Title:	A critical role for ubiquitination in the endocytosis of glutamate receptors
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Keywords:	G protein-coupled receptor (GPCR) endocytosis metabotropic glutamate receptor (mGluR) neurotransmitter receptor
Issue Date:	2017
Publisher:	American Society for Biochemistry and Molecular Biology Inc.
Citation:	Journal of Biological Chemistry, 292(4).
Abstract:	Group I metabotropic glutamate receptors (mGluRs) play important roles in various neuronal processes and elicit changes in synaptic efficacy through AMPA receptor (AMPAR) endocytosis. Trafficking of mGluRs plays an important role in controlling the precise localization of these receptors at specific region of the cell; it also regulates the activity of these receptors. Despite this obvious significance, we know very little about the cellular mechanisms that control the trafficking of group I mGluRs. We show here that ligand-mediated internalization of group I mGluRs is ubiquitination-dependent. A lysine residue (Lys1112) at the C-terminal tail of mGluR1 (a member of the group I mGluR family) plays crucial role in this process. Our data suggest that Lys63-linked polyubiquitination is involved in the ligand-mediated endocytosis of mGluR1. We also show here that the mGluR1 internalization is dependent on a specific E3 ubiquitin ligase, Siah-1A. Furthermore, acute knockdown of Siah-1A enhances the mGluR-mediated AMPAR endocytosis. These studies reveal a novel function of ubiquitination in the regulation of group I mGluRs, as well as its role in mGluR-dependent AMPAR endocytosis.
URI:	https://pubmed.ncbi.nlm.nih.gov/28011638/ (https://pubmed.ncbi.nlm.nih.gov/28011638/) http://hdl.handle.net/123456789/2709 (http://hdl.handle.net/123456789/2709)
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