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Gene Section
Review

VAV3 (vav 3 guanine nucleotide exchange factor)

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Identity

Other names: FLJ40431

HGNC (Hugo): VAV3

Location: 1p13.3

Local order: VAV3 maps to the minus strand of chromosome 1.

DNA/RNA

Description

The VAV3 gene is comprised of 27 exons spanning 393.7 kb on chromosome 1p13.3. It is located on the reverse strand 108113782 bp from pter -108507545 basepairs from pter.

Transcription

There are two known isoforms produced by alternative splicing and a third transcript thought to be derived from alternate promoter usage (Vav3.1). The alpha isoform is the canonical sequence and is derived from the full 27 exons. Isoform beta differs in the N terminus from the alpha isoform as follows: The residues 1-107 in the alpha isoform, MEPWKQCAQW...DLFDVRDFGK, are replaced by MQLPDCPCRAHLP in the beta isoform. The beta isoform is produced from a unique exon 1 spliced to exons 4-27 (Maier et al., 2005). Additionally, a transcript variant encoding only the C terminal SH3 SH2 SH3 domains has been identified and is known as Vav3.1. This variant is derived from a unique exon 18 and exons 19-27 (Maier et al., 2005) and is thought to be produced either by alternative splicing or through alternate promoter usage. The Vav3 mRNA consists of a 54 base pair 5 prime UTR and a 2171 basepair 3 prime UTR (Trenkle et al., 2000). The promoter region of Vav3 contains predicted binding sites for the following transcription factors: STAT3, c-MYB,

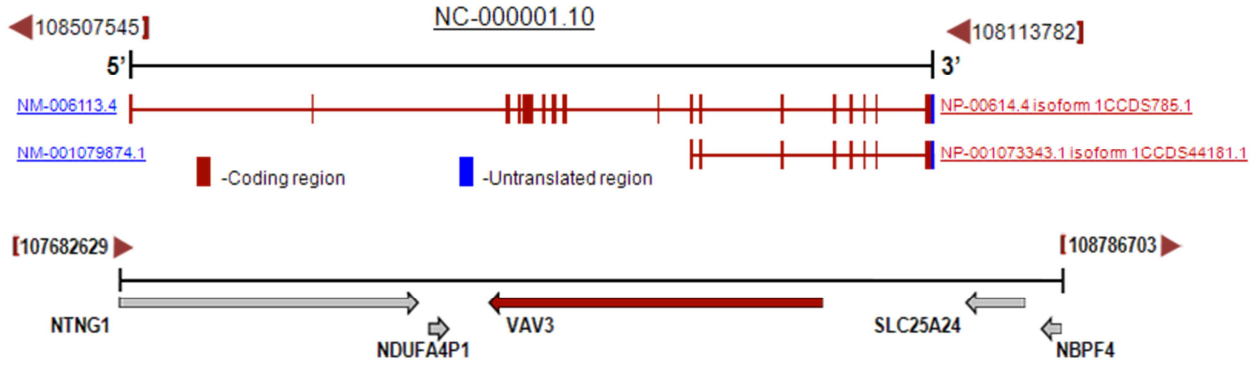

Figure 1. Upper figure shows gene organization for the alpha (canonical) isoform (ID NM 006113.4) and isoform 2 (ID NM 001079874.1) which corresponds to the 287 amino acid Vav3.1 transcript variant (described below). Lower panel illustrates neighboring genes. Figures adapted from NCBI Gene database.

LMO2, GATA-1, GCNF-2, E47, GCNF-1, PAX-5, POU2F1, and FOXO1A (information obtained from data deposited in Genecard database through use of SABiosciences' text mining application and the UCSC genome browser). It is worth mentioning that the gene locus is complex and could potentially produce up to 13 different isoforms resulting from alternative splicing and alternate promoter usage (Thierry-Mieg and Thierry-Mieg, 2006).

