Recruitment of AP-2 complex and clathrin

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**Introduction**

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

**Literature references**


Reactome database release: 74

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Recruitment of early acting proteins such as the FCHo and ITSN proteins stabilizes the transient AP-2:clathrin complex at the plasma membrane and is rapidly followed by incorporation of many more molecules of AP-2 and clathrin. AP-2 binding to the plasma-membrane enriched PI(4,5)P2 is reinforced early in the formation of a CCP by the interaction of AP-2 with PIP5K1C, which synthesizes PI(4)P to PI(4,5)P2 (Krauss et al, 2006; Bairstow et al, 2006; Thieman et al, 2009).

AP-2 recruitment is also promoted by conformational changes upon lipid and protein binding. AP-2 is a heterotetramer consisting of two large subunits (alpha and beta1 adaptin), a medium mu2 subunit and a small sigma2 subunit, and exists in a closed conformation when not part of a clathrin-coated pit (Jackson et al, 2010).

Interactions between the AP-2 mu2 subunit and PIP2 within the lipid bilayer stabilize the 'open' conformation of AP-2, exposing binding sites for cargo proteins. The open conformation is also promoted by interaction of AP-2 with early CCP proteins such as SGIP and FCHo2 (Hollopeter et al, 2014). Recruitment of clathrin stimulates the activity of AAK1, an AP-2 kinase that phosphorylates the mu2 subunit of the adaptor complex at Thr156, further stabilizing the open conformation and promoting cargo recruitment (Olusanya et al, 2001; Ricotta et al, 2002; Conner et al, 2002; Conner et al, 2003).

NECAP1 and 2 may also aid in the assembly of an emergent clathrin-coated pit. NECAP proteins have a WxxF motif at the C-terminus that binds with high affinity to the alpha-ear sandwich domain of AP-2 and an N-terminal PH ear domain that interacts both with AP-2 and a wide range of endocytic accessory proteins containing FxFDxF motifs (Ritter et al, 2003; Wasiak et al, 2002; Ritter et al, 2013). Clathrin and the NECAP PH ear domain appear to compete for an AP-2 binding site. Clathrin-mediated displacement of the NECAP PH ear domain from its lower affinity AP-2 site may allow release this domain, allowing it to transition to a role in recruiting endocytic accessory proteins and cargo (Ritter et al, 2007; Ritter et al, 2013; reviewed in McMahon and Boucrot, 2011).

Finally, studies have highlighted a role for ARF6 and its GTPase activating protein ARFGAP1 in CCP form-
ARFGAP1 and ARF6 appear to contribute to the recruitment of some cargo, but may also play a more generalized role in CCP formation (Moravec et al, 2012; Bai et al, 2011). ARFGAP1 binds directly to AP-2 and its GAP activity is required for CME. Consistent with this, silencing of ARFGAP1 impairs CME (Schmid et al, 2006; Rawet et al 2010; Bai et al 2011). ARFGAP1 has activity towards several ARFs, including ARF6 which is found in some CCPs and is known to regulate CME under some circumstances (Moravec et al, 2003; Palacios et al, 2002; Paleotti et al, 2005; Kraus et al, 2003). ARF6 is thought to contribute to the recruitment of AP-2 and clathrin to the plasma membrane, possibly in part by affecting the lipid composition (Paleotti et al, 2002; Krauss et al, 2003).

Literature references


Editions

2016-05-10 Reviewed Antonescu, CN.
2016-05-11 Authored, Edited Rothfels, K.