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WAVE2

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WASP family verprolin-homologous protein 2 (WAVE2, also called WASF2) was originally identified by its sequence similarity at the carboxy-terminal VCA (verprolin, cofilin/central, acidic) domain with Wiskott-Aldrich syndrome protein (WASP) and N-WASP (neural WASP). In mammals, WAVE2 is ubiquitously expressed, and its two paralogs, WAVE1 (also called suppressor of cAMP receptor 1, SCAR1) and WAVE3, are predominantly expressed in the brain. The VCA domain of WASP and WAVE family proteins can activate the actin-related protein 2/3 (Arp2/3) complex, a major actin nucleator in cells. Proteins that can activate the Arp2/3 complex are now collectively known as nucleation-promoting factors (NPFs), and the WASP and WAVE families are a founding class of NPFs.
The WAVE family has an amino-terminal WAVE homology domain (WHD domain, also called the SCAR homology domain, SHD) followed by the proline-rich region that interacts with various Src-homology 3 (SH3) domain proteins. The VCA domain located at the C-terminus. WAVE2, like WAVE1 and WAVE3, constitutively forms a huge heteropentameric protein complex (the WANP complex), binding through its WHD domain with Abi-1 (or its paralogs, Abi-2 and Abi-3), HSPC300 (also called Brick1), Nap1 (also called Hem-2 and NCKAP1), Sra1 (also called p140Sra1 and CYFIP1; its paralog is PIR121 or CYFIP2).

The WANP complex is recruited to the plasma membrane by cooperative action of activated Rac GTPases and acidic phosphoinositides. Activated Rac indirectly associates with WAVE2 through Sra1 and/or insulin receptor tyrosine kinase substrate p53 (IRSp53). These interactions link Rac activation and the membrane recruitment of WAVE2. How acidic membrane phosphoinositides, including phosphatidylinositol-(4,5)-bisphosphate (PtdIns(4,5)P_2) and phosphatidylinositol-(3,4,5)-triphosphate (PtdIns(3,4,5)P_3), associate with the WANP complex is still unclear. However, purified monomeric WAVE2 binds directly to PtdIns(3,4,5)P_3, and weakly to PtdIns(4,5)P_2, through a basic amino acid cluster located just C-terminal to the WHD domain, suggesting that the interaction between the WANP complex and acidic phosphoinositides is mediated by WAVE proteins.

Binding of Rac and acidic phosphoinositides is also thought to activate the WANP complex at the plasma membrane. Cooperatively, tyrosine phosphorylation and serine/threonine phosphorylation of WAVE2 contribute to its activation. Although the precise mechanism of WANP complex activation remains to be elucidated, a plausible explanation is that the VCA domain, which is likely to be conformationally inhibited in the WANP complex, becomes released from the WANP complex following activation. The activated VCA domain can then simultaneously interact with the Arp2/3 complex and monomeric actin, leading to formation of an actin-nucleus-like core that is necessary to initiate actin polymerization.

Therefore, the WAVE family proteins mediate signals from Rac to the Arp2/3 to polymerize branched actin filaments in the vicinity of the plasma membrane enriched with PtdIns(4,5)P_2 and PtdIns(3,4,5)P_3. This signaling underlies Rac-induced formation of lamellipodial actin networks.

KEYWORDS
Scar-2; Scar2; WAS protein family, member 2; Wasf-2; Wasf2; WASF2; Wave-2; WAVE2

IDENTIFIERS
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PROTEIN FUNCTION
WASP family verprolin-homologous protein 2 (WAVE2) is a member of the Wiskott-Aldrich syndrome protein (WASP) superfamily of proteins, which in mammals consists of WASP, N-WASP, WAVE1, WAVE2, WAVE3, WHAMM, WASH and JMY (Takenawa *et al*. 2007, Kurisu and Takenawa 2009, Insall and Machesky 2009, Campellone and Welch 2010). All WASP superfamily proteins have characteristic VCA (verprolin, cofilin/central, acidic) domains at the carboxy terminus. The VCA domain activates the actin-related protein 2/3 (Arp2/3) complex, a major actin nucleator in cells. The Arp2/3 complex initiates actin polymerization by forming a polymerization nucleus at the side of pre-existing actin filaments, which leads to formation of branched actin networks, such as those seen in lamellipodia. Each WASP superfamily protein has its own unique mechanism of regulation. Early studies indicated that WAVE subfamily proteins (WAVE1-3) are generally activated by Rac GTPases and localized at the lamellipodial tips (Miki *et al*. 1998, Hahne *et al*. 2001, Nakagawa *et al*. 2001, Nozumi *et al*. 2003). Thus, WAVE proteins were thought to be required for lamellipodial actin polymerization and lamellipodium-driven cell motility, a hypothesis for which evidence has been provided by numerous subsequent studies.

