Regulation of actin dynamics for phagocytic cup formation

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18/02/2020
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: 71

This document contains 1 pathway and 24 reactions (see Table of Contents)
Regulation of actin dynamics for phagocytic cup formation

**Stable identifier:** R-HSA-2029482

**Compartments:** plasma membrane, cytosol, extracellular region

The actin cytoskeleton is fundamental for phagocytosis and members of the Rho family GTPases RAC and CDC42 are involved in actin cytoskeletal regulation leading to pseudopod extension. Active RAC and CDC42 exert their action through the members of WASP family proteins (WASP/N-WASP/WAVE) and ARP2/3 complex. Actin filaments move from the bottom toward the top of the phagocytic cup during pseudopod extension.

**Literature references**


**Editions**

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Recruitment of VAV1 to p-6Y-SYK

Location: Regulation of actin dynamics for phagocytic cup formation

Stable identifier: R-HSA-2029458

Type: binding

Compartments: plasma membrane, cytosol, extracellular region

VAV family members are cytoplasmic guanine nucleotide exchange factors (GEFs) for Rho-family GTPases (RAC, RHO and CDC42). VAV1 is found predominantly in hematopoietic cells, whereas VAV2 and VAV3 are more broadly expressed. VAV proteins link the cell surface receptors like FCGR to the intracellular Rho GTPases and the actin cytoskeleton during phagocytosis (Hall et al 2006). Experiments using two-hybrid system suggest that VAV1 with its SH2 domain directly binds to the phosphorylated Y342 of SYK (Deckert et al. 1996). VAV proteins are also recruited to membrane through their PH domain by binding PI(3,4,5)P3 produced by PI3K.

Literature references


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Phosphorylation of VAV

**Location:** Regulation of actin dynamics for phagocytic cup formation

**Stable identifier:** R-HSA-2029453

**Type:** transition

**Compartments:** plasma membrane, cytosol, extracellular region

VAV proteins exist in an auto-inhibitory state folded in such a way as to inhibit the GEF activity of its DH domain. This folding is mediated through binding of tyrosines in the acidic domain to the DH domain and through binding of the CH domain to the C1 region. Activation of VAV may involve at least three different events to relieve this auto-inhibition. Phosphorylation of the tyrosines in the acidic domain causes them to be displaced from the DH domain, binding of a ligand to the CH domain may cause it to release the C1 domain and binding of PIP3 to PH domain may alter its conformation. VAV1 is phosphorylated on Y174 in the acidic domain, and this is mediated by Syk and Src-family tyrosine kinases. Once activated, VAV1 is then involved in the activation of RAC and CDC42 downstream of FCGR.

**Followed by:** Activation of RAC1 by VAV

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**Activation of RAC1 by VAV**

**Location:** Regulation of actin dynamics for phagocytic cup formation

**Stable identifier:** R-HSA-2029451

**Type:** transition

**Compartments:** plasma membrane, cytosol, extracellular region

The organized movements of membranes and the actin cytoskeleton are coordinated in phagocytosis by small GTPases of the Rho family. Specifically, RAC1 and CDC42 are known to be stimulated upon engagement of FCGR and are essential for the extension of the pseudopods that surround and engulf the phagocytic particle (Scott et al 2005). RAC1 is known to regulate actin dynamics. It is active throughout the phagocytic cup and activated RAC1 is necessary to assemble F actin. However, closing the phagocytic cup requires RAC1 to be deactivated (Naakaya et al 2007). Deletion of RAC1 prevents FCGR mediated phagocytosis (Hall et al 2006). RAC1 activation involves transition from an inactive GDP bound to an active GTP bound state catalysed by guanine exchanges factors (GEFs). VAV has been implicated in the activation of RAC1 (Patel et al 2002).

**Preceded by:** Phosphorylation of VAV

**Literature references**


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Recruitment of CRKII:DOCK180:ELMO complex to FCGR

