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Receptor endocytosis *via* ubiquitin-dependent and -independent pathways

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Abstract

The controlled termination of signaling pathways after their ligand-induced activation is an important mechanism to ensure appropriate signal intensity and the consequent cellular response. Most cell surface receptors are downregulated by receptor endocytosis and subsequent lysosomal degradation, processes accompanied by attachment of ubiquitin (Ub) molecules to activated receptors and associated proteins. A significant body of evidence supports the view that mono-Ub functions as an important internalization and degradation signal conserved from yeast to mammals. Yet, the mechanisms underlying ligand-dependent receptor endocytosis seem to be divergent and more complex in mammalian cells. This is not only a consequence of evolution-based expansion of endocytic proteins and protein-interaction domains, but is also caused by enhanced formation of networks and multi-molecular complexes linked to activated receptors in higher eukaryotes. Here, we discuss the current view on the role of Ub-dependent and -independent pathways in receptor internalization and endocytosis in mammalian cells.

Keywords: Receptor endocytosis; Receptor internalization; Ubiquitin; Cbl, receptor tyrosine kinases; G protein-coupled receptors

1. Introduction

Most often an extracellular signal is transduced into the cell *via* receptors that reside in the cell membrane and activate intracellular signaling cascades upon ligand binding. These signals provoke a variety of cellular processes, like differentiation, migration, proliferation or apoptosis, but also, when uncontrolled, can cause diseases, like cancer or neurological disorders. Thus, the appropriate cellular response depends not only on the nature of the signal but is also dose sensitive. This means that both strength and duration of a signal need to be regulated in order to ensure normal cell homeostasis and prevent inappropriate cell proliferation or transformation. For numerous cell surface receptors (e.g. receptor tyrosine kinases (RTKs), G protein-coupled receptors (GPCRs), cytokine and antigen receptors) this is accomplished by the ability of receptors to recruit proteins that mediate their inactivation *via* rapid internalization and lysosomal degradation [1]. This process is functionally and mechanistically distinguishable from the constitutive (i.e. unregulated) internalization and recycling of many plasma membrane proteins that depend mostly on linear amino acid sequences within their cytoplasmic domains. In contrast, the ligand-induced entry of cell surface molecules requires a signal that can be activated to trigger rapid internalization and degradation of the receptor in response to ligand binding. Recently, it has become evident that the modification of the receptor as well as accessory proteins with single ubiquitin (Ub) molecules plays a crucial role in these processes.

The attachment of Ub to substrates is highly regulated and occurs in a three-step process (reviewed in Ref. [2]). First, Ub forms a high-energy thiolester bond with the Ub-activating enzyme (E1). The activated Ub is then transferred to a Ub-conjugating or Ub-carrier enzyme (E2) and ligated to lysine residues in the substrate protein by a Ub ligase (E3) that usually provides substrate specificity. Ub itself contains several lysine residues that can be iteratively targeted by the ubiquitination machinery. Thus, the formation of poly-Ub chains is possible. In many aspects, ubiquitination shows striking similarity to phosphorylation, yet the polypeptide Ub provides a modification with significantly higher diversity because it allows the formation of chains and distinct linkage types by using different

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lysine residues of Ub. For instance, a poly-Ub chain linked through Lys48 targets proteins for proteasomal degradation, while a chain linked through Lys63 is found attached to proteins involved in DNA damage repair [3]. On the other hand, the attachment of a single Ub molecule to a substrate protein (monoubiquitination) has been implicated in sorting of cargo proteins and internalization of cell surface receptors [4,5]. Meanwhile, it has been reported that distinct ubiquitination signals are recognized by a number of Ub-binding proteins. These proteins determine the stability, location or binding properties of ubiquitinated proteins, thus translating a Ub message to a variety of cellular processes, including protein transport, cell cycle progression, apoptosis, differentiation, proliferation, DNA repair and many more [6]. In this review, we discuss recent observations regarding the role and specificity of mono-Ub in ligand-induced internalization and endocytosis of cell surface receptors in mammalian cells.

