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Review

ARHGAP21 (Rho GTPase activating protein 21)

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Abstract

ARHGAP21 is a Rho GTPase-activating protein (RhoGAP). Like other members of the RhoGAP family, ARHGAP21 enhances the intrinsic GTPase activity of small Rho GTPases, leading to their inactivation. ARHGAP21 participates in cellular proliferation, adhesion, migration and vesicle traffic. This review comprises information on DNA/RNA, the encoded protein and protein functions.

Keywords: ARHGAP21; Rho GTPase-activating protein; RhoGAP; cellular proliferation; adhesion; migration; vesicle traffic; glioblastoma multiforme; prostate adenocarcinoma; ovarian cancer; breast cancer; head and neck squamous cell carcinoma.

Identity

Other names: ARHGAP10

HGNC (Hugo): ARHGAP21

Location: 10p12.1 - 10p12.3

DNA/RNA

Description

The entire ARHGAP21 gene has approximately 141,813 base pairs (bp) (Start: 24,583,609 and End: 24,725,421; on the reverse strand) and is composed of 26 exons. The cDNA contains 5877 bp.

Protein

Description

RhoGAPs are usually large proteins with additional domains other than the RhoGAP domain (Tcherkezian and Lamarche-Vane 2007). ARHGAP21 is composed of 1958 amino acids and has a predicted molecular weight of 217 kDa. In addition to the RhoGAP domain, ARHGAP21 comprises a PH (pleckstrin homology) and a PDZ domain (Figure 1).

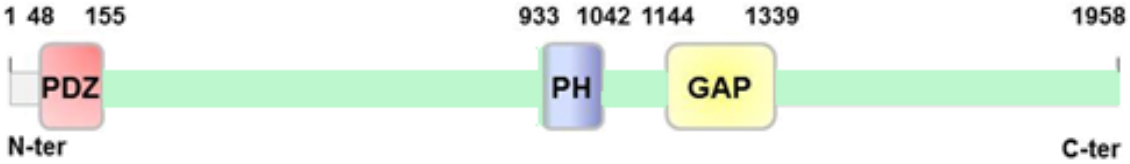

Figure 1. Schematic representation of ARHGAP21 protein. Domain positions were based on National Center for Biotechnology Information (NCBI) (https://www.ncbi.nlm.nih.gov/gene/57584).

Although PH domains can bind to phosphatidylinositol lipids within biological membranes (Harlan et al. 1994; Saito et al. 2001), the ARHGAP21 PH domain has been demonstrated to not bind to lipids (Dubois et al. 2005). ARHGAP21 has been described to be SUMOylated in lysine K1443 by SUMO2/3.
This post-translational modification may possibly explain the higher weight found by mass spectrometry (250 kDa) in contrast with the predicted weight (Bigarella et al. 2009).

Expression

ARHGAP21 gene was widely expressed in a panel of different human tissues. Higher ARHGAP21 gene expression was observed in brain, heart, skeletal muscle, and placenta (Basseres et al. 2002). Results from FANTOM5 project also showed an increased ARHGAP21 gene expression in tissues of the human nervous system, such as cerebellum, diencephalon and hippocampus (Expression Atlas data bank).

Localisation

ARHGAP21 has been shown to localize in the nuclei and cytoplasm of different cell types, such as adenocarcinoma PC3 and LNCAP cells and in glioblastoma T98G cells (Bigarella et al. 2009; Lazarini et al. 2013). In epithelial Caco-2 and JEG-3 cells, ARHGAP21 was detected at the cell-cell junctions and at the nucleus and perinuclear region (Sousa et al. 2005). Breast adenocarcinoma MCF-7 cells and HeLa cells presented ARHGAP21 localization in Golgi complex and in vesicular cytoplasmic structures (Dubois et al. 2005). In cardiomyocytes, ARHGAP21 was relocated from the nucleus to Z-lines and costameres after pressure overload (Borges et al. 2008).

Function

ARHGAP21 acts as a RhoGAP for RHOA, RHOC andCDC42, but not for RAC1 (Dubois et al. 2005; Sousa et al. 2005; Lazarini et al. 2013). Such as occurs with other RhoGAP proteins, the ARHGAP21 RhoGAP activity has not been tested for most Rho GTPases. However, several ARHGAP21 partners have been described, suggesting that ARHGAP21 functions as a scaffold, linking Rho GTPases to other signaling pathways. ARHGAP21 has been shown to interact with ARF1, ARF6 (Dubois et al. 2005), catenin alpha (Sousa et al. 2005), PTK2 (FAK), PRKCZ (PKC zeta) (Borges et al. 2008), arrestin beta (Anthony et al. 2011), tubulin alpha (Barcellos et al. 2013), PRICKLE1 (Zhang et al. 2016). The functions of ARHGAP21 have been investigated in several types of cells. ARHGAP21 plays a role in cell proliferation (Lazarini et al. 2013; Luo et al. 2016), migration (Bigarella et al. 2009; Lazarini et al. 2013), vesicle traffic (Dubois et al. 2005), cell adhesions (Sousa et al. 2005; Barcellos et al. 2013; Zhang et al. 2016) and insulin secretion (Ferreira et al. 2015).

Homology

ARHGAP21 shares homology with other members of the RhoGAP protein family (Tcherkezian and Lamarche-Vane 2007).
ARHGAP21 also presents high homology among different species (Table 1).

