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Chemokine receptor internalization and intracellular trafficking

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Abstract

The internalization and intracellular trafficking of chemokine receptors have important implications for the cellular responses elicited by chemokine receptors. The major pathway by which chemokine receptors internalize is the clathrin-mediated pathway, but some receptors may utilize lipid rafts/caveolae-dependent internalization routes. This review discusses the current knowledge and controversies regarding these two different routes of endocytosis. The functional consequences of internalization and the regulation of chemokine receptor recycling will also be addressed. Modifications of chemokine receptors, such as palmitoylation, ubiquitination, glycosylation, and sulfation, may also impact trafficking, chemotaxis and signaling. Finally, this review will cover the internalization and trafficking of viral and decoy chemokine receptors.

Keywords: Chemokine receptor; Internalization; Trafficking; Endocytosis; Modifications

1. Introduction

Chemokine receptors undergo a basal level of internalization and degradation or recycling in the absence of ligand. Ligand binding can greatly enhance the internalization and trafficking of these G protein-coupled receptors (GPCRs) and can increase the dynamics of receptor sensitization versus desensitization and of receptor recycling versus degradation. The receptor trafficking pathways may vary depending on the presence or absence of ligand. Two major choices are available for this trafficking: clathrin-mediated endocytosis, versus lipid raft/caveolae-dependent internalization. Some receptors take advantage of both of these pathways, while others may follow one pathway the majority of the time. The cell type in which the receptor is expressed may in part determine the likelihood of utilization of one pathway as compared to another. This may be due to the ratio of specific adaptor proteins, the lipid composition of the membrane in proximity to the domain the receptor is localized in, or other poorly characterized determinates. The fate of the receptor after ligand stimulation (to traffic or not to traffic) may affect the length, strength, or type of intracellular signals generated. Moreover, the type of post-translational modifications of the receptor can also have major effects on ligand mediated signaling. In this review, we will cover four major aspects of chemokine receptor trafficking: clathrin mediated endocytosis; caveolae/lipid raft mediated trafficking; effects of receptor trafficking on downstream signal transduction and impact of receptor modifications on receptor trafficking and signaling.

2. Chemokine receptors and the clathrin-mediated endocytic pathway

A major mechanism by which chemokine receptors undergo ligand-induced internalization is through clathrin-mediated endocytosis (Fig. 1) [1–5]. The binding of ligand results in phosphorylation of Ser and Thr residues in the intracellular loops and carboxyl-terminus of the chemokine

