DOCK1 (Dedicator of cytokinesis 1)

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Published in Atlas Database: March 2015

Online updated version: http://AtlasGeneticsOncology.org/Genes/DOCK1ID40354ch10q26.html
Printable original version: http://documents.irevues.inist.fr/bitstream/handle/2042/62524/03-2015-DOCK1ID40354ch10q26.pdf
DOI: 10.4267/2042/62524

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Abstract

Dedicator of cytokinesis (DOCK) is a family of proteins with 11 members in mammal which can regulate cell motility, phagocytosis, myoblast fusion, tumor suppression, neuronal polarization and adhesion. They are classified into four subfamilies A to D. Dock1 (Dock180), the founding member of the family, is a large protein which includes an N-terminal SH3 domain and a flanking helical bundle that are vital to the formation of a functioning complex Dock1-ELMO1 (Gumienny et al.,2001; Grimsley et al.,2004; Komander et al., 2008). Genetic and biochemical studies show that DOCK1 acts as a guanine-nucleotide exchange factor (GEF) for the small GTPase Rac1 (Diyokawa et al., 1998; Nolan et al., 1998). Rac1 is a small GTPase required for myoblast fusion in organisms such as fruit flies, zebrafish and mice (Rochlin et al.,1998). In addition to playing an important role in a broad spectrum of biological processes, numerous studies have demonstrated contributions of DOCK members to the development of cancer. Deciphering the detailed mechanisms by which DOCK proteins participate in tumorigenesis will shed light on the design of new treatment strategies.

Keywords
DOCK1

DNA/RNA

Description
The DOCK1 gene is 6797 base pairs in length encoding a large protein (about 180kDa).

Transcription
Variant (1) represents the longer transcript and encodes the longer isoform (1). Variant (2) uses an alternate splice site at an internal exon, compared to variant 1. The encoded isoform (2) is shorter, compared to isoform 1.

Protein

Description
Dock1 is a 180 kDa protein and largely responsible for regulating Rac-mediated polarization, migration, phagocytosis of apoptotic cells, myoblasts fusion and macrophages in vitro (Cte et al., 2005; Grimsley et al., 2004; Pajcini et al., 2008) DOCK1 and its homologues in Drosophila (Myoblast city) and C.elegans (CED-5) represent an evolutionarily conserved family of proteins which is called CDM (CED-5, DOCK180, MBC)-family (Wu and Horvitz, 1998). DOCK1 has 6 splice variants with two protein-coding transcripts generating products consisting of 1865 and 1886 amino acids respectively. The others are non-protein-coding transcripts. An SH3 domain at the A-terminus and two domain CRK-binding sequences at the carboxyl end have been identified in Dock1 (Hideki Hasegawa et al, 1996).
There are two high sequence homology named DHR-1 and DHR-2 among Dock family members (Jean Francois Cote and Kristiina Vuori, 2002). DHR1 domain is 200-250 amino acids long that binds phospholipids, whereas DHR2 domain of 450-550 amino acids is responsible for the guanine nucleotide exchange activity (25022758).

Expression
DOCK1 is predominantly located in the cytoplasm of cells. Nuclear localization of DOCK1 has also been reported (Zhao et al., 2011).

Function
This family is one of the GEFs being identified as activators of Rho GTPases (Takai et al., 1996; Hasegawa et al., 1996; Erickson and Cerione, 2004). DOCK1 activates Rho GTPase through facilitating the exchange of bound GDP for GTP. GTPases can regulate actin cytoskeleton and be accountable for crucial biological functions, such as cell phagocytosis, cell migration, cell proliferation, cell survival, cell polarity, axonal guidance, transcription and intracellular trafficking (Iwasato et al., 2007; Schmidt and Hall, 2002). In addition to playing an important role in a broad spectrum of biological processes, numerous studies have demonstrated contribution of DOCK members to the development of cancer.