**Location:** Regulation of actin dynamics for phagocytic cup formation

**Stable identifier:** R-HSA-2197697

**Type:** binding

**Compartments:** plasma membrane, cytosol, extracellular region

Macrophages lacking all the three isoforms of VAV did not affect FCGR-mediated phagocytosis suggesting that RAC1 is regulated by GEFs other than VAV downstream of the FCGR (Hall et al 2006). DOCK180, a member of GEFs, is found to be involved in the activation of RAC1. DOCK180 associates with the adaptor protein CRKII and the complex is found to accumulate at the phagocytic cup. DOCK180 is recruited to the sites of phagocytosis by binding to SH3 domain of CRKII through its proline-rich motif (Hasegawa et al 1996). CRKII is likely recruited to the activated FCGR complex by binding phosphorylated ITAM tyrosines on the receptor or through other phosphotyrosines on ancillary proteins that are recruited to the receptor complex (Lee et al 2007). Unlike the usual GEFs, DOCK180 does not contain the conserved Dbl homology (DH) domain. Instead, it has a DHR-2 or DOCKER domain capable of loading RAC with GTP (Brugnera et al 2002). Binding of DOCK180 to RAC alone is insufficient for GTP loading, and a DOCK180-ELMO interaction is required. ELMO1, as well as ELMO2, form a complex with DOCK180 and they function together as a bipartite GEF to optimally activate RAC (Gumienny et al 2001, Brugnera et al 2002).

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Activation of RAC1 by CRKII:DOCK180:ELMO

**Location:** Regulation of actin dynamics for phagocytic cup formation

**Stable identifier:** R-HSA-2029467

**Type:** transition

**Compartments:** plasma membrane, cytosol, extracellular region

RAC1 is activated from inactive GDP-bound state to active GTP-bound form by the GEF activity of DOCK180:ELMO complex.

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RAC1:GTP and PIP3 bind WAVE Regulatory Complex (WRC), activating it

**Location:** Regulation of actin dynamics for phagocytic cup formation

**Stable identifier:** R-HSA-2029465

**Type:** binding

**Compartments:** plasma membrane, cytosol

WASP family verprolin-homologous proteins (WAVEs) function downstream of RAC1 and are involved in activation of the ARP2/3 complex. The resulting actin polymerization mediates the projection of the plasma membrane in lamellipodia and membrane ruffles. WAVEs exist as a pentameric hetero-complex called WAVE Regulatory Complex (WRC). The WRC consists of a WAVE family protein (WASF1, WASF2 or WASF3 - commonly known as WAVE1, WAVE2 or WAVE3), ABI (Abelson-interacting protein), NCKAP1 (NAP1, p125NAP1), CYFIP1 (SRA1) or the closely related CYFIP2 (PIR121), and BRK1 (HSPC300, BRICK). Of the three structurally conserved WAVEs in mammals, the importance of WAVE2 in activation of the ARP2/3 complex and the consequent formation of branched actin filaments is best established. WAVEs in the WRC are intrinsically inactive and are stimulated by RAC1 GTPase and phosphatidylinositols (PIP3). The C-terminal VCA domain of WAVE2 (and likely WAVE1 and WAVE3) which can bind both the ARP2/3 complex and actin monomers (G-actin) is masked in the inactive state. After PIP3 binds to the polybasic region of WAVE2 (and likely WAVE1 and WAVE3) and RAC1:GTP binds to the CYFIP1 (or CYFIP2) subunit of the WRC, allosteric changes most likely occur which allow WAVEs to interact with the ARP2/3 complex and the consequent formation of branched actin filaments is best established. Followed by: p-ERK phosphorylates WAVEs and ABI

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**p-ERK phosphorylates WAVEs and ABI**

**Location:** Regulation of actin dynamics for phagocytic cup formation

**Stable identifier:** R-HSA-2029469

**Type:** transition

**Compartments:** cytosol, plasma membrane

The ARP2/3 complex shows higher affinity for the phosphorylated VCA domain of WAVE2 than for the unphosphorylated VCA domain. WAVE proteins can be phosphorylated by various kinases. Active ERK (Mitogen activated protein kinase 3) phosphorylates the WAVE regulatory complex (WRC) on multiple serine/threonine sites within the proline-rich domains (PRDs) of WAVE2 and ABI1. Phosphorylation of the PRDs would disrupt their interaction with SH3 and PLP binding domains, potentially altering WRC activation. ERK phosphorylates both S343 and T346 in WAVE2 and S183, S216, S225, S392, and S410 in ABI1. Cumulatively, the phosphorylation of both WAVE2 and ABI in the WAVE regulatory complex (WRC) contributes to the RAC-induced WRC conformational change that exposes the VCA domain, leading to binding and activation of ARP2/3 (Mendoza et al. 2011, Nakanishi et al. 2007). ERK phosphorylation sites in WAVE2 are not strictly conserved in WAVE1 and WAVE3 but, based on the amino acid sequence, other potential ERK phosphorylation sites exist.

