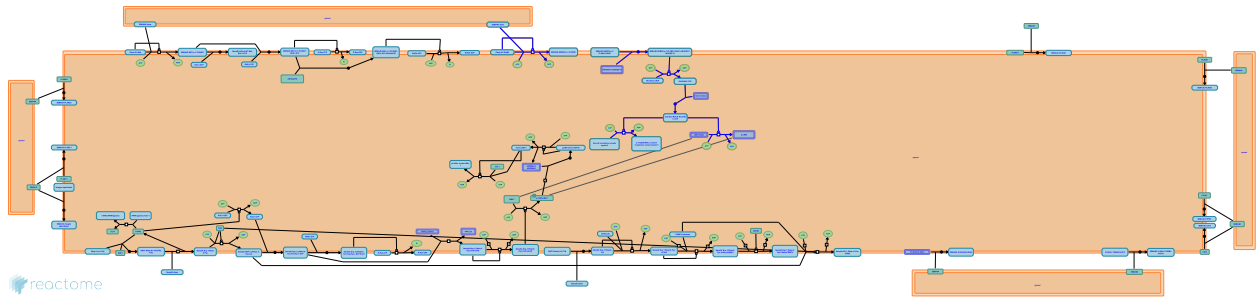


Sema4D induced cell migration and growth-cone collapse



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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.

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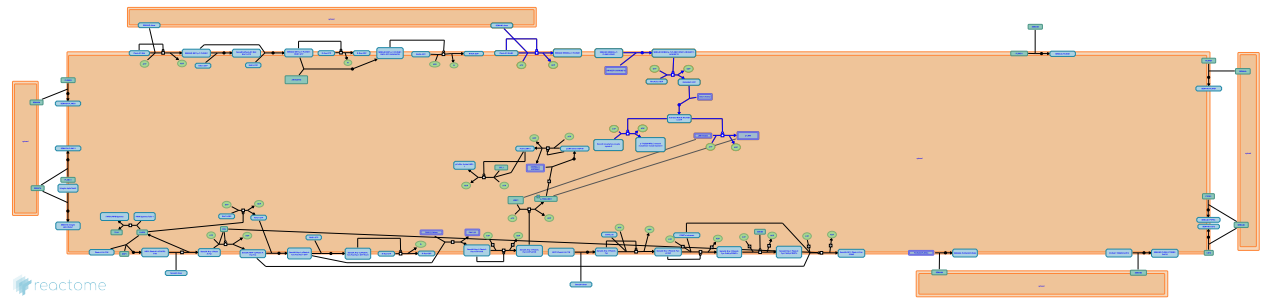
Reactome database release: 70

This document contains 1 pathway and 6 reactions ([see Table of Contents](#))

Sema4D induced cell migration and growth-cone collapse [↗](#)

Stable identifier: R-HSA-416572

Compartments: plasma membrane



Sema4D-mediated attraction of endothelial cells requires Rho, but not R-Ras, signaling. Sema4D-mediated plexinB1 activation activates Rho and its downstream effector ROCK. ROCK then phosphorylates MLC to induce actomyosin stress fiber contraction and to direct the assembly of focal adhesion complexes and integrin-mediated adhesion.

