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Review

WASPs and WAVEs: From molecular function to physiology in hematopoietic cells

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ABSTRACT

The actin cytoskeleton is critically involved in a variety of cell functions. The Arp2/3 complex mediates branching of filamentous actin. The members of the Wiskott–Aldrich syndrome protein (WASP) family are major regulators of the complex. As such, the family proteins are also involved in numerous aspects of cell biology. In this short review, we first define the expanding WASP family. Next, we compare the domain structure of the members, and explain the known or proposed functions of each domain or region. Finally, we demonstrate the well-characterized roles of the proteins in specific cellular functions.

Contents

Abbreviations: Abi, Abelson-interactor; CCP, clathrin-coated pit; CRIB, Cdc42/rac interactive binding; CYFIP, cytoplasmic fragile-X mental retardation interacting protein; EHEC, enterohaemorrhagic *Escherichia coli*; EPEC, enteropathogenic and enterohaemorrhagic *Escherichia coli*; EVH1, ena-VASP homology 1; F-BAR, FCH-Bin/Amphiphysin/Rvs); IMD, IRSp53-MIM homology domain; JMY, for junction-mediating and regulatory protein; mDia1, diaphanous-related formin-1; NPF, nucleation promoting factor; N-WASP, nueral Wiskott–Aldrich syndrome protein; PIP2, phosphatidylinositol-(4,5)-bisphosphate; RCB, Rac binding; TKS4, tyr kinase substrate with four SH3 domains; TKS5, tyr kinase substrate with five SH3 domains; Toca-1, transducer of Cdc42-dependent actin assembly; VCA, V for verprolin-homology, C for cofilin-homology or central and A for acidic; WAML, WASP and MIM like; WAS, Wiskott–Aldrich syndrome; WASH, for Wiskott–Aldrich syndrome protein and Scar homolog; WASP, Wiskott–Aldrich syndrome protein; WH/SH, WAVE/Scar homology; WAVE, WASP family verprolin-homologous proteins; WAWH, WASP without WH1 domain; WH1, WASP homology 1; WHAMM, for WASP homolog associated with actin, membranes, and microtubules; WIP, WASP-interacting protein; XLP, X-linked thrombocytopenia.

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1. Introduction: WASP family proteins

One of the major regulators of actin polymerization is the Arp2/3 complex that promotes the formation of branched actin filament network, typically seen in lamellipodia. Machesky and Gould purified the complex for the first time, and, found that it barely initiated actin polymerization [1], suggesting that some key factors were missing. The key activators of the Arp2/3 complex are now called nucleation-promoting factors (NPFs) [2,3]. WASP family proteins are the best-characterized NPFs and the theme of this review [4–8].

Until recently, WASP family consisted of WASPs and WAVEs (for WASP family verprolin-homologous proteins, also called SCARs). Various mutations in the WASP gene encoding WASP lead to development of Wiskott–Aldrich syndrome (WAS) [7,9]. The closest relative of WASP is N (for neural)-WASP. While WASP is exclusively expressed in hematopoietic cells, N-WASP is ubiquitously expressed and abundant in neuronal cells, hence it is called N-WASP. N-WASP is a vertebrate specific protein, possibly owing to whole genome duplications after the emergence of the vertebrates [8]. Some mutations in the WASP gene cause X-linked thrombocytopenia (XLP), a milder form of WAS [7,9]. It should be borne in mind that the mutations in the WASP gene may result in a disease other than WAS/XLP, and that they are not the sole cause of WAS. Thus, constitutively active mutant of WASP is responsible for X-linked neutropenia [10]. On the other hand, WIP (for WASP-interacting protein) is a major chaperon for WASP, and loss of WIP leads to a markedly reduced expression of WASP both in vitro and in vivo [11,12] A homozygous 1301C > G stop codon mutation in the WIP gene was recently shown to cause a WAS-like hereditary disorder [13]. Similar findings were previously reported for WIP knockout mice [14]. WIP binding to WASP prevents WASP degradation [15]. WASP degradation was inhibited by proteosome and calpain inhibitors [15,16]. However, since protease inhibitors are not absolutely specific, some caution may be required for interpretation of the data obtained using them. On the other hand, it was initially demonstrated that WASP may be a substrate for calpain and also be tyrosine phosphorylated in platelets [17]. Recently, it was reported that tyrosine phosphorylation of WASP may create a cbl-b (an E3 ligase) binding site and thus connect WASP to the ubiquitin/proteosome system [18]. As such, proteasome and calpain are likely major WASP proteases.