In mammals, WAVE2 is ubiquitously expressed, whereas WAVE1 and WAVE3 are predominantly expressed in the brain (Suetsugu *et al*. 1999, Sossey-Alaoui *et al*. 2003). Studies of cells isolated from knockout mice established the essentiality of Wave2 for Rac-mediated lamellipodium formation in mouse

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embryonic fibroblasts and vascular endothelial cells (Yamazaki *et al*. 2003, Yan *et al*. 2003, Suetsugu *et al*. 2003). Therefore, in some cell types, WAVE2, rather than WAVE1 and WAVE3, is likely to be the primary Arp2/3 complex activator that functions downstream of Rac in lamellipodia formation.

WAVE2 is crucial for embryonic development, as shown by knockout mouse studies reported by two independent groups. One group reported that Wave2-deficient mice are embryonic lethal around embryonic day (E)9.5–10 because of defects in the heart and vascular system, presumably caused by reduced cell motility and weakened intercellular adhesion of endothelial cells during angiogenesis (Yamazaki *et al*. 2003). The other group reported that Wave2-deficient embryos die by E12.5, showing multiple developmental anomalies, including smaller body size, hemorrhage and disrupted ventricles of the central nervous system (Yan *et al*. 2003). These two reports clearly show that Wave2 is indispensable for normal embryonic development, although the timing of death caused by Wave2 deficiency is slightly different between the two.

In addition to lamellipodium induction, WAVE2 is implicated in epithelial cell-cell adhesion (Yamazaki *et al*. 2007), Golgi polarity regulation during wound healing (Magdalena *et al*. 2003), macropinocytosis (Sun *et al*. 2003, Innocenti *et al*. 2005), cancer cell invasion (Kurisu *et al*. 2005, Sanz-Moreno *et al*. 2008, Yamazaki *et al*. 2009), T-cell receptor signaling (Nolz *et al*. 2006, Zipfel *et al*. 2006, Nolz *et al*. 2007), regulation of actin cytoskeleton in platelets (Oda *et al*. 2005), megakaryocyte development (Eto *et al*. 2007), hematopoietic stem cell proliferation (Ogaeri *et al*. 2009), dendritic spine morphogenesis in the central nervous system (Choi *et al*. 2005), oligodendrocyte precursor cell migration (Miyamoto *et al*. 2008), pathogen invasion into host cells (*Chlamydia*, *Listeria*, *Salmonella* and enteropathogenic *Escherichia coli*) (Bierne *et al*. 2005, Shi *et al*. 2005, Carabeo *et al*. 2007, Bulgin *et al*. 2009), HIV-1 infection (Harmon *et al*. 2010) and serum response element activation (Ishiguro *et al*. 2004).

REGULATION OF ACTIVITY

The WANP complex

Endogenous WAVE2, like WAVE1 and WAVE3, constitutively forms a heteropentameric protein complex with Abi-1(or its paralogs, Abi-2 and Abi-3), HSPC300 (also called Brick1), Nap1 (also called Hem-2 and NCKAP1), Sra1 (also called p140Sra1 and CYFIP1; its paralog is PIR121 or CYFIP2) (Eden *et al*. 2002, Innocenti *et al*. 2004, Gautreau *et al*. 2004, Nolz *et al*. 2006, Hirao et al. 2006). This five-membered protein complex is referred to as the WAVE regulatory complex or the WANP complex. The WAVE homology domain (WHD domain, also called the SCAR homology domain, SHD), which is commonly found at the N-terminus of WAVE isoforms (WAVE1-3), interacts both with the predicted coiled-coil region of Abi-1/2/3 and that of HSPC300 (Innocenti *et al*. 2004, Echarri *et al*. 2004, Leng *et al*. 2005). At the same time, Abi-1/2/3 directly binds to the Nap1-Sra1 sub-complex (Innocenti *et al*. 2004, Gautreau *et al*. 2004, Steffen *et al*. 2004). Thus, Abi-1/2/3 links WAVE and HSPC300 to the Nap1-Sra1 sub-complex. HSPC300 is a small peptide of approximately 75 amino acids. Each component of the WANP complex is required for the complex to stably exist in cells; lack of any of the components of the WANP complex leads to proteasomal degradation of the whole complex (Blagg *et al*. 2003, Kunda *et al*. 2003, Rogers *et al*. 2003, Steffen *et al*. 2004).