Vav3 can be modified posttranslationally by phosphorylation. Phosphorylation site prediction identifies phosphorylation sites at T131, S134, Y141, Y173, S511, T606 and Y797. Sites residing in the N terminal region have been shown to regulate activation of Vav3 GEF function (Movilla and Bustelo, 1999). In the unphosphorylated state, the GEF domain is prevented from physical association with Rho proteins by the Vav3 N terminal domains. These domains (calponin homology and acidic domains) form an autoinhibitory loop via intramolecular interactions. Vav3 is recruited via its SH2 domain to phosphotyrosine residues on interacting proteins, including activated growth factor receptors. Once bound to active growth factor receptors, or other molecules containing intrinsic tyrosine kinase activity, Vav3 becomes tyrosine phosphorylated (Movilla and Bustelo, 1999; Bustelo, 2002; Zugaza et al., 2002). Tyrosine phosphorylation of Vav3 results in a conformational change that relieves the autoinhibition, thus activating the GEF function by allowing access of Rho proteins to the GEF domain (Movilla and Bustelo, 1999; Yu et al., 2010). Tyrosine 173 in particular is a critical residue in this process (Llorca et al., 2005; Yu et al., 2010). Consistent with an autoinhibitory role of the N terminal regions, removal of both the calponin homology and the acidic domains results in constitutive activation of Vav3 GEF function (Movilla and Bustelo, 1999; Zeng et al., 2000; Zugaza et al., 2002).

Protein

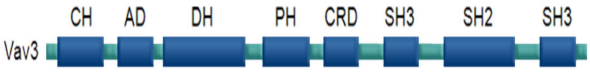

Figure 2. Functional domains of Vav3 proteins and their relative positions. Abbreviations are as follows: CH: calponin homology, AD: acidic domain, DH: DBL homology, PH: pleckstrin homology, CRD: cysteine rich domain, SH3: Src homology 3 and SH2: Src homology 2.

Description

The VAV3 gene encodes a 847 amino acid mature protein. The mature protein has a molecular mass of approximately 98 kDa and functions as a guanine nucleotide exchange factor (GEF) for members of the Rho family of small GTPases (Movilla and Bustelo,1999; Trenkle et al., 2000). Vav3 is structurally complex consisting of multiple functional domains. These domains consist sequentially of a single calponin homology domain encompassing residues 1-119, an acidic domain, a DBL homology domain which confers GEF function. The DBL homology domain is comprised of residues 192-371, followed by a pleckstrin homology domain, spanning residues 400-502 a cysteine rich domain (also termed a zinc finger domain) comprising residues 513-562 and two SH3 domains flanking a single SH2 domain. The SH3-SH2-SH3 cassette comprises the C terminal portion of Vav3 and extends from the N terminal SH3 domain (residues 592-660), to the C terminal SH3 domain (residues 788-847) and includes the intervening SH2 domain (residues 672-766) (Trenkle et al., 2000). Residing within the N terminal SH3 domain is a proline rich region which may be involved in facilitating intramolecular interactions between the C terminal regions (our unpublished observations).

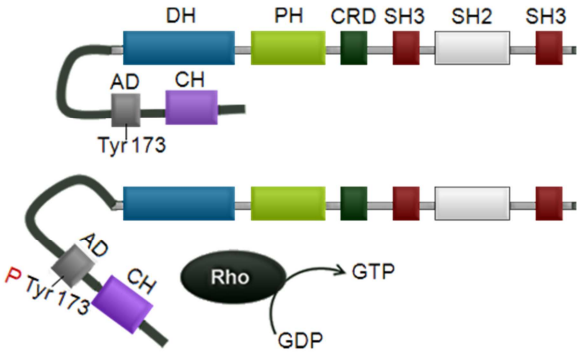

Figure 3. Schematic showing inactive (top panel) and active (bottom panel) conformations of Vav3. Movement of the N terminal regions to allow RhoGTPase access to the DH domain is regulated by phosphorylation events.

Expression

Vav3 is broadly expressed but with highest levels in cells of hematopoietic lineages (Trenkle et al., 2000).

Localisation

Vav3 is located predominantly in the cytoplasm, and is often recruited to the membrane upon activation of the various cell surface receptors that are coupled to Vav3 phosphorylation (Zeng et al., 2000).