**Preceded by:** RAC1:GTP and PIP3 bind WAVE Regulatory Complex (WRC), activating it

**Followed by:** ABL phosphorylates WAVEs

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**ABL phosphorylates WAVEs**

**Location:** Regulation of actin dynamics for phagocytic cup formation

**Stable identifier:** R-HSA-2130194

**Type:** transition

**Compartments:** plasma membrane, cytosol

Abelson interactor-1 (ABL) tyrosine kinase phosphorylates the strictly conserved tyrosine 150 in WAVE2 (Y151 in WAVE1 and WAVE3) (Leng et al. 2003, Chen et al. 2010).

**Preceded by:** p-ERK phosphorylates WAVEs and ABI

**Followed by:** WASPs or WAVEs activate the ARP2/3 complex

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An unknown GEF exchanges GTP for GDP on CDC42:GDP, activating it

**Location:** Regulation of actin dynamics for phagocytic cup formation

**Stable identifier:** R-HSA-2029445

**Type:** omitted

**Compartments:** cytosol

FCGR mediated phagocytosis requires CDC42 to stimulate actin polymerization, generating the force for phagocytic cup protrusion or pseudopod extension. CDC42 activation is restricted at the advancing edge of the phagocytic cup, where actin is concentrated, and is deactivated at the base of the phagocytic cup (Beemiller et al 2010). The mechanism behind the recruitment and activation of CDC42 during FCGR phagocytosis is unknown. VAV regulates the activation of RAC1 but not CDC42 and the GEF responsible for CDC42 activation during FCGR-mediated phagocytosis remains unidentified (Adam et al 2004, Patel et al 2002).

**Followed by:** Activation of WASP and N-WASP by CDC42, RAC1 and CDC42 activate PAK1

**Literature references**


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Wiskott-Aldrich syndrome protein (WASP) and Neural-WASP (N-WASP, WASL) proteins are scaffolds that transduce signals from cell surface receptors to the activation of the ARP2/3 complex and actin polymerization. WASP and N-WASP possess a central GTPase binding domain (GBD) and an NH2-terminal WASP homology domain 1 (WH1) followed by a basic region (B), and a C-terminal VCA region that contains: a V domain (verprolin homology/WASP homology 2), a C domain (connecting), and an A motif (acidic). The VCA region is responsible for binding to and activating the ARP2/3 complex (Bompard & Caron 2004, Callebaut et al 1998). Under resting conditions, WASP and N-WASP are maintained in an autoinhibited state via interaction of the GBD and the VCA domains. This prevents access of the ARP2/3 complex and G-actin to the VCA region. Activated CDC42 binds to the GBD region of WASPs and this interaction releases the VCA region from autoinhibition, enabling binding of the ARP2/3 complex and stimulating actin polymerization (Kim et al 2000, Park & Cox 2009). Phosphoinositides (PtdIns(4,5)P2) interact with the basic (B) region in WASPs and this interaction is important for activation of the WASPs and the ARP2/3 complex (Higgs & Pollard 2000).

Preceded by: An unknown GEF exchanges GTP for GDP on CDC42:GDP, activating it

Followed by: WIP binds WASP/N-WASP, activating them

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WIP binds WASP/N-WASP, activating them

**Location:** Regulation of actin dynamics for phagocytic cup formation

**Stable identifier:** R-HSA-2197691

**Type:** binding

**Compartments:** cytosol, plasma membrane


SH3 domain containing adaptor proteins like GRB2 (Carlier et al. 2000), NCK (Rohatgi et al. 2001) and WISH (DIP/SPIN90) (Fukuoka et al. 2001) bind to the proline rich domain in WASPs and activate the ARP2/3 complex. By binding simultaneously to N-WASP and the ARP2/3 complex, GRB2 works synergistically with CDC42 in the activation of ARP2/3 complex-mediated actin assembly (Carlier et al. 2000).

**Preceded by:** Activation of WASP and N-WASP by CDC42

**Followed by:** Src family kinases (SFKs) phosphorylate WASP/N-WASP

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Src family kinases (SFKs) phosphorylate WASP/N-WASP

Location: Regulation of actin dynamics for phagocytic cup formation

Stable identifier: R-HSA-2197698

Type: transition

Compartments: cytosol, plasma membrane

WASP is phosphorylated on Tyr291 (Cory et al. 2002) and N-WASP (WASL) on Tyr256 (Wu et al. 2004) by Src family of tyrosine kinases and this phosphorylation may release the autoinhibitory intramolecular interactions. The phosphorylation seems to be enhanced by the activation of CDC42. WASP phosphorylation and binding of CDC42 have a synergistic effect on the activation of the ARP2/3 complex (Takenawa & Suetsugu 2007). In N-WASP, the phosphorylation may reduce its nuclear translocation and may sustain it in its functional site in the cytoplasm (Wu et al. 2004).