The intrinsically inactive model versus the constitutively active model

The activity of WAVE proteins can be biochemically monitored by the extent to which WAVE proteins polymerize pyrene-labeled actin through Arp2/3 complex activation. By this measure, the recombinant peptide of the C-terminal VCA domain of WAVEs shows strong activity. It has long been known that the monomer form of full-length WAVE1 has comparable or even higher activity than that of the VCA domain alone (Machesky *et al*. 1999), which contrasts with the case of auto-inhibitory WASP and N-WASP. However, WAVE activity is expected to be tightly regulated in cells to avoid unnecessary actin polymerization that is deleterious to normal cell activities. There must therefore be regulatory mechanisms that keep WAVEs under control.

Initially, it was reported that the native WAVE1 complex chromatographically purified from bovine brain extracts is intrinsically inactive and can be activated by Rac GTPases (Eden *et al*. 2002). In this model, Rac triggers dissociation of the Sra1-Nap1-Abi2 sub-complex from the pentameric WAVE1 complex, which results in release of an active WAVE1-HSPC300 sub-complex. However, later studies had completely different results; the WAVE1 complex purified from rat brain cytosol and recombinant WAVE1 complex that was reconstituted *in vitro* using purified proteins were both constitutively active (Kim *et al*. 2006). The reconstituted WAVE2 complex, reported by another group, was also fully active. This WAVE2 complex did not release the Sra1-Nap1-Abi1 sub-complex following addition of activated Rac (Innocenti *et al*. 2004). On the basis of these studies, it was proposed that the WANP complex is relatively stable in cells, a conclusion that is widely accepted at present, and that its activity is mainly regulated by its subcellular localization. However, disagreements remained as to whether the WANP complex in a resting state is active or inactive.

More recently, several groups re-examined the discrepancy of the basal activity of the WANP complex, showing that both the WANP complex purified from cell extracts and the WANP complex reconstituted *in vitro* are basally inhibited (Suetsugu *et al*. 2006 May, Derivery *et al*. 2009, Ismail *et al*. 2009, Lebensohn *et al*. 2009), and that they can be activated by GTP-bound forms of Rac (Ismail *et al*. 2009, Lebensohn *et al*. 2009). According to these studies, the previously reported constitutive activity of the WANP complex could be attributed to denaturation of the native complex after time-consuming purification procedures and freeze-thaw handling, or to contamination of monomeric forms of WAVE proteins when reconstituting the WANP complex *in vitro*.

Current models for WAVE2 activation

If we accept the intrinsically inactive model of the WANP complex, three mechanisms are proposed for WAVE2 regulation: one is via Sra1, the second is via insulin receptor tyrosine kinase substrate p53 (IRSp53), an adaptor protein whose Src-homology 3 (SH3) domain binds to the proline-rich region of WAVE2, and the third is via phosphorylation. These mechanisms are not mutually exclusive; rather, they may be cooperative and interrelated. However, the epistatic relationship between the three, if any, is yet poorly understood.

