Gene Section
Review

CDC42 (cell division cycle 42 (GTP binding protein, 25kDa))

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Identity

Other names: CDC42Hs; G25K

HGNC (Hugo): CDC42

Location: 1p36.12

DNA/RNA

Description

This gene can be found on chromosome 1 at location 22,235,157-22,292,024.

Transcription

The DNA sequence contains 6 exons and the transcript length is 1,512 bps translated to a 191 residues protein. Alternative splicing of this gene results in three transcript variants that encode two isoforms. The transcript variants 1 and 3 encode the same isoform 1. The variant 3 has an additional exon in the 5' UTR compared to variant 1. The variant 2 encodes isoform 2 and differs from variant 1 at the 3' region including a small part of the coding region and the entire 3' UTR.

Protein

Description

CDC42 encodes a 21.3 kDa, 191 amino acids small GTPase protein that belongs to the Rho family of Ras GTPases superfamily. There are two isoforms produced by alternative splicing from a single gene. The isoform 1, also known as placental isoform, Cdc42p, Cdc42Hs or Cdc42a (Shinjo et al., 1990) has the same amino acid length than isoform 2 but differs from the isoform 2 as follows: 163 R (isoform 2) --> K (isoform 1) and at the C terminus in ten amino acids: 182-191 TQPKRKCCIF

(isoform 2) --> PKKSRRCVLL (isoform 1). The isoform 2, also known as brain isoform, Cdc42b or G25K (Munemitsu et al., 1990), has been chosen as the 'canonical' sequence.

The contribution of CDC42 to cancer progression seems to be tissue specific due to it has been found to have pro-oncogenic and anti-oncogenic properties depending on cellular context.

CDC42 activity regulation:

CDC42 switches between an active GTP-bound state and inactive GDP-bound state. This cycle is regulated by its intrinsic GTPase activity and its interaction with three protein families: guanine exchange factors (GEFs), guanine dissociation inhibitors (GDIs) and GTPase activating proteins (GAPs) (Bishop and Hall, 2000). Due to the exchange of GDP to GTP by CDC42 itself occurs very slowly, GEFs promote such exchange from GDP- to GTP-bound state. GAPs increase the GTP hydrolysis activity. Furthermore, CDC42 is able to interact with membranes via post-translational C-terminal geranylgeranyl lipid modification, however it can be found as a soluble complex association with RhoGDI. Thus, RhoGDIs sequester CDC42-GDP in the cytoplasm through a transfer of geranylgeranyl moiety from membrane to GDI and inhibit its spontaneous GDP/GTP exchange activity. Additionally, CDC42 can be phosphorylated by diverse kinases which regulate its interaction with RhoGDIs (Forget et al., 2002; DerMardirossian and Bokoch, 2005). To date over 70 Rho-GEFs, 60 Rho-GAPs and 3 Rho-GDIs have been identified in mammals, reflecting the complexity of regulation of these classes of proteins.

Biochemical studies of CDC42 show that, in response to external signals originating from cell surface receptors and cell adhesion molecules, GEFs engage

CDC42 and form macromolecular complexes with scaffolding proteins and/or kinases and with specific effector molecules triggering a signalling cascade to direct cellular responses (Cerione, 2004). CDC42 acts as a signal transduction convergence point in intracellular signalling networks, and mediates multiple signalling pathways, including tyrosine kinase receptors, heterodimeric G-protein coupled receptors (GPCR), cytokine receptors, integrins, and physical and chemical stress (Etienne-Manneville, 2004). The upstream signals include cytokines, growth factors, GPCR ligands, proteoglycans and integrins (Symons and Settleman, 2000).