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Editions

2009-03-23	Authored, Edited	Garapati, P V.
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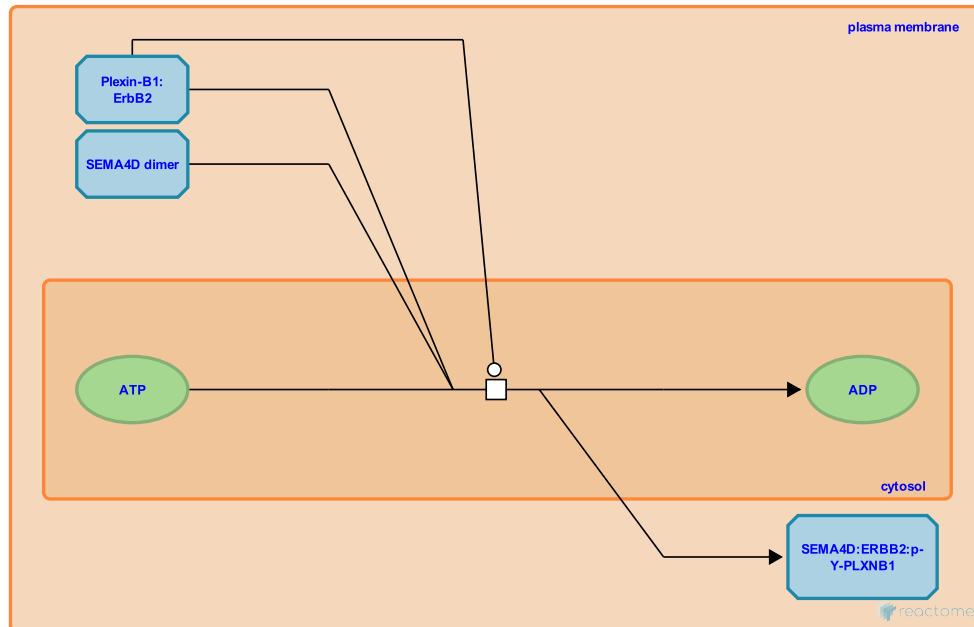
SEMA4D interacts with Plexin-B1:ErbB2 ↗

Location: [Sema4D induced cell migration and growth-cone collapse](#)

Stable identifier: R-HSA-373750

Type: transition

Compartments: cytosol, plasma membrane



Sema4D binds Plexin-B1 to induce repulsive or attractive effects in neuronal and nonneuronal cells. Plexins constitute a large family of transmembrane proteins that function as receptors for semaphorins and their interaction governs cell adhesion and migration in a variety of tissues. All B-class plexins can interact with the receptor tyrosine kinases Met and ErbB2. Upon binding of Sema4D to plexin-B1, the kinase activity of ErbB2 is increased resulting in tyrosine phosphorylation of both Plexin-B1 and ErbB2. ErbB2 has been shown to mediate Sema4D-induced growth cone collapse in hippocampal neurons by the activation of RhoA via plexinB1 and PDZRhoGEF/LARG.

Sequence alignment reveals the presence of 13 conserved tyrosine residues (highly conserved sites 1918, 1953, 2038) but the specific tyrosine residues phosphorylated in the cytoplasmic domain of plexins in response to semaphorin stimulation have not yet been identified.

Followed by: [LARG and PDZ-RhoGEF binds to Plexin-B1](#)

Literature references

Swiercz, JM., Worzfeld, T., Offermanns, S. (2008). ErbB-2 and met reciprocally regulate cellular signaling via plexin-B1. *J Biol Chem*, 283, 1893-901. ↗

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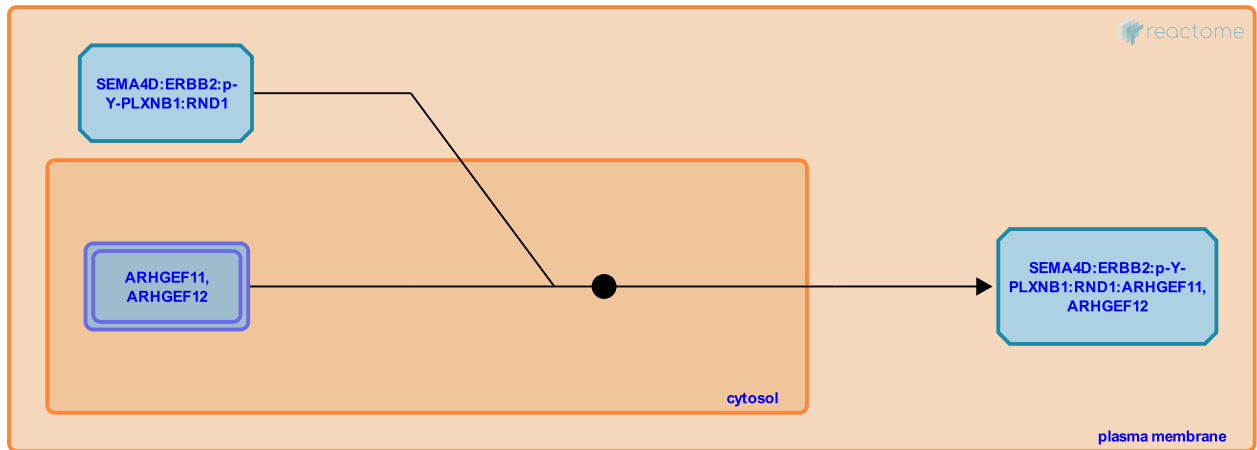
LARG and PDZ-RhoGEF binds to Plexin-B1 [↗](#)

