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Mini review

Endocytic regulation of cytokine receptor signaling

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ABSTRACT

Signaling of plasma membrane receptors can be regulated by endocytosis at different levels, including receptor internalization, endocytic sorting towards degradation or recycling, and using endosomes as mobile signaling platforms. Increasing number of reports underscore the importance of endocytic mechanisms for signaling of cytokine receptors. In this short review we present both consistent and conflicting data regarding endocytosis and its role in signaling of receptors from the tumor necrosis factor receptor superfamily (TNFRSF) and those for interleukins (ILRs) and interferons (IFNRs). These receptors can be internalized through various endocytic routes and most of them are able to activate downstream pathways from endosomal compartments. Moreover, some of the cytokine receptors clearly require endocytosis for proper signal transduction. Still, the data describing internalization mechanisms and fate of cytokine receptors are often fragmentary and barely address the relation between their endocytosis and signaling. In the light of growing knowledge regarding different mechanisms of endocytosis, extending it to the regulation of cytokine receptor signaling may improve our understanding of the complex and pleiotropic functions of these molecules.

1. Introduction

Endocytosis is coupled to regulation of signaling initiated by plasma membrane receptors. Initially, internalization of the activated receptors was considered only as a means for signal attenuation, but now it is clear that endocytosis also regulates the duration of receptor signaling as well as specificity of signaling outputs (reviewed in Barbieri et al. [1]). Endosomes can serve as mobile signaling platforms facilitating formation of multiprotein signaling assemblies and therefore enabling efficient signal transduction in space and time. Signaling events that are initiated at the plasma membrane may continue at the endosomal compartments and terminate by incorporation of the receptor into the intraluminal vesicles (ILVs) of the multivesicular bodies (MVBs).

Although a great number of biochemical and imaging approaches have been undertaken to study how different endocytic routes affect receptor signaling, they have been applied to only a few model receptors with a major focus on epidermal growth factor receptor (EGFR) [2]. Consequently, the review articles published so far have described the involvement of endocytosis in regulation of receptor tyrosine kinases (RTKs), such as EGFR, or G protein-coupled receptors (GPCRs), such as neurotransmitter or chemokine receptors [3–5]. Conversely, no reviews comprehensively summarize the role of endocytosis in signaling of cytokine receptors.

Abbreviations: CIE, clathrin-independent endocytosis; CME, clathrin-mediated endocytosis; DRM, detergent-resistant microdomains; EGFR, epidermal growth factor receptor; GPI-AP, glycosylphosphatidylinositol-anchored proteins; IFN, interferon; IFNAR, type I interferon receptor; IFNGR, type II interferon receptor; IFNR, interferon receptor; IL, interleukin; ILR, interleukin receptor; ILV, intraluminal vesicle; JNK, c-Jun N-terminal kinase; LTβR, lymphotoxin β receptor; MVB, multivesicular body; MβCD, methyl-β-cyclodextrin; PI3K, phosphoinositide 3-kinase; RTK, receptor tyrosine kinase; TNF, tumor necrosis factor; TNFRSF, tumor necrosis factor receptor superfamily.

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In the present review we focus on tumor necrosis factor receptor superfamily (TNFRSF), interleukin receptors (ILRs) and interferon receptors (IFNRs). As opposed to RTKs (tyrosine kinases) and TGFβ receptor superfamily (serine/threonine kinases) they do not possess any intrinsic kinase activity and unlike GPCRs they do not transmit signals through G proteins. Instead, they depend on multiple signaling adaptors that mediate inflammatory and stress responses via signaling pathways involving NF-κB and MAPK (TNF receptor and IL-1 receptor superfamilies) or STAT and MAPK (receptors for IFNs and most of the ILs).

1.1. Mechanisms of receptor internalization

Receptor-mediated endocytosis is initiated at the plasma membrane by several distinct internalization mechanisms (Fig. 1). Their traditional division is based on the involvement of clathrin protein (clathrin-mediated endocytosis, CME) or its absence (clathrin-independent endocytosis, CIE). In CME, activated receptor induces recruitment of clathrin adaptors, such as the AP2 complex, while the subsequent formation of the clathrin coat stabilizes the membrane curvature and drives the invagination. In the final step, the vesicle is released from the plasma membrane by the large GTPase dynamin that assembles around the bud neck [6–8].