CDC42 structure:
Rho proteins consist only of the GTPase domain and short N-terminal and C-terminal extensions. This family is defined by the presence of a Rho-type GTPases like domain located between the fifth β strand and the fourth α helix of their small GTPase domain (Valencia et al., 1991). A comparison of the RhoA-GDP and [Val14]RhoA-GTP[S] crystal structures, reveals that the conformational differences between the GTP and GDP-bound forms are restricted primarily to two surface loops, named switch regions I and II that correspond to CDC42 amino acids 26 and 59 (Bishop and Hall, 2000). Effector proteins utilize such differences to discriminate between the GTP- and GDP- bound forms, although they also interact with other regions of CDC42 protein. Nuclear magnetic resonance (NMR) structures of CDC42 bound to activated CDC42-associated tyrosine kinase (ACK) (amino acids 504-545) and WASP (amino acids 230-288) have provided a better understanding about Rho GTPase-effector interactions. ACK and WASP both contain the conserved GTPase-binding consensus site, the CRIB (CDC42/Rac-interactive binding) motif, which is present in many, though not all, Rac- and CDC42-binding proteins (Abdul-Manan et al., 1999; Mott et al., 1999). This motif is necessary, but not sufficient, for strong binding of the effector to CDC42.

CDC42 effectors:
To date, at least 23 proteins have been identified as potential effectors for CDC42 primarily using affinity chromatography and the yeast two-hybrid system. These proteins are: p70 S6 kinase; MLK2 and MLK3; MEKK1 and MEKK4; PAK1, PAK2, PAK3 and PAK4; MRCKα and MRCKβ; ACK1 and ACK2; PI3K; PLD; PLC-β2; WASP and N-WASP; MSE55 and BORGs; IQGAP1 and IQGAP2; and CIP-4 (Bishop and Hall, 2000).
The most common mechanism of effector activation by Rho GTPases appears to be the disruption of intramolecular autoinhibitory interactions, to expose functional domains within the effector protein.
CDC42 itself seems to be unable to discriminate downstream effectors because most of them, such as PAK, WASP, ACK and MLK3, have the same CDC42-interaction motif with similar binding affinity to active CDC42. So the specificity of CDC42 signalling seems to be dependent on: upstream signals that activate CDC42-GEFs; the interaction of these RhoGEFs with CDC42 effectors forming macromolecular complexes; the translocation of CDC42-effectors by RhoGEFs and RhoGDIs; and CDC42 signalling network components (Sinha and Yang, 2008).

Expression
CDC42 isoform 1 is the most commonly studied form and it is expressed ubiquitously, whereas the isoform 2 is restricted to the brain (Wennerberg and Der, 2004).

Localisation
In mammalian cells CDC42 is predominantly localized at Golgi apparatus but it has been also localized at the plasma membrane and on numerous vesicular structures dispersed throughout the cytosol (Erickson et al., 1996; Osmani et al., 2006).

Function
CDC42 is one of the best characterized members of Rho family. Their involvements in regulating actin cytoskeleton and cell polarity are the best studied functions. In this context, CDC42 plays a role in a wide variety of cellular processes that are dependent on the actin cytoskeleton, such as cytokinesis, phagocytosis, cell migration, morphogenesis, chemotaxis and axon guidance.
Physiologically, CDC42 is implicated in other essential cellular processes such as axon myelination, intracellular trafficking, gene transcription, cell-cycle regulation and cell fate determination. However, the contribution of CDC42 in these different cellular processes could be cell-type specific (Wang and Zheng, 2007; Heasman and Ridley, 2008).
Deregulation of CDC42 is found in several pathogenic processes such as cancer, neurodegenerative disorders and cardiovascular disease (Boettner and Van Aelst, 2002; Broman et al., 2007).

Role in actin cytoskeleton organization: regulation of filopodium formation:
CDC42 regulates signal transduction pathways linking various membrane receptors to the finally filopodia formation in many cell types. Filopodia are thin protrusions that contain parallel bundles of actin filaments that extend from the leading edge in many migratory cells being able to function as sensory probes or in the establishment of cell-cell contacts, for example in axon guidance and neurite extension (Gupton and Gertler, 2007).
CDC42 induces actin polymerization to the filopodia formation by binding to Wiskott-Aldrich syndrome protein (WASP) or through the insulin-receptor substrate p53 (IRSp53) Tyr kinase to induce branched actin filaments using the actin-related protein-2/3 (ARP2/3) complex. CDC42 also induces actin polymerization by activation of mammalian diaphanous2 (mDia2). Moreover, CDC42-mediated activation of the Ser/Thr kinase PAK (p21-activated kinase) phosphorylates LIM kinase (LIMK), which

phosphorylates and inhibits cofilin, thereby regulating actin filament turnover. In the neural growth cone, CDC42 might result in reduced cofilin phosphorylation by unknown mechanism, thereby stimulating actin polymerization and filopodium formation (Heasman and Ridley, 2008).