Sra1-mediated regulation

The VCA domain, which activates the Arp2/3 complex, is usually inhibited in the WANP complex, probably through binding to the Sra1-Nap1 sub-complex (Ismail *et al*. 2009). This intra-complex binding is thought to keep the VCA domain in an inactive state. Recently, Chen *et al*. reported the crystal structure of an engineered WANP complex (mini-WRC) in which the proline-rich region of WAVE1 was replaced with an 18-residue linker and the C-terminal proline-rich region and SH3 domain of Abi2 was deleted to enhance crystallization (Chen *et al*. 2010). According to this structure, the VCA domain is buried in the concave surface of Sra1, reinforcing the hypothesis that the Sra1-Nap1 sequesters the VCA domain. The mini-WRC complex was inactive and could be activated in response to Rac1 binding to the complex (Ismail *et al*. 2009, Chen *et al*. 2010). Active Rac is thought to compete with the VCA domain for binding to Sra1 in the WANP complex and thus to release the VCA domain from the complex, leading to activation of the complex (Kobayashi *et al*. 1998, Chen *et al*. 2010). This mechanism is likely to operate in the native WAVE1 complex as well as in the native WAVE2 complex, given the extensive sequence similarity of the WHD and VCA domains between WAVE paralogs. However, care should be taken when extending the mini-WRC theory. In mini-WRC, the central proline-rich region of WAVE1 spanning 285 residues was missing and amino-terminal two thirds of Abi2 was deleted. Thus, the mini-WRC may not fully recapitulate the native WANP structure. Selective binding of Rac1-GTP over Rac1-GDP to the mini-WRC was not shown, so it remains unclear whether there is regulation of the WANP complex by Rac.

IRSp53-mediated activation

IRSp53 is not a member of the WANP complex, but it binds detectably to WAVE2 in the complexed state (Suetsugu *et al*. 2006 May, Lebensohn *et al*. 2009). WAVE2 has much stronger affinity for IRSp53 than have WAVE1 and WAVE3 (Miki *et al*. 2000), indicating that regulation by IRSp53 is specific to WAVE2. IRSp53 activates the WAVE2 complex *in vitro* and further enhances its activity in the presence of active Rac and phosphatidylinositol-(3,4,5)-trisphosphate (PtdIns(3,4,5)P_3) (Miki *et al*. 2000, Suetsugu *et al*. 2006 May). Because active Rac directly binds to IRSp53 and increases the affinity of IRSp53 for WAVE2 (Miki *et al*. 2000, Abou-Kheir *et al*. 2008), Rac presumably regulates WAVE2 activity through IRSp53. The role of PtdIns(3,4,5)P_3 in WAVE activation is still unclear. The Rac-binding region of IRSp53, known as the IMD/inverse BAR (I-BAR) domain, can bind to negatively charged phospholipids, including PtdIns(3,4,5)P_3 (Suetsugu *et al*. 2006 May, Mattila *et al*. 2007) and, in addition, WAVE2 interacts directly with PtdIns(3,4,5)P_3 (Oikawa *et al*. 2004). These interactions at least facilitate localization of the WAVE2 complex at PtdIns(3,4,5)P_3-enriched membranes. Recently, Lebensohn *et al*. showed that purified native WAVE2 complexes, which contain IRSp53 in their preparations, are activated only on liposomes containing acidic phospholipids (Lebensohn *et al*. 2009). The most prominent in activating WAVE2 were liposomes containing PtdIns(3,4,5)P_3. Therefore, PtdIns(3,4,5)P_3 (and other acidic phospholipids) binding either to WAVE2 or IRSp53 is likely to be required for WAVE2 activation. However, the precise roles and contributions of negatively charged lipids in activating the WANP complex are unclear and need further research.

The IMD/I-BAR domain of IRSp53 is intriguing in the sense that it binds to acidic phospholipids and physically deforms the biological membrane into protrusions (Suetsugu *et al*. 2006 May, Mattila *et al*. 2007, Saarikangas *et al*. 2009). Overexpression of IRSp53 in cultured cells induces microspike-like membrane protrusions, which is mediated by IMD/I-BAR domain binding to acidic phosphoinositides (Suetsugu *et al*. 2006 Nov). Although these microspike-like protrusions and WAVE2-induced lamellipodia appear different in shape, the membrane-deforming activity of IRSp53 may synergize with the activation of Arp2/3 by WAVE2 in lamellipodial extensions.

