

## Gene Section

### Mini Review

# VAV1 (vav 1 oncogene)

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### Identity

**Other names:** VAV

**HGNC (Hugo):** VAV1

**Location:** 19p13.2

### DNA/RNA

#### Transcription

2535 mRNA complete codons.

### Protein

#### Note

Vav1 was discovered when DNA from five esophageal carcinomas were tested for their transforming activity. This newly identified gene represented the sixth oncogene detected in Dr. Barbacid's laboratory and it was thus designated Vav1, after the sixth letter of the Hebrew alphabet. Vav1 was activated as an oncogene in vitro by replacement of 67 amino-acid residues of its amino-terminus (CH region) with 19 amino-acids residues of pSV2neo sequences, co-transfected as a selectable marker.

Wild-type Vav1 produces minimal transformation of NIH3T3 murine fibroblasts only when the protein is grossly over-expressed.

Removal of its amino terminus sequences (65 residues), thus mimicking its original mode of activation, is sufficient to induce Vav1 transformation.

### Description

Vav1 encodes a highly unique protein that contains numerous modular motifs known to play a role in tyrosine-mediated signal transduction cascades, such as a dbl homology (DH) region, which exhibits a guanine nucleotide exchange factor (GEF) activity towards the Rho family GTPases; a pleckstrin homology (PH) domain which interacts with polyphosphoinositides; a Src Homology 2 (SH2) and two Src Homology 3 (SH3) domains that mediate protein-protein interactions; a proline- rich motif that enables binding to SH3 - containing proteins, an acidic-rich (Ac) region and a 'calponin-homology' (CH) region, which functions as an actin-binding domain in other proteins and two nuclear localization signals (NLS).

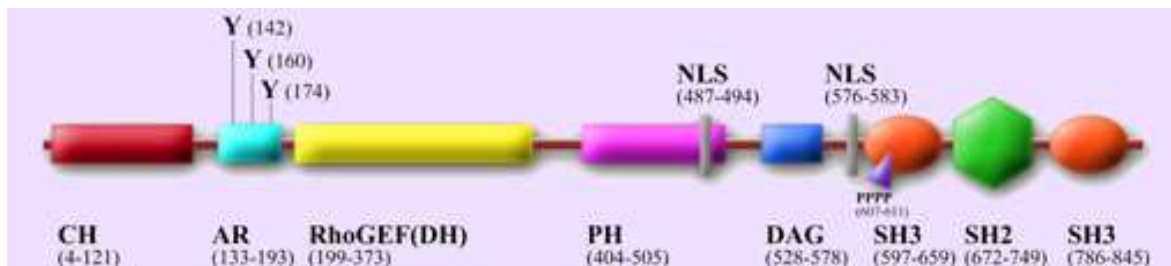
In fact, Vav1 is the only known Rho GEF that combines in the same protein the DH/PH motifs and the structural hallmark of signal transducer proteins, the SH2 and SH3 domains.

### Expression

Vav1 is specifically expressed in the hematopoietic system.

### Function

The Vav1 protein (95 kDa) is rapidly tyrosine-phosphorylated following stimulation of various receptors on hematopoietic cells (TCR, BCR, IgE, etc). Vav1 can then function in various signaling cascades.



First, as a tyrosine-phosphorylated protein, Vav1 operates as a guanine nucleotide exchange factor (GEF) for Rac1, Rac2 and RhoG. It is the only known GEF protein whose activity is regulated by tyrosine phosphorylation.

As a regulator of activation of the Rho/Rac GTPases, Vav1 participates in several processes that require cytoskeletal reorganization, such as the formation of the immunological synapse (IS), phagocytosis, platelet aggregation and spreading. Vav1 can also function in GEF-independent pathways through its association with other proteins such as ZAP-70, SLP-76, Ly-GDI (an inhibitor of Rho/RacGTPases), Grb2 and cytoskeletal proteins such as Zyxin.

Vav1 plays a critical role in stimulation of NFAT (Nuclear Factor of Activated T cells), culminating in the production of numerous vital cytokines. Vav1 also leads to the induction of an intracellular calcium flux by regulating the activation of phospholipase C $\gamma$ 1 (PLC $\gamma$ 1) via phosphoinositide 3-kinase (PI3K) dependent and -independent pathways. The activity of Vav1 also leads to the activation of NF- $\kappa$ B and the extracellular signal regulated kinase (ERK) mitogen-activated protein kinase (MAPK) signaling cascade.

There is compelling evidence from studies of gene-targeted mice to indicate that Vav1 participates in the development and function of many types of immune cell such as the positive- and negative-selection events that are imposed on double-positive thymocytes.

### Homology

Vav1 is one of a larger family of proteins that include Vav2 and Vav3 which unlike Vav1 are also ubiquitously expressed and the Vav homologues in *Drosophila Melanogaster* and in the nematode, *C. elegans*. These proteins are similar in their structure to Vav1, thus also functioning as signal transducer proteins.

## Mutations

### Somatic

Although, no mutants of Vav1 have been reported thus far in "real" human tumors, it was recently found that Vav1 is expressed in the majority of 42 specimens of human neuroblastoma, suggesting a possible

involvement of this protein in the neoplastic process in a subset of neuroblastomas. Furthermore, it was recently found to be involved in a large number of Pancreatic tumors.

## Implicated in

### Disease

Neuroblastoma.

### Disease

Pancreatic tumors.

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