Preceded by: WIP binds WASP/N-WASP, activating them

Followed by: WASPs or WAVEs activate the ARP2/3 complex

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WASPs or WAVEs activate the ARP2/3 complex

Location: Regulation of actin dynamics for phagocytic cup formation

Stable identifier: R-HSA-442592

Type: binding

Compartments: cytosol, plasma membrane

Inferred from: WASP/N-WASP activate the Arp2/3 complex (Rattus norvegicus)

Once WASPs (WASP and N-WASP) and WAVEs (WAVE2 and probably WAVE1 and WAVE3) are activated, their VCA region becomes available for binding to the ARP2/3 complex and actin monomer (G-actin). The actin monomer binds to the V domain and ARP2/3 complex binds to the CA domain. The simultaneous binding of G-actin and the ARP2/3 complex to the VCA region contributes to the activation of the ARP2/3-complex-mediated actin polymerization. The VCA module acts as a platform on which an actin monomer binds to the ARP2/3 complex to trigger actin polymerization (Takenawa & Suetsugu 2007).

Preceded by: Src family kinases (SFKs) phosphorylate WASP/N-WASP, ABL phosphorylates WAVEs

Followed by: Attachment of preexisting mother filament and initiation of branching

Literature references


Attachment of preexisting mother filament and initiation of branching

**Location:** Regulation of actin dynamics for phagocytic cup formation

**Stable identifier:** R-HSA-2029466

**Type:** binding

**Compartments:** cytosol

Once activated, the ARP2/3 complex nucleates new actin filaments that extend from the sides of pre-existing mother actin filaments at a 70-degree angle to form Y- branched networks (Firat-Karalar & Welch 2010). These branched actin filaments push the cell membrane forward to form a pseudopod. The ARP2/3 complex is composed of two Arps (actin-related proteins), ARP2 and ARP3, and five unique proteins ARPC1, ARPC2, ARPC3, ARPC4 and ARPC5 (Gournier et al. 2001). Both ARP2 and ARP3 subunits bind ATP. There are two proposed models to explain the process of actin nucleation by ARP2/3 complex: the barbed-end branching model and the dendritic nucleation/side branching model (Le Clainche & Carlier 2008).

In barbed-end branching model, the branching/ternary complex (G-actin-WASP/WAVE-Arp2/3 complex) binds to the barbed end of the mother filament. G-actin bound to VCA domain or one of the Arp subunits incorporates into the mother filament at the barbed end, thus positioning ARP2/3 complex to initiate the daughter branch on the side of the mother filament. ARP2/3 nucleates the formation of new actin filament branches, which elongate at the barbed ends (Le Clainche & Carlier 2008, Pantaloni et al 2000, Le Clainche et al. 2003, Egile et al. 2005). In side branching model, the branching complex binds to the side of the mother actin filament mimicking an actin nucleus and initiates a lateral branch (Le Clainche & Carlier 2008, Amann & Pollard 2001).

**Preceded by:** WASPs or WAVEs activate the ARP2/3 complex

**Followed by:** Detachment of WASP/WAVE

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Detachment of WASP/WAVE

Location: Regulation of actin dynamics for phagocytic cup formation

Stable identifier: R-HSA-2197690

Type: dissociation

Compartments: cytosol, plasma membrane

After incorporation at the branch, the actin bound to VCA domain of WASP/WAVE undergoes ATP hydrolysis and this destabilizes its interaction with WASP/WAVE. This dissociates the branched junction from the membrane-bound WASP/WAVE (Kovar 2006).

Preceded by: Attachment of preexisting mother filament and initiation of branching

Followed by: Branching and elongation of mother and daughter filaments

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Branching and elongation of mother and daughter filaments

Location: Regulation of actin dynamics for phagocytic cup formation

Stable identifier: R-HSA-2029473

Type: omitted

Compartments: cytosol

ATP bound G-actin monomers are added to the fast growing barbed ends of both mother and daughter filaments. The polymerization of these filaments drives membrane protrusion. In the process of phagocytosis, pseudopodia extend around the antibody-bound particle to form the phagocytic cup. This elongation continues until the filament reaches steady state equilibrium with free G-actin monomers (Millard et al. 2004, Le Clainche et al. 2008).