Regulation by tyrosine and serine/threonine phosphorylation

WAVE2 is phosphorylated at multiple sites. The Abl tyrosine kinase directly binds to the WAVE2 complex and phosphorylates the tyrosine residue at amino acid 150 of human WAVE2. Tyr 150 is critical for WAVE2 activation *in vitro* and for WAVE2-mediated lamellipodia formation in cells (Leng *et al*. 2005, Stuart *et al*. 2006, Nolz *et al*. 2008). Tyr 150 is conserved from plants to humans, suggesting that tyrosine phosphorylation is a basic mechanism of activity regulation maintained throughout evolution. In addition, WAVE2 has multiple serine/threonine kinase phosphorylation sites. Phosphorylation of serine/threonine residues within the proline-rich region, which affects the electrophoretic mobility shift of WAVE2, is directly caused by mitogen activated protein (MAP) kinases in response to growth factor stimulation. Nakanishi *et al*. reported that the MAP kinase Erk2 phosphorylates Ser 308, Thr 346 and Ser 351 of human WAVE2 (corresponding to Ser 308, Thr 344 and Ser 349 in mouse, respectively) (Nakanishi *et al*. 2007). Danson *et al*. reported that Erk2 phosphorylates Thr 346 and Ser 351 (corresponding to Thr 344 and Ser 349 in mouse, respectively) and Jnk2 phosphorylates Ser 343 and Thr 346 in human WAVE2 (corresponding to Ser 341 and Thr 344 in mouse, respectively) (Danson *et al*. 2007). The phosphorylation does not affect the actin polymerization activity of WAVE2, but it is implicated in cell polarity regulation during cell migration (Danson *et al*. 2007). The VCA region is also phosphorylated by ERK2 at Ser 482 and Ser 484 (corresponding to Ser 481 and Ser 483 in mouse, respectively) (Nakanishi *et al*. 2007) and/or by casein kinase 2 at Ser 482, Ser 484, Ser 488, Ser 489 and Ser 497 in human WAVE2 (corresponding to Ser 481, Ser 483, Ser 487, Ser 488 and Ser 496 in mouse, respectively) (Pocha and Cory 2009). Phosphorylation at Ser 482 and Ser 484 decreases *in vitro* actin polymerization activity of WAVE2, but its functional significance remains unclear (Nakanishi *et al*. 2007, Pocha and Cory 2009). Also, phosphorylation within the WHD domain at Ser 137 by the cyclin-dependent kinase Cdk5 is required for platelet-derived growth factor (PDGF)-induced oligodendrocyte precursor cell migration, although effects of this phosphorylation on *in vitro* WAVE2 activity are yet to be determined (Miyamoto *et al*. 2008). However, the native WAVE2 complex treated with the serine/threonine phosphatase PP2A is no longer activated by Rac1 and PtdIns(3,4,5)P_3, highlighting the importance of serine/threonine phosphorylation for activation of the WANP complex (Lebensohn *et al*. 2009).

INTERACTIONS

The domain architecture of WAVE2 is as follows: the WHD domain (amino acids 1-170) at the N terminus, followed by basic amino acid clusters (B region; amino acids 171-201), proline-rich region (amino acids 247-419), the V/WH2 (verprolin-homology/WASP-homology 2) domain (amino acids

435-452 of mouse Wave2), the C (cofilin-homology/central) region (amino acids 463-480 of mouse Wave2) and the C-terminal A (acidic) region (amino acids 481-497 of mouse Wave2). The V/WH2 domain, the C region and the A region are collectively known as the VCA domain, which characterizes the WASP superfamily proteins.

WAVE2 associates with monomeric actin and the Arp2/3 complex through the V domain and the CA region, respectively (Suetsugu *et al*. 1999). The VCA domain serves as a platform that brings an actin monomer and the Arp2/3 complex into close proximity. This spatial arrangement of an actin monomer and the Arp2/3 complex on the VCA platform triggers actin nucleation, leading to polymerization of branched actin filaments (see Pollard *et al*. 2003 and Le Clainche *et al*. 2008 for reviews). The VCA domain of WAVE2 was also shown to mediate the formation of a Arp2/3-vinculin-talin signaling complex (Nolz *et al*. 2007). Furthermore, Eiseler *et al*. reported that the F-actin binding protein cortactin acts as a bridge connecting the active WAVE2/Arp2/3 complexes with actin filaments at extending lamellipodia in breast cancer cell lines, and phosphorylation of cortactin in this complex by protein kinase D controls actin polymerization (Eiseler *et al*. 2010).

