upon clustering of E-cadherin mediated by the *Listeria* protein InlA, which triggers the recruitment of the adaptor Dab2, followed by that of clathrin and actin (Bonazzi et al., 2011; Veiga and Cossart, 2005; Veiga et al., 2007).

TJs form a diffusion barrier in quiescent endothelial and epithelial cells and are key to the impermeability of the blood–brain barrier (Stamatovic et al., 2017). Upon stimuli, such as growth factor addition or Ca^{2+} decrease, the removal of claudins, occludin and ZO-1 from TJs is mediated by CME (Fig. 2ii) (Cong et al., 2015; Ikari et al., 2011; Yamaki et al., 2014). However, the mechanism for the constitutive uptake of TJ components, while maintaining their barrier function, is still unclear (Dukes et al., 2011; Stamatovic et al., 2017). It has recently been proposed that TJ remodeling is mediated by so-called 'cross-over' endocytosis, the removal of TJs from one cell into its neighbor within a double-membrane vesicle (Gehne et al., 2017). Although molecular details are still missing, this process appears to be constitutive and can internalize entire TJs and not only specific claudins. Finally, GJs form intercellular connections, which allow various small molecules, ions and electrical impulses to pass directly between neighboring quiescent cells. Growth factor signals, such as EGF and VEGF, prime quiescent cell layers for their disassembly and cell cycle re-entry by stimulating junction disassembly (Fong et al., 2014; Nimlamool et al., 2015). The concomitant protein kinase C (PKC)- and mitogen-activated protein kinase (MAPK)-induced phosphorylation of connexin 43 (also known as GJA1) licenses it for cellular uptake through CME, thereby disassembling GJs (Fig. 2iv).

Endocytosis is used in quiescent cells to modulate the availability of many growth factor and cytokine receptors at their surface, either through their downregulation or maintenance. For instance, although VEGF internalization and concentration into endosomes is required for signaling and stimulates angiogenesis, its uptake into mature blood vessels is reduced (Nakayama et al., 2013). This decrease is mediated by the phosphorylation of the clathrin adaptor Dab2 by atypical PKC, which blocks the binding of Dab2 to VEGFR and thereby inhibits its endocytosis (Nakayama et al., 2013). Conversely, the continuous removal of several receptors from the cell surface by endocytosis is required to prevent cell cycle re-entry and proliferation of several types of quiescent cells. CME and lysosomal degradation of the tyrosine-kinase receptor Kit maintains the non-proliferative state of mast cells (Cruse et al., 2015). In intestinal crypts, $Lgr5^{+}$ stem cells remain quiescent by escaping Wnt-mediated β-catenin signaling through the active removal of the Frizzled receptors from the cell surface (Koo et al., 2012). There, the stem cell-specific E3 ligase RNF43 ubiquitylates Frizzled receptors, such as Frizzled 5, and induces their endocytosis and subsequent degradation in lysosomes (Koo et al., 2012). Consistent with this, blocking CME of the intestinal crypt stem cell marker Lgr5 diminishes cell fitness, and the broader inhibition of endocytosis by blocking dynamin in intestinal stem cells induces their hyper-proliferation and leads to a severe defect in epithelial homeostasis (Nagy et al., 2016; Snyder et al., 2017).

A third function of endocytosis might be to support the survival of quiescent cells. Lack of growth factor stimulation reduces the activity of the master regulator of cell growth, mammalian target of rapamycin complex 1 (mTORC1) in G0 cells (Gan and DePinho, 2009) (Box 2). Increased cell surface expression of β4-integrin in quiescent cells mediates the cellular uptake of its extracellular matrix (ECM) ligands, the laminins (Muranen et al., 2017). The lysosomal degradation of laminins produces free amino acids, and can thereby restore a basal mTORC1 activity and promote survival (Muranen et al., 2017). The precise mechanism of β4-integrin uptake is, however, unclear. β4-integrin forms heterodimers with α6 chains, which contain a cytoplasmic Yxxφ motif that can interact with AP2 (De Franceschi et al., 2016), suggesting that CME might mediate such uptake (Fig. 2v). To conclude, endocytosis is required for quiescent cells to perform specific cellular functions as well as modulating their cell cycle signaling and survival. However, the precise pathways and mechanisms are still poorly understood.