Function

Vav3 functions as a guanine nucleotide exchange factor mediating activation of Rho GTPases by stabilization of the nucleotide free state of Rho proteins. Specifically, Vav3 has been shown to act as a GEF for RhoA, RhoG and RAC1 (Movilla and Bustelo, 1999; Zugaza et al., 2002). Vav3 couples the activation of growth factor type receptors such as IGFR, EGFR, PDGFR, insulin receptor and ROS receptor (Zeng et al., 2000) to downstream signaling molecules including but not limited to Jun kinase, NFKappa B, MAPK and Stat pathways (Moores et al., 2000; Sachdev et al., 2002). More recently, Vav3 activation by Eph Receptors has been demonstrated (Fang et al., 2008) and a large number of studies have shown the activation of Vav3 upon integrin signaling (Gakidis et

al., 2004; Faccio et al., 2005; Pearce et al., 2007; Sindrilaru et al., 2009).
Vav3 is implicated in B cell induced antigen presentation to T cells (Malhotra et al., 2009) and mediates both B and T cell signaling events and alteration of macrophage morphology (Sindrilaru et al., 2009). Additionally, protein interactions with the C terminal SH3 SH2, SH3 cassette have revealed roles in scaffolding through adaptor like actions (Bustelo, 2001; Yabana and Shibuya, 2002).
Additional functions of Vav3 in distinct tissues are listed below.
Nervous system: NGF-induced neurite outgrowth in PC12 cells requires Vav3-mediated activation of Rac. This process involves P13K activation which occurs upstream of Vav3 (Aoki et al., 2005). Vav3 is also important for neuronal migration during development (Khodosevich et al., 2009). Additionally, Vav3 knockout mice show defects in Purkinje cell dendrite branching, granule cell migration and survival. Functionally the animals show deficiencies in motor coordination and gaiting consistent with a role for Vav3 in neuronal guidance, cerebellar development and function (Quevedo et al., 2010).
Skeletal system: Studies in osteoclasts support a role for Vav3 in mediating proper bone deposition. Specifically, Vav3 deficient osteoclasts exhibit abnormalities in actin cytoskeletal rearrangements, cell spreading, and resorptive activities. Consistent with the actions of Vav3 on integrin signaling, the osteoclast defects were found to be due to impaired integrin engagement. Further, Vav3 deficient mice have increased bone density and are refractory to PTH-mediated bone resorption (Faccio et al., 2005).
Cardiovascular system: An important role for Vav3 in maintaining proper cardiovascular homeostasis was suggested by experiments performed in Vav3 null mice. These mice exhibited many symptoms of cardiovascular dysfunction including tachycardia, hypertension and cardiovascular remodeling. Consistent with these symptoms, the mice also exhibited a high degree of sympathetic tone including elevated circulating levels of catecholamines and renin-angiotensin-aldosterone hyperactivity, resulting in progressive loss of both cardiovascular and renal homeostasis (Sauzeau et al., 2006).
Vascular smooth muscle: Vav3 is both necessary and sufficient for rat vascular smooth muscle cell proliferation. These effects occur through a Rac-1 dependent mechanism, involving the effector Pak 1 (Toumaniantz et al., 2010).
Platelets: Consistent with a role for Vav3 in mediating integrin-based responses, Vav3 and Vav1 together are required for collagen exposure-mediated PLC activation in platelets. This signaling pathway occurs through the major platelet integrin alphaIIbbetaIII (Pearce et al., 2004).
Angiogenesis: Mice deficient in both Vav3 and Vav2 show reduced endothelial migration in response to the presence of tumor cells. Additionally Vav2 and Vav3 were found to be necessary and sufficient for Eph A receptor-mediated angiogenesis both in vitro and in vivo (Hunter et al., 2006).

Homology

Vav3 is conserved among vertebrates including dog, cow, mouse, rat, chicken and zebrafish, and has been shown to be present and conserved in Drosophila melanogaster (Movilla and Bustelo, 1999; Couceiro et al., 2005). Vav3 displays over 50% amino acid identity with other members of the Vav family of GEFS, Vav1 and Vav2 which have a similar arrangement of functional domains and regulation (Trenkle et al., 2000).