Through the N-terminal WHD domain, one of Abi isoforms and HSPC300 directly bind to WAVE2. In addition, Nap1 (or its isoform Hem1) and Sra1 (or its isoform PIR121) bind to the WAVE2-HSPC300-Abi sub-complex, forming a stable pentameric protein complex, the WANP complex (Innocenti *et al*. 2004, Steffen *et al*. 2004, Gautreau *et al*. 2004, Nolz *et al*. 2006, Hirao *et al*. 2006). Rac GTPase does not bind directly to WAVE2. Instead, Rac binds to Sra1 and IRSp53 to regulate WANP complex activity (Kobayashi *et al*. 1998, Miki *et al*. 2000, Steffen *et al*. 2004, Suetsugu *et al*. 2006 May, Chen *et al*. 2010). The WANP complex is recruited to the plasma membrane by cooperative action of activated Rac GTPases and acidic phosphoinositides. Activated Rac indirectly associates with WAVE2 through Sra1 and/or IRSp53. Purified recombinant Sra1 directly interacts with GTP-bound forms of Rac, but not with the GDP-bound forms. IRSp53 also binds directly to Rac-GTP through its N-terminal IMD/I-BAR domain and to WAVE2 through its C-terminally located SH3 domain. These interactions link Rac activation and membrane recruitment of WAVE2. IRSp53 interacts strongly with WAVE2, but weakly with WAVE1 or WAVE3. Thus, IRSp53 is likely to specifically enhance WAVE2 membrane targeting.

In addition to HSPC300 and Abi-1/2/3, dysbindin-1 binds to the WHD domain in neuronal cells (Ito *et al*. 2010). TOCA-1, an F-BAR-containing protein, also interacts with WAVE2 indirectly via Abi1 (Giuliani *et al*. 2009).

The B region interacts with PtdIns(3,4,5)P_3 and weakly with phosphatidylinositol-(4,5)-bisphosphate (PtdIns(4,5)P_2) (Oikawa *et al*. 2004). The region responsible for this interaction is in a basic amino acid cluster found at amino acids 173-179 within the B region. PtdIns(3,4,5)P_3 binding makes WAVE2 favor localization at PtdIns(3,4,5)P_3-enriched membranes, such as the leading edge of migrating cells. Furthermore, PtdIns(3,4,5)P_3 binding to WAVE2 seems to be involved in activation of the WANP complex (Lebensohn *et al*. 2009, Chen *et al*. 2010).

The following proteins bind directly to the proline-rich region of WAVE2: IRSp53 (Miki *et al*. 2000), profilin (Oda *et al*. 2005), the Arg/Abl-binding protein ArgBP2 (Cestra *et al*. 2005), vinexin β (Mitsushima *et al*. 2006) and the nonreceptor tyrosine kinase c-Abl (Leng *et al*. 2005). Among these, IRSp53 (Suetsugu *et al*. 2006 May, Lebensohn *et al*. 2009) and c-Abl (Stuart *et al*. 2006, Nolz *et al*. 2008) interact with the WANP-complexed form of WAVE2. It is unclear whether other interactors can interact with the WANP-complexed form.

Takahashi and Suzuki reported that IQGAP1 (a GTPase activating protein) and a kinesin (KIF5B) form a complex with WAVE2 (Takahashi and Suzuki 2008). In a later study they showed that Pak1, a downstream effector of Rac1, constitutively binds to WAVE2 and recruits stathmin (oncoprotein 18), forming a complex with WAVE2 and kinesin (Takahashi and Suzuki 2009). In addition to these, WAVE2 was also shown to form a complex with BetaPIX (a Rho guanine nucleotide exchange factor also called Cool 1) and Git1 (a GTPase activating protein) in human breast cancer cell lines (Morimura *et al*. 2009).

Finally, the following proteins are reported to interact with multiple regions of WAVE2: the formin mDia2, Cdk5 and both catalytic and regulatory subunits of protein kinase A (Beli *et al*. 2008, Miyamoto *et al*. 2008, Yamashita *et al*. 2011).

PHENOTYPES

Two independent groups report Wave2-knockout mouse studies.