Role in axon myelination:
The formation of myelin sheaths in the central nervous system is the result of a complex series of events involving oligodendrocyte progenitor cell (OPC) proliferation, directed migration, and the morphological changes associated with axon ensheathment and myelination. Ablation of CDC42 in cells of the oligodendrocyte lineage leads to the formation of a unique and stage-specific myelination phenotype. This is characterized by the extraordinary enlargement of the inner tongue of the oligodendrocyte process and concomitant formation of a myelin outfolding as a result of abnormal accumulation of cytoplasm in this region (Thurnherr et al., 2006). Furthermore, OPCs, oligodendrocytes, and Schwann cells use actin polymerization-driven protrusion dependent on CDC42 effector N-WASP to advance in the processes for motility in the developing nervous system. In addition, it has been also demonstrated that p34 (a component of the Arp2/3 complex), WASP/WAVE proteins, actin, alpha-tubulin, Rac, CDC42, vinculin, and focal adhesion kinase are detected in water-shocked myelin purified from brain, so the same mechanism could be implicated in ensheathing axons at myelination (Bacon et al., 2007).

Role in migration and chemotaxis:
CDC42 has been involved in chemotaxis and directed migration of several cell types both in vitro and in vivo, including macrophages, T cells, fibroblasts and D melanogaster haemocytes (Heasman and Ridley, 2008). In macrophages, inhibition of CDC42 blocks chemotaxis toward CSF gradient without affecting mobility. Furthermore, CDC42 deletion in primary mouse embryonic fibroblasts (MEFs) causes abnormal cell spreading, reduced adhesion to fibronectin, defective mobility in wound healing, and decreases chemotaxis toward a serum gradient. These effects are associated with deficiencies of PAK1, GSK3β, myosin light chain and FAK phosporylation (Yang et al., 2006). In addition, an increase in CDC42 activity can stimulate migration speed, for example in neutrophils isolated from Cdc42GAP-knockout mice (Szczur et al., 2006). Conversely, directed migration of CDC42-null fibroblastoid cells has been reported to be normal (Wang and Zheng, 2007).

Role in cell polarity:
Polarity is involved in essentially every aspect of cell and developmental biology. All cell types polarize, at least transiently, during division or to generate specialized shapes and functions in proliferation, differentiation and morphogenesis. Moreover although the functional characteristics of cell polarity are extremely variable, depending on the cell type and the biological context, CDC42 has stood out as playing a central role in controlling of multiple signal transduction pathways which drives to cell polarity in all cell eukaryotic cells, irrespective of the biological context (Etienne-Manneville, 2004).

CDC42 seems to function primarily through the polarity protein partitioning-defective-6 (PAR6) and thereby with PAR3 and/or atypical protein kinase C (aPKC) isoforms to induce polarity in several cellular contexts (Goldstein and Macara, 2007). However, CDC42 can also function independently of the PAR complex through its effector myotonic-dystrophy-kinase-related CDC42-binding kinase (MRCK) (Gomes et al., 2005).

Role in cell cycle regulation and survival:
CDC42 is important in cell cycle through its involvement in G1/S-phase transition and its role in mitosis (Jaffe and Hall, 2005; Olson et al., 1995).

CDC42 blocks G1 progression in a variety of mammalian cell types, but the mechanisms are cell-type dependent and have proven difficult to elucidate. Multiple pathways seem to link CDC42 to the control of cyclin-D1 levels. The transcription of cyclin D1 is controlled by the ETS, AP-1 and nuclear factor-kappaB (NFkappaB), and many studies have been identified pathways that link CDC42 to these transcription factors (Perona et al., 1997; Sahai and Marshall, 2002). Furthermore, CDC42 stimulated the expression of cyclin E through its effector p70 S6 kinase (Chou et al., 2003).

During mitosis, spindle microtubules interact with chromosomes at the kinetochore, a complex of at least 50 proteins that includes the CDC42-specific effector mDia3. Inhibition of CDC42 or depletion of mDia3 causes a mitotic arrest in which many chromosomes are not properly attached to microtubules (Yasuda et al., 2004).