Location: [Sema4D induced cell migration and growth-cone collapse](#)

Stable identifier: R-HSA-416594

Type: binding

Compartments: cytosol, plasma membrane



Plexin-B1 activates RhoA and induces growth cone collapse and cytoskeletal reorganization through Rho-specific guanine nucleotide exchange factors PDZ-RhoGEF (ARHGEF11) and leukemia-associated RhoGEF (LARG, ARHGEF12). Plexin-B1 directly interacts with PDZ-RhoGEF through its c-terminal PDZ domain binding motif. It has been suggested that Rnd1, which binds to the cytoplasmic part of plexin-B1, can promote the interaction between plexin-B1 and PDZ-RhoGEF. The PDZ domain of LARG is directly involved in the interaction with the c-terminal sequence of Plexin-B1.

Preceded by: [SEMA4D interacts with Plexin-B1:ErbB2](#)

Followed by: [Activation of Rho by LARG and PDZ-RhoGEF](#)

Literature references

- Swiercz, JM., Kuner, R., Offermanns, S. (2004). Plexin-B1/RhoGEF-mediated RhoA activation involves the receptor tyrosine kinase ErbB-2. *J Cell Biol*, 165, 869-80. [↗](#)
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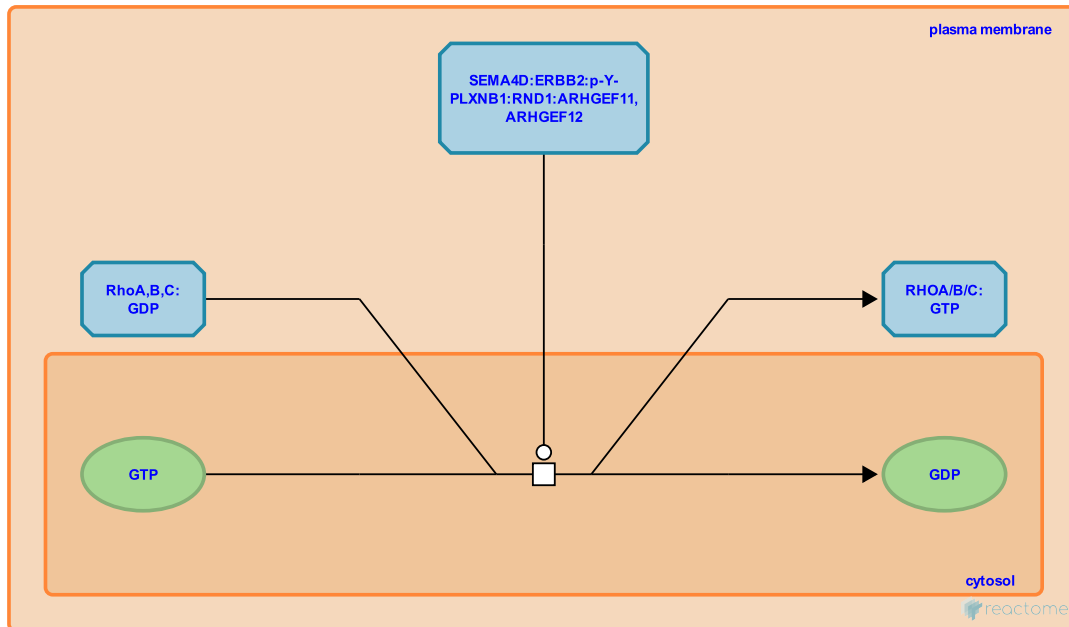
Activation of Rho by LARG and PDZ-RhoGEF ↗

