Atlas of Genetics and Cytogenetics
in Oncology and Haematology

OPEN ACCESS JOURNAL

INIST-CNRS

Gene Section
Review

FMNL1 (formin like 1) methyltransferase)

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Published in Atlas Database: October 2016
Online updated version : http://AtlasGeneticsOncology.org/Genes/FMNL1ID46313ch17q21.html
Printable original version : http://documents.irevues.inist.fr/bitstream/handle/2042/68240/10-2016-FMNL1ID46313ch17q21.pdf
DOI: 10.4267/2042/68240

Abstract

Formin-like 1 (FMNL1) is a member of the Formin protein family, which are regulators of actin and microtubule cytoskeletal dynamics. FMNL1 belongs to the subfamily of formins knows as Diaphanous-related formins (DRF) and is involved in processes such as phagocytosis, cell adhesion, podosome dynamics, cell migration, cytokinesis, and polarity control. It has been suggested that spatial and temporal regulation of FMNL1 is controlled by small Rho GTPases. The present review contains data on FMNL1 DNA/RNA, protein encoded and function.

Identity

Other names: FRL1, FRL alpha

HGNC (Hugo): FMNL1

Location: 17q21.31

DNA/RNA

Description

FMNL1 full-length cDNA (Favaro et al., 2003) was obtained from the EST IL5-MT0208-210201-356-f01 (GenBank Accession No. BI028593), generated from the Human Cancer Genome Project (Dias Neto et al., 2000). The entire FMNL1 gene is located in chromosome 17 (17q21) and has a size of approximately 25.8 Kb (start: 45221444 and end: 45247320 bp; orientation: Plus strand) and contains 17 exons. The FMNL1 cDNA contains 3973 bp and is located in chromosome 17 (17q21).

Protein

Description

Formin proteins are characterized by a unique and highly conserved C-terminal formin homology (FH) 2 domain, responsible for its interaction with actin (Wallar and Alberts, 2003; Higgs, 2005). Diaphanous-related formins (DRF) are characterized by regulatory domains at the N-terminus, including the GTPase binding domain (GBD), Diaphanous inhibitory domain (DID), and dimerization domain (DD), and a single C-terminal Diaphanous autoregulatory domain (DAD) (Figure 1). DRFs are regulated by an autoinhibitory interaction of DAD with DID (Li and Higgs, 2003). This autoinhibition is relieved through binding of an activated RhoGTPase to the GBD, resulting in activation of formin to polymerize actin filaments (Kuhn and Geyer, 2014)(Figure 2).

Figure 1. Domain structure of FMNL1. Amino acid positions are identified. GBD; GTPase binding domain, DID; Diaphanous inhibitory domain; DD; dimerization domain. FH1 and FH2; Formin homology 1 and 2 domain. DAD; Diaphanous autoregulatory domain.

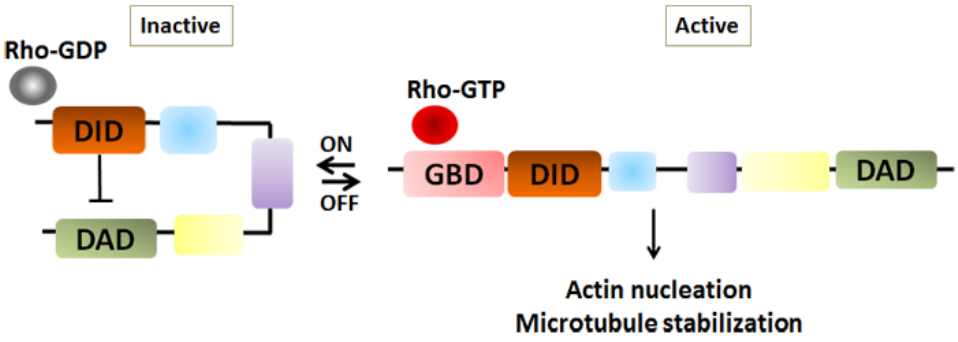

Figure 2. Schematic model of regulation of DRF by RhoGTPases. DRF are autoinhibited in an inactivated state by the interaction of DAD with DID. Upon the interaction of an activated Rho GTPase with the GBD, the C-terminal autoregulatory domain is displaced from its N-terminal recognition site, resulting in the activation of formin and consequently the polymerization of actin filaments. Adapted from (Alberts, 2002).

Expression

In normal tissues, FMNL1 expression is restricted to peripheral blood mononuclear and homing tissues such as thymus, spleen, lymph nodes and bone marrow (Favaro et al., 2003; Schuster et al., 2007). In bone marrow, FMNL1 expression was restricted to myeloid cells and in lymph nodes, mature lymphocytes stain strongly for FMNL1 (Gardberg et al., 2014).