Preceded by: Detachment of WASP/WAVE

Followed by: Extension of pseudopodia by myosin-X in a PI3K dependent manner

Literature references


RAC1 and CDC42 activate PAK1

**Location:** Regulation of actin dynamics for phagocytic cup formation

**Stable identifier:** R-HSA-2029456

**Type:** transition

**Compartments:** cytosol, plasma membrane

PAK1, a downstream effector of CDC42 and RAC1, is found localized in phagosomes. Upon activation, PAK1 phosphorylates LIMK, which directly phosphorylates and inactivates cofilin, a protein that mediates depolymerization of actin filaments. Thus, RAC and CDC42 coordinate actin dynamics by inducing actin polymerization via ARP2/3 on one hand, and inhibiting actin depolymerization via LIMK and cofilin on the other (Garcia-Garcia & Rosales 2002).

PAK1 exists as homodimer in a trans-inhibited conformation. The kinase inhibitory (KI) domain of one PAK1 molecule binds to the C-terminal catalytic domain of the other and inhibits catalytic activity. GTPases RAC1/CDC42 bind the GBD domain of PAK1 thereby altering the conformation of the KI domain, relieving inhibition of its catalytic domain, and allowing PAK1 autophosphorylation that is required for full kinase activity (Parrini et al. 2002, Zhao & Manser 2005).

**Preceded by:** An unknown GEF exchanges GTP for GDP on CDC42:GDP, activating it

**Literature references**


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**Autophosphorylation of PAK1**

**Location:** Regulation of actin dynamics for phagocytic cup formation

**Stable identifier:** R-HSA-2029454

**Type:** transition

**Compartments:** cytosol

PAK1 needs autophosphorylation for complete activation. PAK1 is autophosphorylated at several sites, but S144 flanking the kinase inhibitor region and T423 within the catalytic domain are the two conserved sites that regulate the catalytic activity (Chong et al. 2001, Parrini et al. 2001).

**Literature references**

Parrini, MC., Lei, M., Harrison, SC., Mayer, BJ. (2002). Pak1 kinase homodimers are autoinhibited in trans and dissociated upon activation by Cdc42 and Rac1. Mol Cell, 9, 73-83.


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PAK1 phosphorylates LIMK1

Location: Regulation of actin dynamics for phagocytic cup formation

Stable identifier: R-HSA-2029460

Type: transition

Compartments: cytosol

LIM kinases are serine protein kinases with a unique combination of two N-terminal LIM motifs, a central PDZ domain, and a C-terminal protein kinase domain. LIMK1 is one of the downstream targets of PAK1 and is activated through phosphorylation by PAK1 on T508 within its activation loop (Edwards et al. 1999, Aizawa et al. 2001). LIM-kinase is responsible for the tight regulation of the activity of cofilin (a protein that depolymerizes actin filaments) and thus maintains the balance between actin assembly and disassembly. Phosphorylated cofilin is inactive, resulting in stabilization of the actin cytoskeleton.

Literature references


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**Dimerization of LIMK1 by Hsp90**

**Location:** Regulation of actin dynamics for phagocytic cup formation

**Stable identifier:** R-HSA-419645

**Type:** binding

**Compartments:** cytosol

After phosphorylation on Thr 508, LIMK undergoes homodimerization. Homodimer formation is promoted by the binding of heat shock protein 90 (Hsp90) to a short sequence in the kinase domain of LIMKs. LIMKs are further phosphorylated after homodimer formation and transphosphorylation of the kinase domain.

**Literature references**


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Transphosphorylation of pLIMK1

**Location:** Regulation of actin dynamics for phagocytic cup formation

**Stable identifier:** R-HSA-419644

**Type:** omitted

**Compartments:** cytosol

Binding of Hsp90 to the LIMK proteins protects them from degradation and promotes their dimer formation and transphosphorylation. It is estimated that LIMK1 contains at least 5 phospho-amino acids primarily phospho-serines, in its kinase domain. The positions of these serine residues are not known. Transphosphorylation of these serine residues in LIMK1 increases its stability.