WAVE was identified by homology with WASP [19]. It was also independently discovered in a genetic screening for second-site suppressors of a mutation in one of the cAMP receptors, in Dictyostelium discoideum [20]. Three Mammalian WAVEs, WAVE1–3, have been well documented, although rat cells may also express WAVE5A [8]. Currently little is known of WAVE5A, except that it is predicted to have a very long proline–serine rich region. A common feature of WASPs and WAVEs is a poly-proline region, followed by a VCA (V for verprolin-homology; C for cofilin-homology or central; A for acidic) domain, although plant WAVEs lack the poly-proline region [4–6,8]. The same feature has been identified in several other proteins that also activate the ARP2/3 complex. The new WASP family members include WASH (for Wiskott–Aldrich syndrome protein and Scar homolog) [21], WHAMM (for WASP homolog associated with actin, membranes, and microtubules) [22], and JMY (for junction-mediating and regulatory protein) [23], which is a WHAMM homolog. Recently, WAML (for WASP and MIM like) and WAWH (for WASP without WH1 domain) proteins were identified through an extensive search in the database [8]. Here, these new WASP family proteins will only briefly be mentioned, since the knowledge on these proteins is expanding rapidly and their full description certainly requires a separate review [24].

2. Structures of WASP and WAVE proteins

In this section, the structures of both WASPs and WAVEs are described side by side for easy comparison (Fig. 1). WASP and N-WASP consist of an N-terminal WH1 (for WASP homology 1; also known as an Ena-VASP homology 1, EVH1) domain, a basic domain containing multiple lysine and arginine residues, a Cdc42/rac interactive binding (CRIB) motif, an autoinhibitory domain, a poly-proline region, and a C-terminal VCA region. The V domain in the VCA binds to G-actin and the CA domain to the Arp2/3 complex. The V domain is duplicated in N-WASP. The significance of the duplication is not clear. However, it has been suggested that the tandem V domains of N-WASP would promote actin nucleation and help localize N-WASP between the barbed ends and the membrane more efficiently than a single V domain [6]. At inactive state, the C domain binds to the autoinhibitory domain. Binding of small molecular G-proteins to the CRIB motif may relieve the intramolecular link. A pathogen reportedly exploits this mechanism of WASP activation. Enterohaemorrhagic *Escherichia coli* (EHEC) injects two proteins, Tir and EspFU/TccP, into host intestine cells(type III translocation). EspFU/TccP reportedly binds to and activates the host N-WASP mimicking the C domain [25]. Activated by this pseudo C-domain, N-WASP, reportedly triggers actin polymerization, and facilitates type III translocation [26]. Interestingly, the Arp2/3 complex may assume an open and inactive state or a closed and active one [27,28]. The WASPs, once open and active, bind to and activate the complex.

Based on NMR studies on the WIP, associated with the N-WASP WH1 domain, the interacting surface of WH1 corresponds to a hotspot for mutations in patients with WAS [29]. The findings are consistent with the essential role of WIP in stability of WASP, as mentioned in the previous section. In addition to WIP, tyrosine kinases, Fyn and Btk, reportedly bind to the WH1 domain rather than the proline-rich region [30,31]. It has been suggested that these interactions may facilitate WASP tyrosine phosphorylation.

WAVE1–3 also have the poly-proline rich region and the VCA domain. However, WAVEs do not have a CRIB motif and instead of the WH1 domain, an N-terminal WAVE/Scar homology (WH/SH) domain is present. Unlike WASP, WAVE proteins form a huge 400 kDa WAVE regulatory complex that consists of WAVE, a protein from the cytoplasmic fragile-X mental retardation interacting protein (CYFIP) family, NAP1, one of Abelson-interactor (Abi) 1–3, and HSPC300 [32,33]. Similar to WH1 domain in WASP, the WH/SH domain plays a critical role in stabilization of WAVE proteins. It was shown that the conserved coiled-coil motifs in the WH/SH domain may bind to those in Abi and HSPC300 [32,34]. Similar to the WASP–WIP relationship, the loss of the WAVE regulatory complex is thought to destabilize WAVEs. Unlike WH1 in WASP, the WH/SH domain binds to rac indirectly through a protein of the CYFIP family in the WAVE regulatory complex. The biding of rac to the complex is essential in rac-triggered activation of WAVE proteins from structural determination of the WAVE complex [33,83]. Among new WASP family members, WASH is also thought to function in a huge heteropentameric complex in a fashion, similar to WAVEs, although the members of the complex are distinct from those in the WAVE-regulatory complex [24].

A basic domain is present both in WASPs and WAVEs. Phosphatidylinositol-(4,5)-bisphosphate (PIP2) binds to the basic region amino terminal to the CRIB motif, and may contribute to the release of intramolecular constraint of WASP proteins in cooperation with activated CDC42 and also the translocation of WASPs to the membrane [35–37] On the other hand, the basic domain of WAVE2 binds to phosphatidylinositol (3,4,5)-triphosphate rather than PIP2 [38]. Because of the differences, for example, PI-3 kinases may preferentially affect WAVE functions and locations.