The mechanisms of clathrin-independent internalization routes are less well defined. In fact, CIE is a common designation for several distinct internalization pathways, which depend on actin polymerization and its regulators, such as actin polymerizing factors and Rho GTPases [9]. Clathrin-independent internalization often takes place at the plasma membrane microdomains called lipid rafts, that initially were viewed as the sole common feature of many CIE routes. Lipid rafts are enriched in cholesterol and glycosphingolipids, that create a liquid-ordered microenvironment in a less ordered surrounding. Lipid rafts are important domains for assembly of complexes transducing extracellular signals. Several examples are presented in this review, whereas other well established signaling events initiated in lipid rafts are T-cell receptor-dependent signaling cascades [10] or H-Ras-mediated Raf activation [11]. Due to their small size, native lipid rafts cannot be observed in standard light microscopy, that was a reason for using rather crude techniques to study their function. One of them is cholesterol depletion, which can potentially affect non-raft elements of the plasma membrane. Another approach enables separation of cell membranes to detergent-soluble or detergent-resistant fractions, the latter containing lipid raft microdomains. However, beside other limitations, this technique cannot distinguish the plasma membrane from intracellular membranes. Therefore, the data acquired with both methods have to be interpreted with caution and need validation with more precise approaches [11].

Detailed molecular mechanisms and functional classification of the CIE pathways are under intense research and their nomenclature is a matter of debate. Still, they can be subdivided depending on the involvement of dynamin. The best studied dynamin-dependent CIE is caveolar internalization [12]. Caveolins are integral membrane proteins resident in the lipid rafts. In the nonmuscle cells, caveolins 1 and 2 bind additional adaptors and coat small membrane domains, forming a cup-shaped invagination called caveolae. Another well-defined CIE route is IL-2 receptor (IL-2R) endocytosis, described in detail later in this review. Briefly,

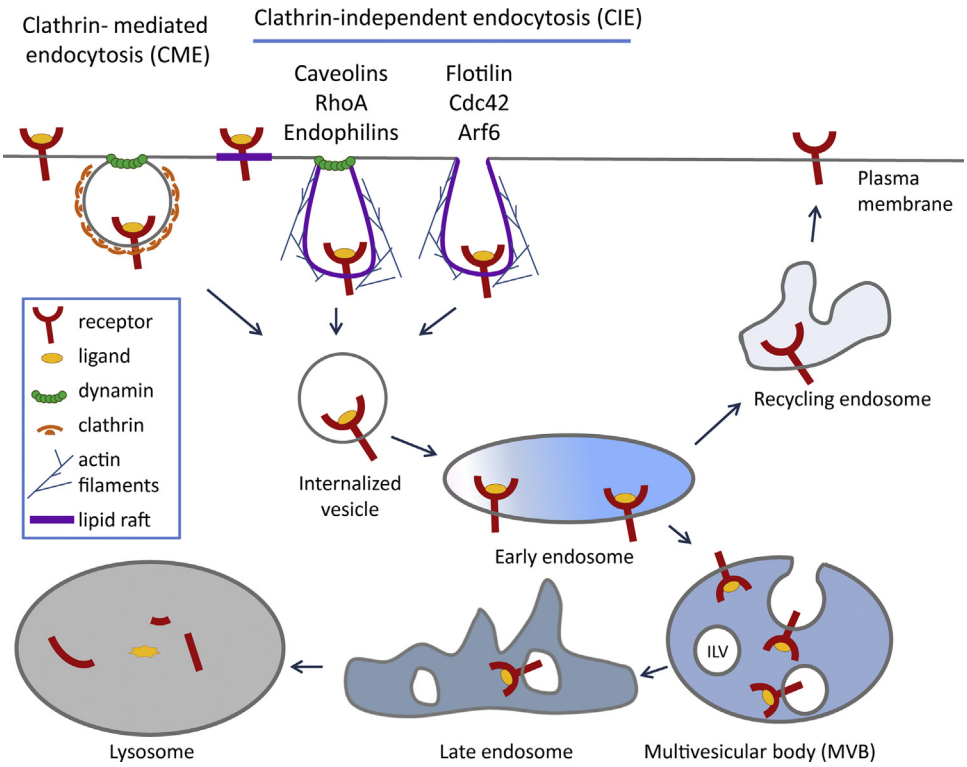

Fig. 1. Receptor-mediated internalization and endocytic trafficking routes. Plasma membrane receptors can be internalized by means of clathrin-mediated (CME) or clathrin-independent (CIE) endocytosis. CIE often occurs at the plasma membrane microdomains called lipid rafts and can be subdivided based on involvement of dynamin in scission of internalized vesicles and on involvement of the listed molecular regulators. After internalization, receptors are trafficked to early endosomes from where they are sorted to recycling endosomes or multivesicular bodies (MVB). Recycling endosomes return the receptors to the plasma membrane, while MVBs sequester them through incorporation into intraluminal vesicles (ILV). Subsequent maturation of MVBs to late endosomes and their fusion with lysosomes leads to degradation of ILVs and their cargo. Increasing acidification of endosomal lumen is marked by progressive color change from blue to grey (see main text for details).