% Identity for: *Homo sapiens* ARHGAP21	Symbol	Protein	DNA
vs. P. troglodytes	ARHGAP21	99.5	99.5
vs. M. mulatta	ARHGAP21	98.2	98.0
vs. C. lupus	ARHGAP21	87.1	85.6
vs. B. taurus	ARHGAP21	87.3	85.0
vs. M. musculus	Arhgap21	87.3	84.0
vs. R. norvegicus	Arhgap21	86.9	83.3
vs. G. gallus	ARHGAP21	74.9	75.1
vs. X. tropicalis	arhgap21	65.1	67.4
vs. D. rerio	arhgap21	57.9	59.5

Table 1. Comparative identity of human ARHGAP21 with other species (Source: http://www.ncbi.nlm.nih.gov/homologene)

Mutations

Somatic

COSMIC (Catalogue of somatic mutations in cancer) reported 70 synonymous substitutions, 194 missense substitution, 24 nonsense substitution, 4 insertion frameshift, 1 deletion inframe, 8 deletion frameshift
(http://cancer.sanger.ac.uk/cancergenome/projects/cosmic).

Implicated in

Head and neck squamous cell carcinoma (HNSCC)

ARHGAP21 was identified as a differentially expressed gene in hypopharyngeal carcinoma, using Differential Display analysis.
The increased ARHGAP21 expression in tumor tissues compared to normal matched tissues was further confirmed with additional techniques, such as reverse Northern hybridization. Immunohistochemistry analysis revealed a weak cytoplasmic ARHGAP21 staining in neoplastic cells of (HNSCC), whereas no staining was detected in normal uvula epithelium (Carles et al. 2006). However, studies on ARHGAP21 functions in HNSCC have not been published to date.

Glioblastoma multiforme

ARHGAP21 functions were investigated in glioblastoma cell lines. In T98G and U138MG cells, both N-terminal and C-terminal portions of ARHGAP21 interacted with Focal Adhesion Kinase (FAK). Confocal micrographs showed that this interaction possibly occurs in the perinuclear region. FAK phosphorylation in Tyr397 and in Tyr925 was higher in T98G cells silenced for ARHGAP21, in comparison with control cells. Phosphorylation of Scr and $p130^{CAS}$, two downstream FAK effectors, was also increased. T98G cells silenced for ARHGAP21 displayed morphological changes, which resembled epithelial mesenchymal transition. These cells also presented higher Cdc42 activity and increased rate of migration and MMP-2 secretion, indicating a possible tumor suppressor role in glioblastoma cells (Bigarella et al. 2009).

Prostate adenocarcinoma

ARHGAP21 function was investigated in prostate adenocarcinoma cells (Barcellos et al. 2013; Lazarini et al. 2013). However, ARHGAP21 expression in primary cells and impact in patient prognosis remains unknown. ARHGAP21 has been shown to inactivate RhoA and RhoC, though not Cdc42, in PC3 cells (human prostate adenocarcinoma cell line). PC3 cells with ARHGAP21 overexpression presented a round morphology, with increased protrusions and decreased adhesion in the tissue culture plastic plate. A similar phenotype was observed after p190 RhoGAP overexpression. ARHGAP21 silencing decreased PC3 cell proliferation, whereas increased random migration speed in fibronectin coated plates. In addition, microarray assays revealed a number of genes with altered expression in PC3 cells silenced for ARHGAP21, such as genes involved in the endothelin-1 signaling pathway (Lazarini et al. 2013). In DU145 cells, another model of prostate adenocarcinoma, ARHGAP21 interacted with tubulin alpha and was relocated from the perinuclear region to the front of the polarized cells after initiation of migration. DU145 cells silenced for ARHGAP21 also presented increased migration rate. However, stimulation with HGF had no effect upon the migration and scattering of the cells silenced for ARHGAP21. A decreased effect of HGF treatment was also observed in epithelial-mesenchymal transition (EMT) markers of DU145 cells silenced for ARHGAP21, in comparison to control cells (Barcellos et al. 2013).

Ovarian Cancer

ARHGAP21 expression was reported to be reduced in cancer ovarian tissues compared to adjacent non-tumorous tissue, using quantitative PCR analysis. Reduced ARHGAP21 expression correlated with poor survival of patients. In contrast, lentiviral overexpression ARHGAP21 in A2780 and HO-8910 ovarian cancer cell lines led to decreased proliferation.

When A2780 cells overexpressing ARHGAP21 were subcutaneously injected into Nude mice, a decreased tumor volume was observed. ARHGAP21 overexpression also induced G0/G1 phase cell cycle arrest and apoptosis, whereas decreased the adhesion on fibronectin, migration and invasiveness of A2780 and HO-8910 cells (Luo et al. 2016).

Breast cancer

ARHGAP21 has shown a role in lateral signaling of MDA-MB-231 breast cancer cell line. Prickle (Pk) is a core planar cell polarity (PCP) component (Gray et al. 2011) and Pk1 has been demonstrated to interact with ARHGAP21, using affinity purification and mass spectrometry assay in MDA-MB-231 cells. The RhoGAP ARHGAP23 was identified as another Pk1 interactor. Separate knockdown of ARHGAP21 or ARHGAP23 induced no significant effect on the migration of MDA-MB-231 stimulated with active conditioned media (ACM) derived from fibroblast L cells. However, combinatorial silencing of both ARHGAPs inhibited ACM-induced migration. Pk1, ARHGAP21 and ARHGAP23 localized at non-protrusive membranes that are lateral to active protrusions. Concomitant ARHGAP21/23 silencing also induced a round morphology and diffuse protrusive activity. In addition, MDA-MB-231 silenced for ARHGAP21/23 presented increased RhoA activity and subsequent increase of myosin light chain 2 and focal adhesion activities, as well as alteration in mechanical properties of cell membrane. According to this study, the Pk1-ARHGAP21/23 complex confines protrusive activity of MDA-MB-231 cells through the regulation of RhoA activity (Zhang et al. 2016).

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