Mutations

Note

None described. SNP analysis has revealed several genetic polymorphisms, the implications of which remain unclear. The single nucleotide polymorphisms resulting in differing amino acid sequence are as follows: residue 139, D to N, residue 298, T to S, residue 616 P to S, and residue Q to H. There are multiple SNPS residing in both the 3'UTR and 5'UTR regions. The implications of these are not known.

Implicated in

Prostate cancer

Note

Vav3 mRNA and protein are up-regulated during progression of human prostate cancer cells to androgen independence in cell culture and in vivo experimental studies (Lyons and Burnstein, 2006; Lyons et al., 2008). Further, the importance of this upregulation to the disease process has been elucidated by more recent studies showing that Vav3 mRNA is up-regulated in prostate cancer tumor specimens obtained from men undergoing androgen deprivation therapy compared to levels in primary tumors (Holzbeierlein et al., 2004; Best et al., 2005; data deposited in public databases). Vav3 protein is overexpressed (relative to benign tissue) in almost one-third of prostate cancer tumor specimens (Dong et al., 2006).
Additionally, Vav3 mRNA is up-regulated in androgen independent tumors in the Nkx3.1; Pten mouse model of prostate cancer (Banach-Petrosky et al., 2007; Ouyang et al., 2008) and targeted expression of a constitutively active form of Vav3 in prostate epithelium of transgenic mice leads to overactivity of the androgen receptor signaling axis and adenocarcinoma (Liu et al., 2008). Mechanistic studies show that Vav3 stimulates ligand independent androgen receptor activation by a GEF-dependent mechanism that requires the Rho GTPase, Rac 1 in prostate cancer cells (Lyons et al., 2008). Additionally, Vav3 enhances androgen receptor transcriptional

activity in the presence of low concentrations of androgen through a GEF independent pathway that requires the Vav3 PH domain (Lyons and Burnstein, 2006).

Breast cancer

Note

Lee et al. reported that 81% of human breast cancer specimens exhibited higher levels of Vav3 compared to benign tissue (Lee et al., 2008). In addition, Vav3 enhances the transcriptional activity of the estrogen receptor in a GEF dependent manner (Lee et al., 2008).

Gastric cancer

Note

Downregulation of RUNX3, a member of the runt domain-containing family of transcription factors that has tumor suppressive actions, has been implicated in promoting human gastric carcinogenesis. Silencing of RUNX3 expression via methylation was found in 75% of primary tumors and 100% of gastric metastasis. Stable reexpression of RUNX3 strongly inhibited peritoneal metastases. Further analysis suggested that Runx3 expression resulted in the downregulation of a number of genes including Vav3 thereby providing a potential line between Vav3 expression and gastric malignancy (Sakakura et al., 2005).

Hepatocellular carcinoma

Note

Vav3.1 was down regulated in HepG2 cells in response to treatment with the hepatocellular carcinoma chemotherapeutic triterpenoid agent astragoloside. Downregulation of Vav3.1 was highly correlated with a decrease in malignant transformation, suggesting a role for Vav3.1 in the antitumor actions of astragoloside (Shen et al., 1997).

Glioblastoma

Note

Vav3 is upregulated in glioblastoma as compared to nonneoplastic or lower grade gliomas. Down regulation of Vav3 by siRNA reduced glioblastoma invasion and migration. Further upregulation of Vav3 was shown to be an indicator of poor patient survival (Salhia et al., 2008).

Tumor growth and angiogenesis

Note

A role for Vav3 in promoting tumor growth and angiogensis has been revealed through studies using mice deficient in both Vav2 and Vav3 (Brantley-Sieders et al., 2009). Vav2, Vav3 knockout mice transplanted with B16 melanoma or Lewis lung carcinoma cells showed decreases in tumor growth, tumor survival and neovascularization of tumors as compared to wild type control mice. The reduction in vascularization and tumor growth was found to be secondary to a reduction in endothelial cell migration (Brantley-Sieders et al., 2009).

Type 1 diabetes mellitus

Note

Alteration in Vav3 expression may be an etiological factor in the development of beta islet cell destruction characteristic of type 1 diabetes (Fraser et al., 2010).

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