Endocytosis in terminally differentiated cells

Terminally differentiated cells have irreversibly exited the cell cycle and cannot resume proliferation (Box 2). Mature neurons, skeletal muscles, kidney podocytes, adipocytes and intestine enterocytes are examples of specialized terminally differentiated cells that perform tissue-specific functions (Guo et al., 2009; Herrup and Busser, 1995; Lasagni et al., 2013; Latella et al., 2001). Therefore, their endocytic activities differ widely depending on the exact cell types and functions performed, as outlined below.

Endocytosis at neuronal synapses is required following neurotransmitter release for the rapid recycling of synaptic proteins from the cell surface. Ultrafast endocytosis, which is clathrin-independent and endophilin- and dynamin-dependent, and perhaps reminiscent of FEME (see Box 1), retrieves membranes and proteins from the synaptic cleft within milliseconds (Gan and Watanabe, 2018; Watanabe et al., 2018). CME mediates synaptic vesicle recycling as well, but does so away from the active synaptic zone and with slower kinetics (Gan and Watanabe, 2018). A third form of uptake, activity-dependent bulk endocytosis (ADBE), operates in response to sustained and elevated neuron stimulation and shares similarities with macropinocytosis (Cousin, 2017). Endocytosis at the synapse has been intensely studied and summarized in recent reviews (Cousin, 2017; Gan and Watanabe, 2018; Maritzen and Haucke, 2018).

Endocytosis also occurs at the postsynaptic membrane, reducing surface-receptor levels after long patterned stimuli, a mechanism known as long-term depression (LTD). The most common LTD mechanism involves the downregulation of postsynaptic heterotetrameric α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR) from the surface of glutaminergic synapses. Constitutive endocytosis of AMPAR at the postsynaptic membrane is believed to be clathrin independent (Fujii et al., 2017). However, constitutive CME of the receptor, as well as other cargos, have been reported to occur there, as well as at dendrites and in the soma

(Rosendale et al., 2017). Upon LTD-inducing stimulation, AMPAR is sorted into clathrin-coated pits and efficiently removed from the plasma membrane, thereby reducing the sensitivity of neurons to neurotransmitters (Lee et al., 2002; Rosendale et al., 2017). During axon growth and before synapse formation, macropinocytosis, CME and an endophilin-dependent pathway (akin to FEME) are required to modulate attractive and repulsive receptors (Chen and Tai, 2017; Tojima and Kamiguchi, 2015; Chang et al., 2017). Finally, macropinocytosis mediates neuron-to-neuron transmission of protein aggregates, perhaps also supporting the spread of amyloids during neurodegenerative diseases (Yerbury, 2016).

Skeletal muscle fibers form large flat AP2 and clathrin lattices (Vassilopoulos et al., 2014; Liu et al., 2018), which, together with actin and α-actinin, control sarcomere maintenance, but are also endocytically active. Cardiomyocytes display active endocytosis of transferrin and integrins by means of CME, and of dextran by means of macropinocytosis (Ottesen et al., 2015; Soeiro et al., 2002; Swildens et al., 2010). They also actively internalize β1-adrenergic receptor (Morisco et al., 2008), which mostly enters cells through FEME in proliferating cells (Boucrot et al., 2015). Interestingly, Dab2 may not be involved in cardiomyocyte gap junction remodeling, in contast to its role in quiescent epithelial and endothelial cells (Waxse et al., 2017), suggesting that there are differences in the underlying mechanisms.