2. Monoubiquitination and receptor endocytosis in yeast

A first link between Ub and internalization was the discovery that the Ste6p transmembrane protein accumulates as Ub-conjugated species in the cell membrane of endocytosis-deficient yeast [7]. Since then the number of proteins reported to be ubiquitinated at the plasma membrane has been constantly growing (Table 1), including GPCRs (Ste2p, Ste3p), ion channels, permeases (Gal2p, Mal61p, Gap1p, Fur4p) and multidrug transporters (Pdr5p). Like most of the yeast plasma membrane transporters and receptors these molecules exhibit constitutive and accelerated endocytosis in response to environmental cues. The yeast endocytic pathway involves internalization and transport to the lysosome-like vacuole, whereby most of the endocytosed proteins are permanently inactivated by degradation. Initial evidence that ubiquitination promotes internalization came from studies with the GPCRs Ste2p and Ste3p. In yeast strains lacking Ub-conjugating enzymes the internalization and degradation of both proteins is significantly reduced [8,9]. In addition, substitution of a single lysine to arginine in the cytoplasmic tail of Ste2p abolishes ubiquitination and constitutive as well as ligand-induced endocytosis indicating that ubiquitination is required for the internalization of this receptor. The final proof that a single Ub molecule is also sufficient to trigger internalization of yeast cell membrane proteins was achieved with a receptor Ub chimera that lacks all other internalization signals or when Ub was appended to a protein that usually does not undergo Ub-dependent internalization. Both of these chimerae underwent rapid ligand-independent internalization [10–12]. Thus, it seems that mono-Ub acts as an autonomous signal for endocytosis in yeast. The discovery of Ub-binding motifs, like the Ub-interacting motif (UIM), in core components of the endocytic machinery further corroborated the role of Ub in the endocytic process (reviewed in Ref. [6]). Deletion of the UIMs of the yeast epsin genes *EDE1* and *ENT1* resulted in a loss of Ub binding and a complete block of Ste2p internalization [13]. Several recent observations support the idea that the activated receptors are not the only target of the ubiquitination machinery in the endocytic process. Studies on the Ub ligase E3 Rsp5p have revealed that various accessory molecules, like Vps9, are also ubiquitinated upon Ste2p activation and that the constitutive internalization of the receptor requires Rsp5p action [14]. Other studies show that linear amino acid sequences, particularly the NPFXD motif, can serve as an efficient internalization signal [15]. The NPFXD motif is present in the cytoplasmic tail of Ste3p, which shows Ub-dependent constitutive internalization, but Ub-independent ligand-induced internalization. A mutant Ste3p lacking all eight Ub-acceptor sites accumulates at the cell membrane of unstimulated cells but undergoes internalization upon ligand stimulation [16]. Taken together, studies in yeast have demonstrated that mono-Ub plays critical roles in regulation of multiple steps in receptor internalization and endocytosis. Furthermore, they revealed that additional Ub-independent pathways, e.g. those linked to linear peptide sequences of trafficking receptors, might control ligand-dependent internalization of some receptor types.

Table 1
Ubiquitinated plasma membrane proteins

Saccharomyces cerevisiae	
ABC transporter	Ste6p
GPCR	Ste2p, Ste3p
Permeases	Fur4p, Gal2p, Mal61p, Gap1p, Tat2
Multidrug transporter	Pdr5
Mammalian cells	
RTKs	EGFR, PDGFR, c-Kit, c-Met, FGFR, CSF-1
GPCRs	FSHR, β_2-AR, CXCR4, V2R, AT(1A)
Heterodimeric type I/II receptor	TGFbeta receptor
Ion channels	EnaC, GluR, GlyR
Cytokine receptors	GHR, IL-2R
Immune response	FcgammaRIIA, TCR
Development	Notch

3. Multiple pathways controlling receptor endocytosis in mammalian cells

Although both the ubiquitination machinery and the major components of the endocytic pathway are similar in yeast and mammals, the mechanisms of ligand-dependent endocytosis are divergent and more complex in mammalian cells. This is in part due to the existence of mammalian-specific signaling cascades, like the RTK

pathway, that are not found in yeast. In addition, novel pathways controlling receptor internalization have emerged in mammalian cells. Especially, at early steps of internalization several redundant mechanisms as well as various entry routes into the cell (like caveolae or lipid rafts) have evolved in mammals that make the picture more complex. In the following paragraphs, we will discuss in more details multiple pathways controlling early steps of endocytosis of the epidermal growth factor (EGF) receptor, a prototypic RTK, and several GPCRs.