Furthermore, MEFS produced by gene targeting as CDC42 loss cell model are defective in G1/S-phase transition and survival, correlating with deficient NFkappaB transcription and defective JNK, p70 S6 kinase and ERK 1/2 activation (Yang et al., 2006). Moreover, in Cdc42GAP-/- hematopoietic stem/progenitor cells, the decrease in number of cells is associated with increased apoptosis of these cells and the activation of JNK-mediated apoptotic machinery (Wang et al., 2006).

Role in cell fate determination:
CDC42 is essential for skin progenitor cell differentiation into the hair follicle lineage by regulating beta-catenin turnover through CDC42-Par6-Par3-PKC ς-glycogen synthase kinase 3β signalling pathway (Wu et al., 2006). Moreover, CDC42 is important in the neural cell fate determination through the regulation of polarity following cell division at the apical surface mediated by the Par6-Par3-aPKC complex (Capello, 2006). Finally, conditional knock out of CDC42 in the bone marrow causes defects in multiple hematopoietic lineages, suppressing

erythropoiesis but increasing myelopoiesis (Yang et al., 2007).

Role in intracellular trafficking:

In mammals, CDC42 is localized predominantly at Golgi complex. In Golgi apparatus, the activated form of CDC42 is able to associate with COPI complex. This complex is important in vesicle trafficking because regulates the intracellular trafficking and processing of EGF receptor. Several studies have demonstrated that CDC42 regulates polarized (basolateral) transport in Madin-Darby canine kidney (MDCK) cells. In addition, disruption of CDC42 function also inhibited both the basolateral transport of the low-density lipoprotein receptor and retrograde transport from the Golgi to the ER. Despite these clues, the underlying mechanistic role of CDC42 in trafficking remains unknown (Cerione, 2004).

Furthermore, secramine, a molecule that inhibits membrane traffic out of the Golgi apparatus, inhibits activation of CDC42, mimicking the effects of dominant-negative CDC42 expression on protein export from the Golgi and on Golgi polarization in migrating cells (Pelish et al., 2006).

Role in transcriptional control:

The activation of many Rho effector proteins results in the modulation of the activity of several transcription factors that play an important role at various levels of Rho signalling implicating them in many cellular functions (Benitah et al., 2004). Specifically, CDC42 is implicated in the regulation of several transcription factors such as NFkappaB, STAT3 and SRF. CDC42 is able to activate the NFkappaB pathway through JNK signalling dependent pathway by a mechanism that involves phosphorylation of IκBα and translocation of p50/p50 and p50/p65 dimers to the nucleus (Perona et al., 1997). In addition, the silencing of CDC42 in two bladder cancer cell lines decrease phosphorylation levels of the transcription factor STAT3 leading to the inhibition of the cellular proliferation and the induction of apoptosis (Wu et al., 2008). The constitutively active form of CDC42, Cdc42.V12, induces transcription via SRF through JNK/SAPK activation and acts synergistically at the c-fos serum response element (SRE) with signals that activate TCF (ternary complex factor) (Hill et al., 1995).

Recently, it has been described a novel mechanism of transcriptional regulation mediated by CDC42 through the promoter hypermethylation of the ID4 gene in a colorectal cancer cell line (Gomez del Pulgar et al., 2008).

Dual role in cancer:

It has been suggested that the contribution of CDC42 in tumour progression is tissue-specific. Depending on the cellular context, this Rho GTPase promotes or inhibits tumour progression. However, there are more cell types where CDC42 is a pro-oncogenic factor (Vega and Ridley, 2008).

CDC42 contributes to cancer development through its different roles in: intracellular trafficking, cell cycle regulation and survival, polarity, migration and transcriptional control (Vega and Ridley, 2008).

1. <u>Intracellular trafficking:</u> This process has been associated with the control of cell growth by the regulation of the processing and degradation of EGF receptor. The overexpression of a mutant form of CDC42 (F28L), which dissociates from GDP at a rate that is at least 50-fold faster than wild-type CDC42, produces an accumulation of EGF receptors. This accumulation causes an excessive mitogenic signalling through the Ras-Erk pathway that leads to cellular transformation (Wu et al., 2003). In this context, CDC42 stimulates and contributes to Ras-induced transformation in mouse fibroblasts in vitro (Qiu et al., 1997).