Location: [Sema4D induced cell migration and growth-cone collapse](#)

Stable identifier: R-HSA-416588

Type: transition

Compartments: cytosol, plasma membrane



The RhoGEFs LARG and PDZ-RhoGEF complexed with Plexin-B1 stimulate the exchange of GDP for GTP on RhoA through their DH and PH domains.

Preceded by: [LARG and PDZ-RhoGEF binds to Plexin-B1](#)

Followed by: [ROCK activation by RHO](#)

Literature references

Oinuma, I., Katoh, H., Harada, A., Negishi, M. (2003). Direct interaction of Rnd1 with Plexin-B1 regulates PDZ-RhoGEF-mediated Rho activation by Plexin-B1 and induces cell contraction in COS-7 cells. *J Biol Chem*, 278, 25671-7. ↗

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Swiercz, JM., Kuner, R., Offermanns, S. (2004). Plexin-B1/RhoGEF-mediated RhoA activation involves the receptor tyrosine kinase ErbB-2. *J Cell Biol*, 165, 869-80. ↗

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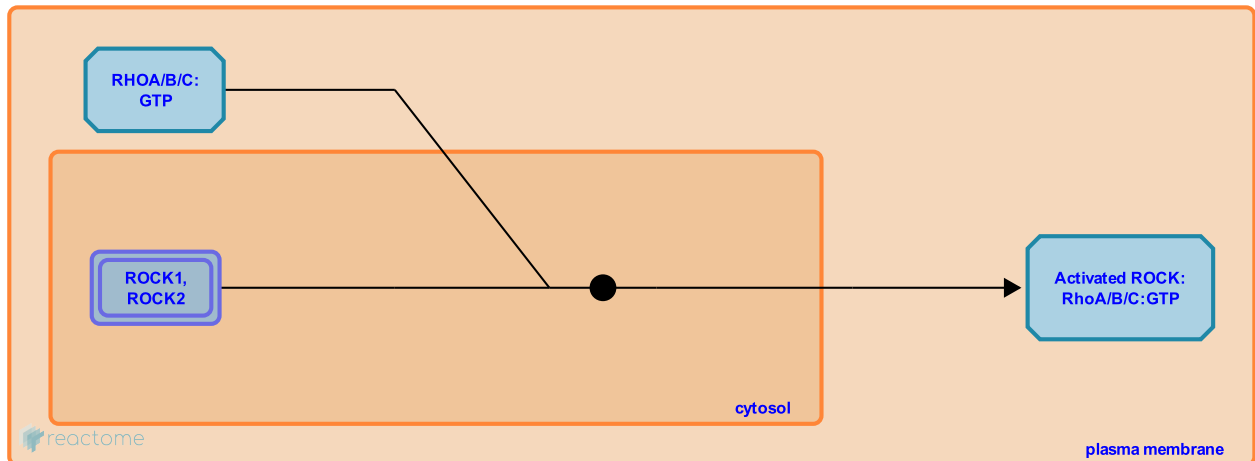
ROCK activation by RHO ↗

Location: [Sema4D induced cell migration and growth-cone collapse](#)

Stable identifier: R-HSA-419049

Type: binding

Compartments: cytosol, plasma membrane



ROCKs are primarily known as downstream effectors of RHO, but they can also be activated by arachidonic acid, which binds to the pleckstrin homology domain, releasing an autoinhibitory loop within ROCK and allowing catalytic activity (Araki et al. 2001). Proteolytic cleavage at the C-terminus by caspase-3 and granzyme B also activates ROCK1 and ROCK2, causing plasma membrane blebbing during apoptosis (Coleman et al. 2001, Sebbagh et al. 2005). Multiple targets of ROCK contribute to the stabilization of actin filaments and the generation of actin-myosin contractile force.