The EGF receptor undergoes ligand-induced dimerization and activation of its cytoplasmic kinase domain that leads to tyrosine autophosphorylation of the dimers. The phosphotyrosines of the EGF receptor serve as docking sites for various effectors and adaptor proteins, including proteins that have been implicated in the downregulation of the activated receptor. Whether tyrosine kinase activity of EGF receptors is essential for their ligand-dependent internalization is still a matter of controversy. Initial reports have shown that the internalization of kinase-deficient receptors or receptors lacking any cytoplasmic domain is significantly reduced compared to the ligand-dependent rate of endocytosis of wild-type receptors [17,18]. On the other hand, inhibition of the EGF receptor, by either mutation in their kinase domains or by treatment with small synthetic inhibitors, had no effect on the ligand-dependent receptor internalization and recruitment to the early endosomal compartment [19,20], Whereas, endosomal sorting of the internalized EGF receptor at the multivesicular body level was dependent on its kinase activity [19]. To add even more complexity to these pathways, serine/threonine phosphorylation of the EGF receptor is implicated in the regulation of receptor internalization. Phosphorylation at threonine 654 of the EGF receptor by PKC inhibits receptor downregulation [21,22], and phosphorylation of serine residues in the carboxy-terminus promotes receptor internalization and degradation [23].

More recent findings have revealed that the RING-type Ub ligase Cbl (Casitas B-lineage lymphoma) plays a central role in ligand-dependent downregulation of EGF receptors. Cbl binds to tyrosine-phosphorylated EGF receptors and targets them for endocytosis by mediating their ubiquitination (reviewed in Refs. [1,24]). It was proposed that multiple mono-Ubs attached to EGFR or PDGFR serve as signals mediating both receptor internalization and degradation [5]. Consistent with this hypothesis, an EGFR-Ub chimera, having the entire cytoplasmic part of the EGFR replaced by Ub, was endocytosed independently of ligand binding. This supports the view that Ub functions as an internalization signal for this receptor as well [25]. However, endocytosis of the EGFR-Ub chimerae was half as efficient as the internalization of wild-type EGFR [25]. Thus, under physiological conditions, Ub-independent mechanisms can further promote EGF receptor internalization. Recently, several groups have demonstrated that the family of CIN85/CD2AP proteins [26] may play a crucial role in Ub-independent downregulation of RTK as well as T cell receptors in the immunological synapse [27–29]. It was shown that Cbl itself becomes phosphorylated by the activated EGFR, which leads to the recruitment of CIN85 (Cbl-interacting protein of 85 kDa) and endophilins, components of the endocytic machinery [1,27]. Notably, the formation of the EGFR/Cbl/CIN85 complex is independent of the ligase activity of Cbl and receptor ubiquitination, supporting a dual role for Cbl in receptor endocytosis as a Ub ligase and an endocytic adaptor protein.

Another layer of functional redundancy in mediating downregulation of EGF receptors is emphasized by the action of multiple scaffold proteins that bind to activated receptors and regulate their endocytosis [1]. One example is the adaptor protein Grb2 that is recruited to the tyrosine-phosphorylated receptor *via* its SH2 domain and seems to facilitate EGFR internalization by activating the GTPase dynamin, a crucial player in endocytosis of clathrin-coated pits [1]. Grb2 colocalizes with activated EGFRs in clathrin-coated pits and siRNA-mediated depletion of endogenous Grb2 leads to a significant decrease in ^{125}I-EGF internalization [30]. An alternative pathway for receptor internalization is mediated by Eps15 (EGFR pathway substrate clone 15) and related proteins (epsin and Eps15R), which become phosphorylated and ubiquitinated upon agonist binding to EGF receptors [6]. Eps15 interacts with the AP-2/clathrin complex that is responsible for coated pit formation and is involved in the internalization of several constitutively internalized receptors, like the transferrin receptor [31,32]. However, its tyrosine phosphorylation and ubiquitination occur specifically upon ligand stimulation and seem to be exclusively required for ligand-dependent EGF receptor internalization [33].