2. <u>Cell cycle regulation and apoptosis:</u> Many of the effects of Rho GTPases on G1 progression are thought to reflect the crucial role of anchorage- or adhesion-dependent signals for cell proliferation (Jaffe and Hall, 2005). Indeed, CDC42 could affect cell cycle progression by regulating chromosome misalignment during cell division, leading to multinucleated cells (Yasuda et al., 2006). Moreover, CDC42 contributes to immune escape of cancer as mediator of resistance to cytotoxic T lymphocytes (CTL)-mediated growth suppression of MEFs and HCT116 colorectal cancer cells. This event occurs through the prevention of CTL-induced apoptosis via mitogen-activated protein kinase (MAPK) signalling and posttranscriptional stabilization of Bcl-2 (Marques et al., 2008). By contrast, the overexpression of the active form of CDC42 in Jurkat T lymphocytes induces apoptosis through a JNK-dependent signaling pathway leading to caspase activation (Chuang et al., 1997).

3. <u>Polarity and migration:</u> CDC42 is predicted to inhibit invasion by promoting epithelial polarity, yet conversely also stimulated migration. Indeed, CDC42 contributes to cancer cell invasion in single cells with a mesenchymal morphology in vitro. It is also important for collective cancer cell invasion, where it acts through its effector MRCK to stimulate actomyosin contractility (Friedl and Wolf, 2003). In addition Rho activity alteration (RhoA, Rac1 and CDC42) has been linked with loss of polarity, an important fate in epithelial-mesenchymal transition (EMT) (Patel et al., 2005).

4. <u>Transcriptional control:</u> The implication of CDC42 in gene transcription has been also proposed as a mechanism of participation in tumour progression (Benitah et al., 2004). In this context, the activation of NFkappaB pathway by RhoA, Rac1 and CDC42 leads to the transcriptional expression of COX2, a protein highly implicated in cancer and inflammation processes (Benitah et al., 2003). Furthermore, RNAi-mediated inhibition of CDC42 produces a significant inhibition of cell proliferation and an induction of apoptosis in human in bladder cancer cell lines through the downregulation of STAT3 phosphorylated levels (Wu et al., 2008). Recently, the epigenetic transcriptional

silencing of the putative tumour suppressor gene ID4 by CDC42 seems to be an important event in colorectal carcinogenesis (Gomez del Pulgar et al., 2008).

Finally, the involvement of CDC42 in the carcinogenic process is highly associated to aberrant expression and activity of the protein (Gomez del Pulgar et al., 2005; 2008).

Mutations

Note

Unlike Ras proteins that are constitutively activated to oncoproteins by point mutations in human cancer, Rho family proteins are likely to be activated in vivo by different mechanisms such as overexpression of the GTPase or deregulation of the expression of regulatory proteins. Thus, no point mutations in the coding sequence of CDC42 gene were found in invasive breast and colon cancer samples (Rihet et al., 2001).

Implicated in

Breast cancer

Oncogenesis

CDC42 protein levels are highly increased in breast cancer compared with the corresponding normal tissue from the same patient (Fritz et al., 1999; 2002). This evidence is enforced with the results from a mouse model of breast carcinoma, where the expression of a dominant inhibitory mutant of CDC42 reduces the number of focal contacts, inhibits colony formation in soft agar in vitro and affects cell growth in vivo. Furthermore, this inactive form reduced intravasation into the peripheral blood and lung metastases (Bouzahzah et al., 2001).

ErbB1 and ErbB2 are often overexpressed in breast cancer and such overexpression is correlated with poor prognosis. Activated CDC42 contributes to the accumulation of ErbB1 in cells through the regulation of c-Cbl function. Thus, different therapeutic strategies targeting ErbB receptors and CDC42 have been proposed in this cancer type (Hirsch and Wu, 2007).

Testicular cancer

Oncogenesis

Western blot analyses revealed that CDC42 was significantly overexpressed in tumoral samples from 57 patients with testicular germ cell tumors compared with each non-tumor counterparts. The expression of CDC42 protein was significantly greater in tumors of higher stages than lower stages. Thus, CDC42 may be involved in the progression of testicular germ cell tumors (Kamai et al., 2004).