Preceded by: [Activation of Rho by LARG and PDZ-RhoGEF](#)

Followed by: [Myosin regulatory light chain phosphorylation by ROCK](#), [LIM kinase phosphorylation by ROCK](#)

Literature references

- Ishizaki, T., Maekawa, M., Fujisawa, K., Okawa, K., Iwamatsu, A., Fujita, A. et al. (1996). The small GTP-binding protein Rho binds to and activates a 160 kDa Ser/Thr protein kinase homologous to myotonic dystrophy kinase. *EMBO J*, 15, 1885-93. ↗
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2015-01-28	Revised	Orlic-Milacic, M.

Myosin regulatory light chain phosphorylation by ROCK ↗

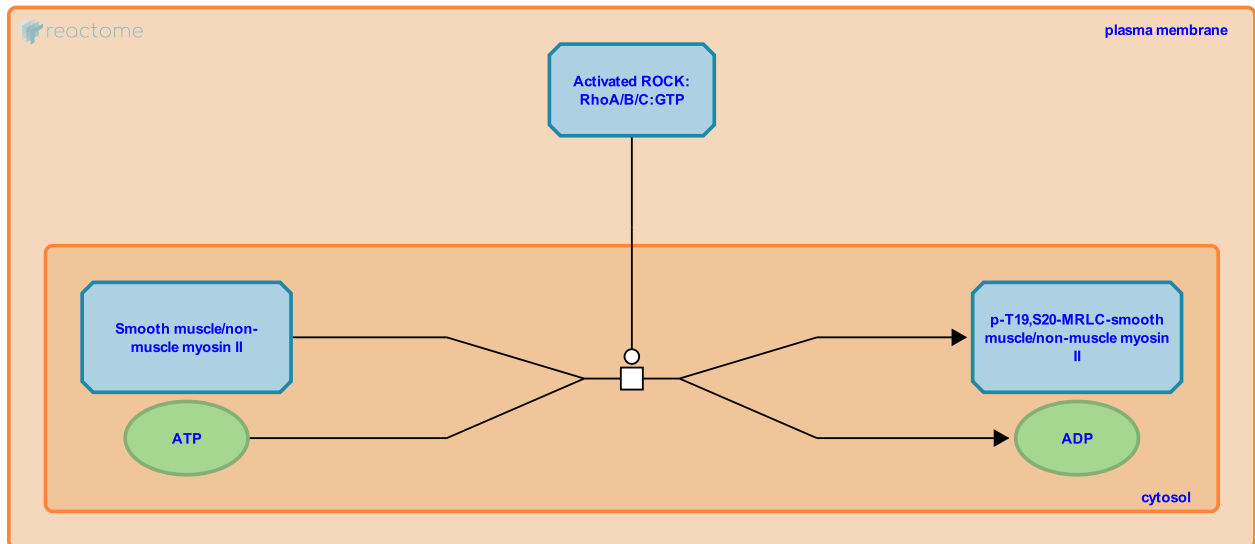
Location: [Sema4D induced cell migration and growth-cone collapse](#)

Stable identifier: R-HSA-419197

Type: transition

Compartments: cytosol, plasma membrane

Inferred from: [Myosin regulatory light chain phosphorylation by Rock2 \(Gallus gallus\)](#)



Nonmuscle myosin II (NMM2) is an actin-based motor protein that plays a crucial role in a variety of cellular processes, including smooth muscle contraction, cell migration, polarity formation, and cytokinesis. NMM2 consists of two myosin heavy chains encoded by MYH9, MYH10, MYH14 (NMHC-IIA, B and C) or MYH11, two copies of MYL6 essential light chain protein, and two regulatory light chains (MRLCs), MYL9 and MYL12B. Myosin II activity is stimulated by phosphorylation of MRLC. Diphosphorylation at Thr-19 and Ser-20 (commonly referred in the literature as Thr-18 and Ser-19) increases both actin-activated Mg^{2+} ATPase activity and the stability of myosin II filaments; monophosphorylation at Ser-20 is less effective (Ikebe and Hartshorne 1985, Ikebe et al. 1988). Kinases responsible for the phosphorylation include myosin light chain kinase (MLCK), ROCK kinase, citron kinase, myotonic dystrophy kinase-related CDC42-binding protein kinase, and Zipper-interacting protein (ZIP) kinase. ROCK activity has been shown to regulate MRLC phosphorylation by directly mono- or diphosphorylating MRLC (Amano et al., 1996, Ueda et al., 2002, Watanabe et al. 2007).