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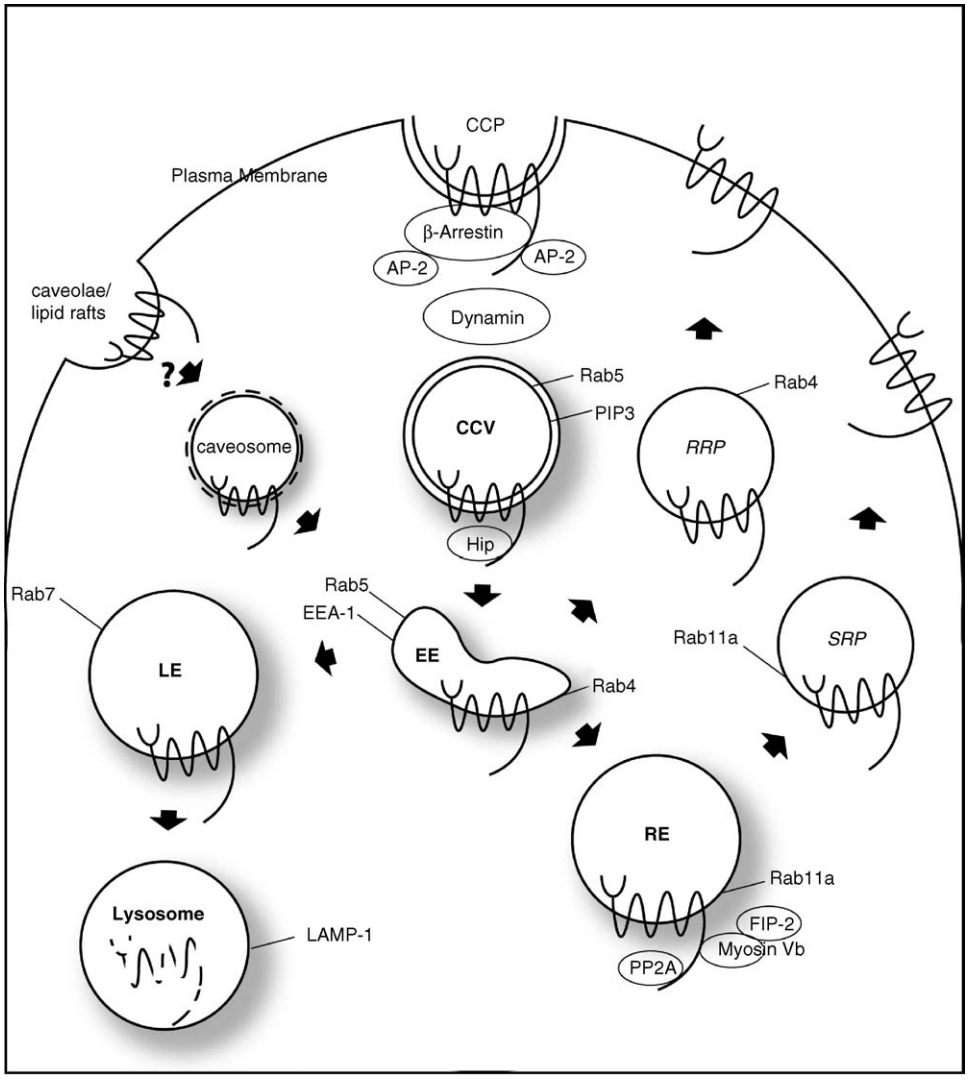

Fig. 1. Schematic of Endocytosis. CCP: clathrin-coated pit, CCV: clathrin-coated vesicle, EE: early endosome, LE: late endosome, RE: recycling endosome, RRP: rapid recycling pathway, SRP: slow recycling pathway, EEA-1: early endosomal antigen-1, FIP-2: Rab11-family interacting protein-2, LAMP-1: lysosomal-associated membrane protein-1.

receptor by G protein-coupled receptor kinases (GRKs) (Table 1) [6–9]. Phosphorylation results in the uncoupling of the G protein subunits from the receptor and receptor desensitization in some cases [8,10]. In addition, the phosphorylation of these residues and/or the presence of di-leucine motifs in the carboxyl-terminal domain of chemokine receptors are important for the recruitment of adaptor molecules that link the receptor to a lattice of clathrin that facilitates receptor internalization. Two adaptor molecules that play important roles in chemokine receptor internalization are adaptin 2 (AP-2) and β-arrestin. β-arrestin binds with higher affinity to the phosphorylated receptor, to the β2-adaptin subunit of the AP-2 heterotrimeric protein complex, and to clathrin to mediate endocytosis [11–15]. It was originally thought that β-arrestin binding to GPCRs was only mediated through phosphorylated residues in the

Table 1
Factors that regulate chemokine receptor internalization

Regulatory factors	Receptors	Reference
Carboxyl-terminal residues/phosphorylation sites	CXCR1, CXCR2, CXCR3 [CXCL9, CXCL10], CXCR4, CCR5, US28	[16,22,24,68,72–74,81,165]
di-Leucine motifs	CXCR2, CXCR4, CCR5	[24,70,72,73]
Intracellular loops	CXCR3 [CXCL11], CXCR4, CCR5	[16,17,22]
Dynamin	CXCR1, CXCR2, CXCR3, CXCR4, CCR2, CCR5, D6, US28	[1,2,4,21–25]
Chaperone proteins/Hip	CXCR2	[75]