Another type of terminally differentiated cells with reported endocytic activity are adipocytes. CME is active in adipocytes and mediates the uptake of typical CME cargos such as transferrin (Kao et al., 1998), as well as the internalization of the key glucose transporter GLUT4 (also known as SLC2A4) upon insulin stimulation (Blot and McGraw, 2006; Shigematsu et al., 2003). Endocytosis of GLUT4 in resting adipocytes occurs primarily through a clathrin-independent pathway, perhaps caveolae, which, however, is inhibited following insulin stimulation, thereby allowing CME to take over the transporter uptake. Insulin-induced GLUT4 internalization in muscle cells differs from that in adipocytes in that it is insensitive to the disruption of caveolae-mediated endocytosis, but is instead completely abrogated upon dynamin inhibition (Antonescu et al., 2008). Both adipocytes and cardiomyocytes exhibit striking amounts of caveolae (Thorn et al., 2003), but it is not clear how many of them mediate the actual uptake of cargos. Mechanoprotection and provision of membrane reservoirs might be the prevailing functions of caveolae in these cells, as both adipocytes and myoblasts undergo dramatic changes in size and shape when they undertake lipid storage, or contraction and hypertrophy, respectively (Kozera et al., 2009; Huang et al., 2013; Lo et al., 2015; Briand et al., 2014).

Podocyte epithelia develop specialized foot processes that are connected by the slit diaphragm, forming a size-selective filtration barrier (reviewed in Inoue and Ishibe, 2015). Endocytic processes (primarily CME) and actin remodeling play a major role in the maintenance of the filtration barrier and the uptake of integrins and lipoproteins (reviewed in Inoue and Ishibe, 2015). The formation of podocytes is dependent on the CME and FEME proteins dynamin, synaptojanin and endophilin (Soda et al., 2012). It has been shown that the integrity of the slit diaphragm is maintained by the interaction of the receptor nephrin with podocin and its endocytosis via CIE (Qin et al., 2009). The BAR domain protein pacsin-2 has been shown to play a role in nephrin uptake, but the molecular details of the endocytic pathway remain unclear (Dumont et al., 2017).

Recent work measuring CME in isogenic cells derived from gene-edited human embryonic stem cells (hESCs) has revealed striking differences in endocytic activity and mechanisms upon differentiation (Dambournet et al., 2018; Schöneberg et al., 2018). Intestinal epithelial cells differentiated from hESCs and grown into organoids had uniform CME dynamics both at their apical, lateral and basal membranes (Schöneberg et al., 2018). Moreover, both hESCs and derived neuronal progenitor cells (NPCs) had rapid (∼45 s) and productive formation of clathrin-coated vesicles (Dambournet et al., 2018). However, cells that differentiated into fibroblasts showed slower (∼75 s) and less productive CME. This was correlated with a doubling in AP2 levels upon differentiation, which, once it had been corrected back to levels close to that of the parental hESCs, showed restored efficient and rapid CME (Dambournet et al., 2018). In addition, unlike in hESCs and NPCs, CME in fibroblasts did not require the actin cytoskeleton (Dambournet et al., 2018). Finally, inhibition of phosphoinositide 3-kinase (PI3K), while having no effect in hESCs, improved the productivity of CME in fibroblasts, but decreased it in NPCs (Dambournet et al., 2018). Thus, these experiments convincingly show that the molecular needs for CME differ in a manner depending on the cell type and adapt upon differentiation.