One reports that Wave2$^{-/-}$ mouse embryos show hemorrhages and die at about E10 (Yamazaki *et al*. 2003). Although Wave2 deficiency has no significant effect on vasculogenesis, it decreases sprouting and branching of endothelial cells from existing vessels during angiogenesis. In Wave2$^{-/-}$ endothelial cells, cell polarity forms in response to vascular endothelial growth factor; however, the formation of lamellipodia at the leading edges and capillaries is severely impaired. Collectively, the authors concluded that Wave2 is essential for cardiovascular development during embryogenesis.

The other group reports that Wave2-deficient embryos die by E12.5 with multiple developmental anomalies, including smaller body size, hemorrhage and disrupted ventricles of the central nervous system (Yan *et al*. 2003). In addition, mouse embryonic fibroblasts isolated from Wave2-knockout embryos have a dramatically slower proliferation rate than those from wild-type and heterozygous mice.

These two reports clearly show that Wave2 is indispensable for normal embryonic development, although the timing of death caused by Wave2 deficiency is slightly different between the two. Using Wave2-knockout fibroblasts, both groups showed that Wave2 is essential for lamellipodia formation downstream of Rac and PDGF-induced cell motility (Suetsugu *et al*. 2003, Yan *et al*. 2003). These fibroblasts express Wave1, suggesting a non-redundant role of Wave2 in these processes.

MAJOR SITES OF EXPRESSION

WAVE2 is ubiquitously expressed (Suetsugu *et al*. 1999, Sossey-Alaoui *et al*. 2003).

SPLICE VARIANTS

No splice variant is reported.

REGULATION OF CONCENTRATION

Formation of the heteropentameric protein complex that consists of WAVE, Abi-1/2/3, Nap1, Sra1 and HSPC300

contributes to the stability of each component of the complex in cells (Blagg *et al*. 2003, Kunda *et al*. 2003, Rogers *et al*. 2003, Steffen *et al*. 2004, Innocenti *et al*. 2005, Nolz *et al*. 2006, Yamazaki *et al*. 2007). Decreased expression of any component of the WANP complex leads to decreased amounts of the other components. The decrease in WAVE2 levels in the absence of other complex components is thought to be mediated by ubiquitin-proteasome-dependent protein degradation (Kunda *et al*. 2003). Calpain-mediated degradation of WAVE2 is another possible mechanism (Oda *et al*. 2005).

The amount of WAVE2 protein is aberrantly upregulated or downregulated in cancer cells (see Kurisu and Takenawa 2010 for a review), although it is unclear whether the aberrations seen in cancer cells are due to dysregulation in the above-mentioned degradation pathways. WAVE2 upregulation is reported in many types of cancer, including melanoma and carcinomas of liver, breast, lung and colon, and this often positively correlates with cancer malignancies, such as invasion and metastasis (Kurisu and Takenawa 2005, Yang *et al*. 2006, Semba *et al*. 2006, Iwaya *et al*. 2007 Mar, Iwaya *et al*. 2007 Jul, Fernando *et al*. 2007, Wang *et al*. 2007).

ANTIBODIES

Polyclonal anti-WAVE2 antibodies are commercially available (Santa Cruz Biotechnology and Millipore):

Goat polyclonal antibody against WAVE2 (C-14; Santa Cruz catalog number sc-10394) (Miyamoto *et al*. 2008). Raised against a peptide mapping near the C terminus of WAVE2 of human origin. Detects mouse, rat and human proteins. Applications: western blotting (WB), immunoprecipitation (IP) and immunofluorescence.

Goat polyclonal antibody against WAVE2 (D-16; catalog number sc-10392) (Danson *et al*. 2007). Raised against a peptide mapping within an internal region of WAVE2 of human origin. Detects the human protein. Applications: WB, IP and immunofluorescence.

Rabbit polyclonal antibody against WAVE2 (H-110; catalog number sc-33548) (Miyamoto *et al*. 2008). Raised against a peptide corresponding to amino acids 206-315 mapping within an internal region of WAVE2 of human origin. Detects the mouse, rat and human proteins. Applications: WB, IP and immunofluorescence.

Rabbit polyclonal antiserum against WAVE2 (Upstate catalog number 07-410). Raised against a peptide corresponding to amino acids 186-200 of human WAVE2. Detects the human and rat proteins. Applications: WB.