Thus, the engagement of multiple pathways is needed for rapid and efficient ligand-induced receptor internalization and subsequent targeting for lysosomal degradation. This is in contrast to ligand-independent and constitutive internalization of RTKs that is slower and mediated by fewer low-affinity interactions between the receptor and components of the endocytic machinery. In addition, subsequent sorting of internalized EGF receptors in the endosome also requires multiple signals, including intrinsic tyrosine kinase activity, endocytic sequence motifs located in the cytoplasmic domain of the receptor, receptor ubiquitination as well as numerous signals in the endosomes that direct receptors for lysosomal degradation. The molecular mechanisms underlying these processes have been described in much detail in recent reviews [4–6,34,35].

4. Novel functions of ubiquitination in GPCR endocytosis in mammalian cells

Even though it has been known for a long time that ubiquitination of GPCRs in yeast cells is essential for their internalization [8,9], only recently it has been demonstrated

that the agonist-induced internalization of several GPCRs (e.g. β_2-adrenergic receptor, chemokine receptor CXCR4 and vasopressin 2 receptor) is accompanied by ubiquitination of the activated receptors in mammalian cells as well [36–38]. Interestingly, ubiquitination of the β_2-adrenergic receptor is neither sufficient nor required for its internalization [36]. GPCR activation leads to ubiquitination of β-arrestin [36], an adaptor protein implicated in the internalization of most GPCRs (reviewed in Refs. [39,40]). β-Arrestin has been shown to directly interact with AP-2 and clathrin. Thus, similarly to CIN85 in downregulation of activated RTKs [27,29], β-arrestin may provide a link between the activated receptor and components of the endocytic machinery. It even appears that β-arrestin ubiquitination by the E3 ligase MDM2, rather than GPCR ubiquitination, is required for efficient internalization [41,42]. Correspondingly, a ubiquitination-deficient β_2-adrenergic receptor mutant is normally internalized while in MDM2$^{-/-}$ mouse embryonic fibroblasts the receptor is ubiquitinated but not internalized [36].

Whereas the E3 ligase responsible for β_2-adrenergic receptor ubiquitination is not yet known, it has been recently shown that the chemokine receptor CXCR4 becomes ubiquitinated by the HECT-type E3 ligase AIP4 at the plasma membrane [38]. Like the β_2-adrenergic receptor, ubiquitination of CXCR4 is not required for internalization as demonstrated by using ubiquitination-deficient receptor mutants that internalized in a normal fashion [43]. However, siRNA-mediated depletion of AIP4 resulted in a marked decrease of ligand-induced CXCR4 degradation [38]. Furthermore, Hrs as a component of the endocytic transport machinery was found to be required for CXCR4 downregulation. Hrs colocalizes with both AIP4 and CXCR4 in endosomes and becomes ubiquitinated by AIP4 [38]. Thus, in analogy to RTKs ubiquitination of GPCRs and accessory proteins appears to be essential for their sorting to the degradative pathway, rather than for removing them from the cell surface.

5. Summary and perspectives

Taken together, different lines of evidence suggest that the ligand-induced endocytosis of cell surface receptors in mammalian cells is not regulated by one exclusive pathway but is rather covered by several redundant mechanisms, including ubiquitination of the receptors and endocytic regulatory proteins. These pathways can substitute for each other under physiological conditions and can be involved in the regulation of multiple entry routes into the cell. On the other hand, mono-Ub signals appear to carry an evolutionary conserved role in the endosomal sorting of internalized activated receptors for degradation in the lysosome. Understanding the molecular details of these pathways is of great importance as many types of cancer are associated with hyperactivation of receptor signaling. Indeed, novel anticancer drugs have already been designed to induce the downregulation of oncogenic receptors. One highlighting example is represented by the monoclonal antibody Herceptin/Trastuzumab directed against the extracellular domain of the tumorigenic ErbB-2, which has been successfully used for treatment of metastatic breast cancer (reviewed in Ref. [44]). Its effectiveness can be at least partially attributed to increased ubiquitination and degradation of the ErbB-2 receptor [44].

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