FMNL1 is highly expressed in a variety of hematopoietic malignancies, including cells from patients with lymphoid and myeloid leukemias and non-Hodgkin's lymphomas, as well as malignant lymphoid and myeloid cell lines and in renal carcinoma cell lines (Favaro et al., 2003; Favaro et al., 2006; Schuster et al., 2007). Recently, Gardberg et al reported that FMNL1 to be also expressed in smooth muscle cells and myoepithelial cells (Gardberg et al., 2014).

Localisation

Immunohistochemical analyses have shown that FMNL1 staining is cytoplasmatic (Gardberg et al., 2014).

Function

Many functions have been attributed to FMNL1, such as cell adhesion, cytokinesis, cell polarization and migration in mitosis (Yayoshi-Yamamoto et al., 2000; Seth et al., 2006; Esue et al., 2008; Mersich et al., 2010). The silencing of FMNL1 reduces cell proliferation as well as migration of human leukemia cells and tumor growth (Favaro et al., 2013). FMNL1 is needed for cytotoxicity, polarization and maintenance of the Golgi complex in T-cells (Gomez et al., 2007; Colon-Franco et al., 2011). FMNL1 is involved in podosome dynamics in macrophage cell lines (Mersich et al., 2010) and a new splice variant of FMNL1, FMNL1γ, has been reported to induce polarized membrane nonapoptotic blebbing (Han et al., 2009). During mouse oocyte meiotic maturation, FMNL1 has shown to affect both actin dynamics and spindle formation, through a RHOA -FMNL1- GOLGA2 (GM130) pathway, leading to oocyte polar body extrusion (Wang et al., 2015; Yin and Sun, 2015)

Homology

FMNL1 shares homology with that of the other members of the formin protein family.

FMNL1 also has a high homology among different species (Table 1).

% Identity for:*Homo sapiens* FMNL1	Symbol	Protein	DNA
vs. P. troglodytes	FMNL1	99.0	99.0
vs. M. mulatta	FMNL1	98.0	96.0
vs. C. jacchus	FMNL1	95.0	95.0
vs. N. galili	Fmnl1	94.0	88.0
vs. B. taurus	FMNL1	93.0	86.0
vs. M. musculus	Fmnl1	93.0	85.0
vs. M. putorius	FMNL1	91.0	88.0
vs. C. lupus	FMNL1	91.0	87.0
vs. R. norvegicus	Fmnl1	89.0	84.0
vs. G. gallus	FMNL1	72.0	86.0
vs. I. punctalus	fmnl1	69.0	82.0

Table 1. Comparative identity of human FMNL1 with other species (Source: http://www.ncbi.nlm.nih.gov/homologene)

Mutations

Somatic

Recurrent mutations in the FMNL1 gene are rare, and 123 substitution missense, 4 substitution nonsense, 57 substitution synonymous, 5 insertion inframe, 1 insertion frameshift, 9 deletions inframe and 3 deletion frameshift mutations are reported in COSMIC (Catalogue of somatic mutations in cancer; http://cancer.sanger.ac.uk/cancergenome/projects/cosmic).

Implicated in

T-cell non-Hodgkin's lymphoma

A study performed in 54 frozen biopsies of T non-Hodgkin's lymphoma (NHL) patients and five reactive lymph nodes showed that FMNL1 protein expression was detected in all samples. However, FMNL1 expression was highest in the T-cell NHL, when compared with others NHL (follicular NHL and diffuse large B-cell NHL) and reactive lymph nodes (Favaro et al., 2006).

Leukemia

FMNL1 protein is overexpressed in malignant cells from patients with lymphoid and myeloid leukemias, including chronic lymphocytic leukemia (CLL), acute B- and T-lymphoblastic leukemia and acute myeloid leukemia (Krackhardt et al., 2002; Favaro et al., 2003; Schuster et al., 2007). These findings are consistent with FMNL1 expression in human leukemic cell lines and also with a large-scale meta-analysis of gene expression in humans (A-AFFY-33, array platform) (Lukk et al., 2010; Favaro et al., 2013).

Breast cancer

Eight basal type breast cancer samples were tested for FMNL1 expression. In three cases, FMNL1 expression was restricted to inflammatory cells and in five samples, FMNL1 staining was observed in a subset of the malignant epithelial cells (Gardberg et al., 2014).

To be noted

Allorestricted MHC class I-restricted T cell receptor (TCR) with specificity for FMNL1 and potent activity against CLL cells were isolated (Schuster et al., 2007). Recently, MHC class-II-restricted $CD4^+$ T cells and TCR with specificity for leukaemia antigens, including FMNL1 were also isolated (Weigand et al., 2012)..

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This article should be referenced as such:

Rodrigues Lopes M, Favaro P. FMNL1 (formin like 1). Atlas Genet Cytogenet Oncol Haematol. 2017; 21(5):166-169.