Description
DHR domain DOCK1 and its homologues in Drosophila (Myoblast city) and Ca elegans (CED-5) represent an evolutionarily conserved family of proteins which is called CDM (CED-5, DOCK180, MBC)-family(Wu and Horvitz, 1998). This family is one of the GEFs being identified as activators of Rho GTPases (Takai et al., 1996; Hasegawa et al., 1996; Erickson and Cerione, 2004). The other family is Db family (Hart et al., 1991) and all their members contain the Db Homology (DH) and the Pleckstrin Homology (PH) domains (Klinger et al., 2004; Srivastava et al., 1986; Worthylake te al., 2004; Feng et al., 2002; Baird et al., 2005). While DH domains directly catalyze GDP-GTP exchange, PH domains target proteins to membranes and mediate protein-protein interactions. DOCK 180-related proteins can catalyze nucleotide exchange without homology to DH/PH domains, which are characterized by two protein domains named DOCK homology regions 1 and 2 (DHR-1 and DHR-2, respectively) (Brugnera et al., 2002; Cote and Vuori, 2002). DOCK1 contains 1864 amino acids, a Src-homology 3 (SH3) domain at the amino terminus, a few proline-rich motifs at the carboxyl terminus and a potential phosphatidylinositol trisphosphate (PtdInsP3)-interacting motif near its C terminus (Hasegawa et al.m 1996; Kobayashi et al 2001). Inactivation of the DHR-2 (also known as CZH2 or DOCKER) in DOCK1 can inhibit Rac activation, cell migration and clearance of apoptotic cells. This demonstrates the necessity and sufficiency of DHR-2 to promote GDP/GTP exchange on various GTPases. DHR-2 has been suggested to consist of about 500 residues (Brugnera et al., 2002; Cote and Vuori, 2002). DHR-2 domains of these family members have been shown to interact with the nucleotide-free form of Rho GTPase leading to the exchange of GDP for GTP(Meller et al., 2004; Lin et al., 2006; Miyamoto et al., 2006; Nishikimi et al 2005). DHR-1 domain (also known as CZH1) is located upstream of DHR-2 domain (Meller et al., 2002) and is a novel PtdIns (3,4,5)P3-binding module which directly interacts with phosphoinositides (PI), playing an important role in Rac-mediated cell polarity and migration including myoblast fusion(Cote and Vuori, 2002).

SH3 domains Src-homology3 (SH3) domains are protein-protein interaction modules in intracellular signal transduction. DOCK1 contains an SH3 domain at its N-terminus. SH3 domains have been reported to bind to a proline-finch motif at the C-terminus of ELMO (gumienny et al., 2001) which will be regulating the activation status of DOCK1. In DOCK1, SH3 domain interacts with DHR-2 domain directly which is dependent on a proline-rich region in DHR-2 domain, but inhibits some functions of the DHR-2 domain, such as binding to nucleotide-free Rac and facilitating GTP loading(Lu et al., 2005).

Interaction with ELMO ELMO is an evolutionarily conserved upstream regulator of Rac that takes effect at the same step as DOCK 1 in phagocytosis of apoptotic cells and cell migration (Gumienny et al., 2001). DOCK2-5 and DOCK 1 have an aminoterminal Src-homology (SH)-3 domain which can interact with ELMO proteins and cooperate to activate Rac (Grimsley et al., 2004; Hiramoto et al., 2006). Other Dock-related proteins such as DOCK 6-8 and DOCK9-11 cannot physically interact with ELMO proteins due to the lack of a recognizable
SH3 domain. Some studies showed that deletion mutants of DOCK 180 that fail to bind to ELMO could not efficiently activate Rac even when overexpressed in cells (Grimsley et al., 2004). Other studies suggested that owing to auto-inhibition, the isolated DHR-2 appears to have much higher GEF activity than total DOCK 180 (Lu et al., 2005; Cote et al., 2007). Co-expression of ELMO is required to relieve the auto-inhibited state (Lu et al., 2004; Santy et al., 2005). The ELMO-DOCK1 complex is located in the cytoplasm and will be translocated to the cell membrane, which is the key step for DOCK1 to activate Rac (Debakker et al., 2004; Katoh and Negishi et al., 2003; Hasegawa et al., 1996; Katoh et al., 2006). All three mammalian ELMO 1-3 proteins have no obvious catalytic activity. They have three recognizable features including armadillo repeats at the N-terminus, an atypical PH domain and a complex prolin-rich region at the C-terminus. In fact, the functions of ELMO proteins in mediating Rac signaling remain largely unknown, and the interaction between ELMO and DOCK is still unclear. Some data indicate that there are two contact regions between DOCK1 and ELMO1. The atypical ELMO1 PH domain and an uncharacterized region between the SH3 and DHR-1 domains primarily interact with each other. This interaction is sufficient to promote complex formation. N-terminal SH3 domain of DOCK1 and the C-terminal PxxP motifs of ELMO1 are involved in the second contact (Komander et al., 2008). The PH domain and proline-rich motifs are implicated in binding to DOCK protein (Manishha et al., 2011). It has been documented that the SH3 domain of DOCK1 binds to a proline-rich (pro-rich) motif at the C-terminus of ELMO, and this in turn would activate DOCK 1. This is the second interaction. So when either of these motifs is mutated, the interaction of ELMO and DOCK1 is completely interrupted (Gumienny et al., 2011; Lu et al., 2005). The PH domain of ELMO stabilizes the DOCK1-nucleotide-free Rac complex through binding "in trans" instead of interacting directly with either Rac or DOCK 180 (Lu et al., 2004). The atypical PH domain of ELMO plays a crucial role in increasing the catalytic activity of DOCK 180 towards Rac. ELMO1 or ELMO2, could coexpress with DOCK1, and overexpression of ELMO1 together with DOCK1 synergistically enhances phagocytosis(Zhou et al., 2001). ELMO PH domain could slightly enhance the catalytic activity of DOCK 1 toward Rac by about twofold in vitro. But this effect could be efficient in vivo because the Ced-12 PH domain mutations let Ced-12-null worms failed to rescue the migration defects (Lu et al., 2004). Therefore, the mechanism of action of Elmo remains inconclusive. Further studies are required to clarify the controversies.