Head and neck squamous cell carcinoma

Oncogenesis

Immunohistochemical analysis has revealed that the protein CDC42 is overexpressed in head and neck

cancer specimens (n=15). Moreover, CDC42 overexpression is found in premalignant and squamous cell cancer cell lines relative to normal keratinocytes (Abraham, 2001).

Melanoma

Oncogenesis

CDC42 protein expression is increased in tumoral samples from patients with fatal outcome using immunohistochemical assays. In this group a positive correlation is found between melanocytic CDC42 expression and Breslow thickness (Tucci et al., 2007). Besides, activation of CDC42 by surface antigens has been implicated in melanoma cell growth and invasion signals to promote cell-spreading. In keeping with this, autotoxin promotes invasiveness and angiogenesis through CDC42 in this cancer type (Eisenmann et al., 1999; Jung et al., 2002). In addition, DOCK10, a CDC42 GEF, activates CDC42 promoting amoeboid invasion of melanoma cells (Gadea et al., 2008).

Colorectal cancer

Oncogenesis

The protein levels of CDC42 are found to be overexpressed with high incidence (60%) in colorectal cancer samples. Such overexpression is significantly correlated with the histopathological grade of the tumor reflecting the plausible role of CDC42 in cell polarity and actin cytoskeleton. In addition, the CDC42 overexpression is associated with silencing of the putative tumor suppressor gene ID4 with statistical significance (Gomez del Pulgar et al., 2008). Moreover, leptin induces CDC42 activation promoting lamellopodium formation and concomitantly enhanced cell invasion in human colon cancer cells (Jaffe and Schwartz, 2008).

Hepatocellular carcinoma

Oncogenesis

Western blot expression of CDC42 in twenty patients with hepatocellular carcinoma (HCC) is higher in cancer tissues with HBV infection than para-cancerous liver tissues and cancer tissues without HBV infection (Chang et al., 2007). In addition, EB1 overexpression was associated with poorly differentiated HCC, which generally correlate with poor prognosis of these patients. Network analysis reveals that EB1 functions downstream of RhoA and CDC42 by interacting with mDia2 (Orimo et al., 2008). In the other hand, in a human HCC cell line, the protein BNIPL-2 is involved in the activation of CDC42 and enhances the migration and invasion of cancer cells in vitro, but also promotes cancer metastasis in vivo (Xie et al., 2007). By contrast, liver conditional CDC42 knock out mice suffer a chronic liver disease that leads to hepatocarcinogenesis. These tumors grow slowly and lack expression of nuclear beta-catenin. Lung metastases are observed at the late stage of carcinogenesis (Van Hengel et al., 2008).

Lung cancer

Oncogenesis

Although alterations of CDC42 expression or activation have not been described in any human lung tumor tissue yet, its inactivation or downregulation might be involved in lung tumor progression. Indeed, mRNA levels of CDC42 showed no change in adenomas, but were underexpressed in adenocarcinomas in mouse lung cancer considering as candidate "lung tumor progression" gene because its expression changes may specifically affect lung tumor progression in mice (Yao et al., 2002). In addition, in non small cell lung cancer (NSCLC) cell lines the tumor suppressor gene LKB1 maintains active CDC42 levels and downstream PAK phosphorylation to the regulation of epithelial cell polarity (Zang, 2008).

Other cancer types

Oncogenesis

Although to date there is no data available about the alteration of CDC42 expression or activation in patients with bladder cancer or lymphoma, there are some evidences that point CDC42 as an important factor in the development and progression of these cancer types. In the case of lymphomas, in anaplastic large cell lymphoma (ALCL) cell line, the oncogenic fusion protein NPM-ALK forms a complex with the GEF VAV1, enhancing its activation and consequently increasing CDC42 activation. This signalling regulates cell shape and migration. Genetic knockdown of CDC42 or pharmacological inhibition of CDC42 by secramine resulted in a cell cycle arrest and apoptosis of ALCL cells. Furthermore, CDC42 is necessary for the growth and the maintenance of already established lymphomas in vivo (Ambrogio et al., 2008).

In the case of bladder cancer, CDC42 silencing results in a significant inhibition of cell proliferation from G0/G1- to S-phase in two human bladder-cancer cell lines, EJ and T24, and an induction of apoptosis of EJ cells. These results suggest that CDC42 silencing may be a novel approach for therapy of bladder cancer (Wu et al., 2008).

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