Table 1: Functional States

STATE DESCRIPTION	LOCATION	REFERENCES
WAVE2	cytoplasm	
WANP complex	cytoplasm	Eden S *et al.* 2002; Gautreau A *et al.* 2004; Hirao N *et al.* 2006; Innocenti M *et al.* 2004; Nolz JC *et al.* 2006; Steffen A *et al.* 2004; Suetsugu S *et al.* 2006
WANP-PY150/c-Abl	cytoplasm	Leng Y *et al.* 2005; Stuart JR *et al.* 2006
WANP-2PS341,T344	cytoplasm	Danson CM *et al.* 2007
WANP-2PT344,S349	cytoplasm	Danson CM *et al.* 2007
WANP-5PS481,483,487,488,496	cytoplasm	Pocha SM and Cory GO 2009
WANP-P	cytoplasm	Lebensohn AM and Kirschner MW 2009
WANP-P-PIP3	plasma membrane	Oikawa T *et al.* 2004; Suetsugu S *et al.* 2006
WANP-P-PIP3/Rac-GTP	plasma membrane	Eden S *et al.* 2002; Innocenti M *et al.* 2004; Suetsugu S *et al.* 2006
WANP-P-PIP3/Rac-GTP/Arp2/3 complex	plasma membrane	Suetsugu S *et al.* 1999; Carabeo RA *et al.* 2007
WANP-P/IRSp53	cytoplasm	Abou-Kheir W *et al.* 2008; Connolly BA *et al.* 2005; Lebensohn AM and Kirschner MW 2009; Miki H and Takenawa T 2002; Miki H *et al.* 2000; Nakagawa H *et al.* 2003; Robens JM *et al.* 2010; Shi J *et al.* 2005; Suetsugu S *et al.* 2006
WANP-P-PIP3/IRSp53	plasma membrane	Lebensohn AM and Kirschner MW 2009; Miki H *et al.* 2000; Suetsugu S *et al.* 2006
WANP-P-PIP3/Rac-GTP/IRSp53	plasma membrane	Miki H *et al.* 2000; Suetsugu S *et al.* 2006
WANP-P-PIP3/Rac-GTP/Arp2/3/IRSp53	plasma membrane	Miki H *et al.* 2000
WANP/c-Abl	cytoplasm	Stuart JR *et al.* 2006; Nolz JC *et al.* 2008
WAVE2-PS137	cytoplasm	Miyamoto Y *et al.* 2008
WAVE2-5PS304,T344,S349,S481,S483	Unknown	Nakanishi O *et al.* 2007; Pocha SM and Cory GO 2009
WAVE2/ArgBP2	cytoplasm	Cestra G *et al.* 2005
WAVE2/Profilin	cytoplasm	Miki H *et al.* 1998; Oda A *et al.* 2005
WAVE2/Vinexinβ	cytoplasm	Mitsushima M *et al.* 2006
WAVE2/Abi1/dysbindin1	cytoplasm	Ito H *et al.* 2010
WAVE2/Abi1/Toca-1	cytoplasm	Giuliani C *et al.* 2009
WAVE2/GIT1/BetaPIX	Unknown	Morimura S *et al.* 2009
WAVE2/IQGAP1/KIF5B	Unknown	Takahashi K and Suzuki K 2008
WAVE2/Pak1	Unknown	Takahashi K and Suzuki K 2009
WAVE2/KIF5B/Pak1/stathmin	Unknown	Takahashi K and Suzuki K 2009
WAVE2/Arp2/3 complex	Unknown	Suetsugu S *et al.* 1999
WAVE2/Arp2/3/mDia2	cytoplasm	Beli P *et al.* 2008
WAVE2/Arp2/3/Vinculin	Unknown	Nolz JC *et al.* 2007
WAVE2/Arp2/3/Vinculin/Talin	Unknown	Nolz JC *et al.* 2007
WAVE2/Arp2/3/cortactin	Unknown	Eiseler T *et al.* 2010
WAVE2/PKA holoenzyme	cytoplasm	Yamashita H *et al.* 2011
WAVE2-proteo	Unknown	Oda A *et al.* 2005

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This molecule exists in 33 states , has 33 transitions between these states and has 0 enzyme functions.(Please zoom in the pdf file to view details.)