**Binding to Crk** Crk is an adaptor protein consisting mostly of SH2 and SH3 domains which is also involved in signaling processes, such as cell adhesions, differentiation, migration, proliferation, and phagocytosis of apoptotic cells (Clark and Brugge, 1995; Juliano and Haskill, 1993; Richardson and Parsons, 1995). Crk gene can be translated into two proteins, Crk-I and Crk-II which are primarily isolated as oncogenic products (Mayer et al., 1988; Matsuda et al., 1992). DOCK180/DOCK1 can bind with the SH3 of the Crk through PxxP region in its C-termini (Matsuda et al., 1996). It has been shown that DOCK 1 has two C-terminal CRK-binding sequences. DOCK1 binds with Crk on the basis of a biochemical interaction. The complex will be transiently translocated to the membrane resulting in changes in cell morphology (Hasegawa et al., 1996).

**Essential for myoblast fusion** Mammalian myogenesis arises from the fusion of mononucleated myoblasts. Myogenic cells fuse with each other to form multinucleated myotubes (Horsley and Pavlath, 2004). Myoblast fusion is responsible for development during embryogenesis and postnatal maintenance, growth, and helps regenerate injured tissue (Cerletti et al. 2008; Rudnicki et al., 2007). Proper regulation of myoblast fusion events determines myofiber length, appropriate contractile capacity and muscle function (Allen et al., 1999). In fact, the understanding of myoblast fusion of higher vertebrates remains poor. Current knowledge is largely derived from genetic analyses performed in Drosophila (Chen and Olson, 2004; Taylor, 2003) and in vivo experiments in vertebrates (Cote and Vuori, 2007).

In Drosophila melanogaster, fusion-competent myoblasts and founder cells regulate the formation of multinucleate muscle fibers. At cellular level, the processes of myoblast fusion include alignment, actin cytoskeleton rearrangement at the contact sites and membrane fusion (Knudsen and Horvitz, 1977; Wakelam, 1985; Peckham, 2008; Duan and Gallagher, 2009). CDM superfamily consists of founding members such as MBC, human DOCK1, Caenorhabditis elegans CED-5 (Wu and Horvitz, 1998) and almost 20 additional members (Cote and Vuori, 2002). Myoblast city (mbc) is highly important in Drosophila melanogaster embryo for multinucleate fibers formation.

It has been reported that Mbc together with ELMO, function as an atypical bipartite GEF to directly control Rac1 in vivo. Drosophila eye experiments show that Mbc and ELMO interaction will increase the activity of Ras (Gersbrecht et al., 2008).

**Homology**

In mammals, dedicator of cytokinesis (DOCK) represents a new family of proteins comprising 11 members named DOCK1 (also known as Dock180) to Dock11. They are classified into four subfamilies denoted Dock-A, -B, -C, -D. 11 members are
classified as following: DOCK-A subfamily (DOCK1, DOCK2 and DOCK5); DOCK-B subfamily (DOCK3 and DOCK4); DOCK-C subfamily (DOCK6, DOCK7 and DOCK8); DOCK-D subfamily (DOCK9, DOCK10 and DOCK11) (Bridget Biersmith et al., 2011).

**Implicated in**

**Breast cancer**

Expression of DOCK1 correlates with poor survival for HER2+ and basal breast cancer patients (Eckhardt et al., 2012; Perou et al., 2000). Dock1 protein interacts with HER2 and enhances HER2-induced Rac activation and cell migration (Laurin et al., 2013).

**Glioblastoma**

EGFRvIII, a constitutively active EGFR mutant, promotes glioma tumorigenesis and invasion through protein kinase A-dependent phosphorylation of DOCK1 (Feng H et al., 2014).

**Ovarian cancer**

Correlation of high Dock1 expression with poor survival for patients has been reported. Dock1 overexpression contributes to enhanced ovarian cancer cell migration and invasion (Zhao F et al., 2011).

**Lung cancer**

Dock1 can upregulate PTTG which could play a role in actin cytoskeleton remodeling, cell migration and induction of epithelial mesenchymal transition in lung cancer. The integrin alpha(V)beta(3)-FAK (focal adhesion kinase) signaling pathway is involved. (Shah PP et al., 2012).

**Gastric cancer**

Among genes involved in extracellular signal-regulated kinase (ERK) downstream signaling pathways activated by Cytotoxin-associated antigen (CagA), a H. pylori immunoprotein, single nucleotide polymorphism of Dock1 was found to be significantly associated with risk of developing gastric cancer with marginal gene dose effects. (Yang JJ et al., 2011).

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Atlas Genet Cytofatogen Oncol Haematol. 2016; 20(3)

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