**Literature references**


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Phosphorylation of cofilin by LIMK-1

**Location:** Regulation of actin dynamics for phagocytic cup formation

**Stable identifier:** R-HSA-399950

**Type:** transition

**Compartments:** cytosol, plasma membrane

**Inferred from:** Limk1 phosphorylates Cfl1, inactivating it (Homo sapiens)

The EPHB2-FAK pathway partially promotes dendritic spine stability through LIMK-mediated cofilin (CFL1) phosphorylation (Shi et al. 2009). CFL1 is a member of the ADF (actin-depolymerizing factor) protein family that is involved in regulating actin dynamics in the growth cone. It binds to actin in a one-to-one molar ratio, and stimulates both the severing of actin filaments and depolymerization of actin sub-units from the actin filament end. Activated LIMK phosphorylates CFL1 on the conserved serine 3 residue located near the actin-binding site. After phosphorylation, CFL1 is inactive, loses its affinity for actin and dissociates from G-actin monomers. Once freed, ADP-actin monomers can exchange ADP with cytoplasmic ATP, ready for reincorporation at the barbed end of a growing filament (Gungabissoon & Bamburg 2003).

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Extension of pseudopodia by myosin-X in a PI3K dependent manner

Location: Regulation of actin dynamics for phagocytic cup formation

Stable identifier: R-HSA-1861595

Type: transition

Compartments: plasma membrane, cytosol

Myosin-X (Myosin 10) is one of the downstream effectors of PI3K in FCGR-phagocytosis and is involved in pseudopod extension and closure of phagocytic cups. It is recruited to the forming phagosome by binding, through its second PH domain to membrane PIP3, a major product of PI3-kinase (Cox et al. 2002). Myosin-X may act as a motor to transport membrane cargo molecules to the forming pseudopods, influencing actin dynamics. It is not understood with certainty how myosin X contributes to the mechanism of pseudopod extension. It selectively binds to actin bundle such that each head may bind, in an ATP-sensitive manner, to two adjacent actin filaments within the actin bundle. Myosin X hydrolyze ATP and converts this chemical energy to mechanical energy moving toward the plus end/barbed end of the actin filament facing towards the tip of the growing pseudopods (Araki 2006, Chavrier 2003, Watanabe et al 2010).

Preceded by: Branching and elongation of mother and daughter filaments

Literature references


Editions

2012-01-04 Authored, Edited Garapati, P V.
2012-05-15 Reviewed Rosales, C.
Role of myosins in phagosome formation

Location: Regulation of actin dynamics for phagocytic cup formation

Stable identifier: R-HSA-2029476

Type: omitted

Compartments: phagocytic cup, extracellular region, cytosol, plasma membrane

In addition to the membrane remodeling for pseudopod extension, particle internalization requires a contractility force pulling the forming phagosome into the cytoplasm. Myosin motor proteins are the actin-binding proteins, with ATPase activity move along actin fibers, and produce the driving force for phagosome formation and transport. Several myosin motors including myosins IC, II, V, IXb are involved in FCGR-mediated phagocytosis as force generators and actin-based transport motors (Swanson et al. 1999). Nonmuscle myosin II, is a motor protein known to generate intracellular contractile forces and tension by associating with F-actin. It has been observed to localize around forming phagosomes and suggested a role in phagocytic-cup squeezing during FCGR-mediated phagocytosis. Each myosin II motor protein exists as a complex consisting of two copies each of myosin II heavy chain (MHC), essential light chains (ELC), and myosin regulatory light chain (MRLC). Selective inhibition of myosin II by ML-7, a myosin light-chain kinase (MLCK) inhibitor, prevents phagocytic cup closure, but not pseudopod extension for the formation of phagocytic cups in FCGR-mediated phagocytosis (Grooves et al. 2008, Araki 2006). Tight ring of actin filaments within the elongating pseudopodia squeezes the deformable particles. In the classical zipper model for phagocytosis, the pseudopod extends over the IgG-coated particles, in which FCGRs in the phagocyte plasma membrane interact sequentially with Fc portions of IgG molecules zipper the membrane along the particle. This sequential IgG-FCGR binding might not occur by itself, but requires forced zipper closure, where myosin-II contractile activity may promote the binding between the FCGR and its ligands, to facilitate the efficient extension and subsequent closure of phagocytic cups (Araki 2006, ). Myosin IC mediates the purse-string-like contraction that closes phagosomes. Myosin-V has been implicated in membrane trafficking events (Swanson et al. 1999).

Literature references


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