Preceded by: [ROCK activation by RHO](#)

Literature references

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2015-01-28	Revised	Orlic-Milacic, M.

LIM kinase phosphorylation by ROCK ↗

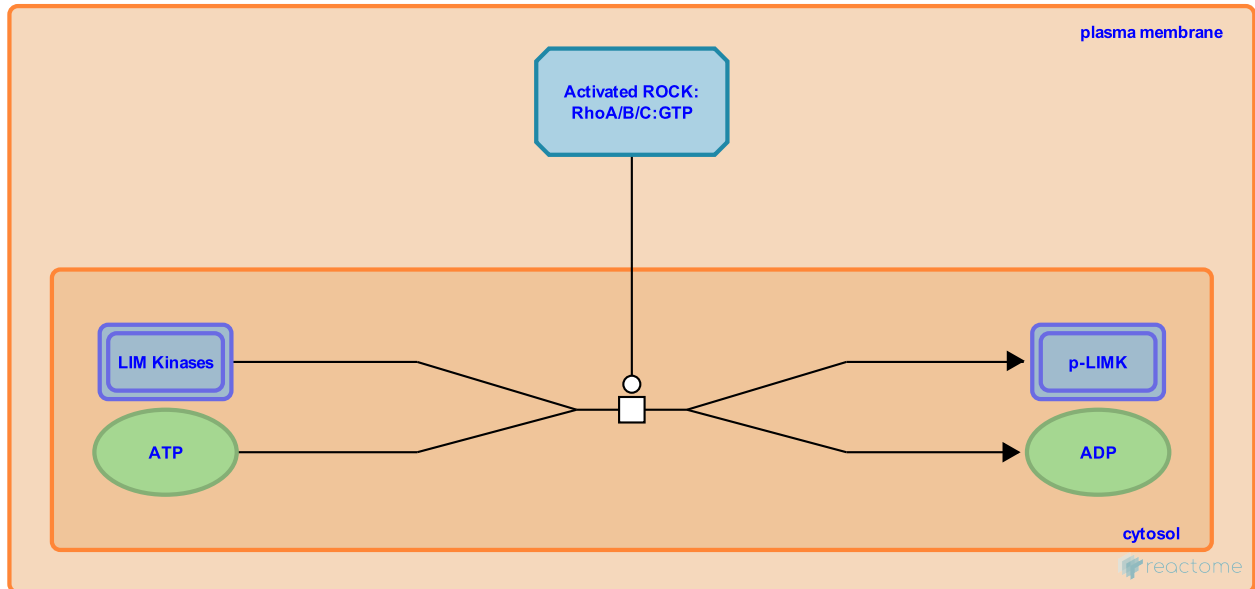
Location: [Sema4D induced cell migration and growth-cone collapse](#)

Stable identifier: R-HSA-419087

Type: transition

Compartments: cytosol, plasma membrane

Inferred from: [ROCK1 phosphorylates LIMK2 \(rat\) \(Homo sapiens\)](#)



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. ROCK1 and ROCK2 phosphorylate and activate LIM kinases LIMK1 and LIMK2 at Thr508 and Thr505, respectively (Ohashi et al. 2000, Sumi et al. 2001). These threonine residues lay within the activation loop of the kinase domain. LIMKs phosphorylate and inactivate cofilin, an actin depolymerizing factor, resulting in stabilization of the actin cytoskeleton (Pandey et al. 2006).

Preceded by: [ROCK activation by RHO](#)

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