Endocytosis in senescent cells

Cellular senescence is the state in which normal, non-transformed, cells cease to replicate permanently, following telomere shortening beyond a critical length or irreversible DNA damage (Muñoz-Espín and Serrano, 2014) (Box 2). High levels of β-galactosidase and $p16^{Ink4A}$ (encoded by *CDKN2A*) are typically used to identify senescent cells (Sharpless and Sherr, 2015). Only cancer cells escape senescence, as mutations in the machinery mediating telomere shortening and DNA damage checkpoints, in particular in p53 (also known as TP53), are hallmarks of oncogenic transformation (Hanahan and Weinberg, 2011). Non-transformed cells become senescent upon aging and might constitute the majority of cells in an old organism (Box 2). As many cellular processes are altered during senescence, it is not surprising that endocytosis is also perturbed. Senescent fibroblasts retain normal levels of growth factor receptors and associated signaling proteins, but do not respond to proliferative stimuli by growth factors such as EGF, even at very high doses (Park et al., 2000). Thus, they differ from quiescent cells in that they cannot re-enter the cell cycle, sustain high mTORC1 activity and are not able to generate functional primary cilia (Carroll et al., 2017; reviewed in Terzi et al., 2016).

The literature measuring endocytosis in naturally occurring senescent cells instead of acutely damaged cells (e.g. induced by peroxide or high UV doses) is still very limited. However, the hypo-responsiveness of senescent cells to growth factors may be explained by: (1) the concomitant upregulation of caveolin-1 and -2 levels (Park et al., 2000); (2) the paradoxical absence of functional caveolae, which impairs EGFR dimerization and activation (Ikonen and Parton, 2000; Wheaton et al., 2001); and (3) the downregulation of the clathrin adaptor amphiphysin, which could account for the decreased CME (Park et al., 2001). Reduction of caveolin-1 and overexpression of amphiphysin were proposed to be sufficient to restore the responsiveness of senescent cells to growth factors (Park et al., 2000; Cho et al., 2003).

In addition, cells with elevated senescent-specific splice variants of the transcriptional regulator ING1 overexpress the clathrin adaptor scaffold intersectin-2 (Rajarajacholan et al., 2013). Over-representation of intersectin-2 disrupts the stoichiometry required for clathrin-coated pit formation, resulting in impaired endocytosis and activation of the $p16^{Ink4a}$ senescence signaling axis

(Rajarajacholan et al., 2013). However, reduced CME is unlikely to be sufficient to induce senescence, as the knockdown of AP2 causes growth arrest, but does not recapitulate the senescent phenotype (Olszewski et al., 2014). Thus, the responses to irreversible DNA damage or critical telomere shortening might induce some adaptations in endocytosis, but the molecular details are yet to be fully elucidated.

Conclusions and future perspectives

The various cell types in an organism reside in different proliferative states to serve distinct physiological functions, and it is therefore only logical that they have different endocytic needs. Our molecular understanding of endocytosis in non-proliferating cells is lagging behind that of dividing cells, so it is still too early to conclude whether the mechanisms used by each pathway differ in these different scenarios. However, current evidence supports the notion that CME is broadly active in dividing, quiescent and terminally differentiated cells, but perturbed in senescent cells. However, the cargos internalized by CME vary depending on the specific cell cycle state. The activity of clathrin-independent pathways, including macropinocytosis, also varies for different cell states and is perhaps linked to the specialized functions performed by either quiescent or terminally differentiated cells.

Furthermore, it is important to remember that most of our current knowledge of endocytic mechanisms is derived from studies of proliferating cells, and the mechanisms prevailing in non-dividing cells might be quite different, especially because *in vitro* cell lines are all transformed cell lines, with the exception of hTERT-immortalized diploid cell lines (Bodnar, 1998). Indeed, cancer cells bear many mutations and often have different endocytosis activity compared to their non-tumorous counterparts (Elkin et al., 2015). Some transformed cells have elevated and adaptive CME (Chen et al., 2017), which may support cancer cell survival and metastasis (reviewed in Schmid, 2017). The frequent G12V activating mutation in K-Ras reduces CME and to some extent clathrin-independent uptake, but induces constitutive macropinocytosis (Commisso et al., 2013; Elkin et al., 2015). Thus, it is possible that many studies in the literature have been reporting endocytic mechanisms that might be more closely describing tumor rather than normal cells. Further characterization of proliferating non-cancer cells might thus help to us to gain a better understanding of endocytosis and serve as a useful reference for quiescent, terminally differentiated or senescent cells.

Competing interests

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