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REVIEW

WIP: A multifunctional protein involved in actin cytoskeleton regulation

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Abstract

Knowledge of the dynamics of actin-based structures is a major key to understanding how cells move and respond to their environment. The ability to reorganize actin filaments in a spatial and temporal manner to integrate extracellular signals is at the core of cell adhesion and cell migration. Several proteins have been described as regulators of actin polymerization: this review will focus on the role of WASP-interacting protein (WIP), an actin-binding protein that participates in actin polymerization regulation and signal transduction. WIP is widely expressed and interacts with Wiskott–Aldrich syndrome protein (WASP) (a hematopoietic-specific protein) and its more widely expressed homologue neural WASP (N-WASP), to regulate WASP/N-WASP function in Arp2/3-mediated actin polymerization. WIP also interacts with profilin, globular and filamentous actin (G- and F-actin, respectively) and stabilizes actin filaments. In vivo WIP participates in filopodia and lamellipodia formation, in T and B lymphocyte activation, in mast cell degranulation and signaling through the Fcε receptor (FcεR), in microbial motility and in Syk protein stability.

Keywords: WIP; WASP; N-WASP; Arp2/3; Actin cytoskeleton; Signal transduction

Contents

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Introduction

Controlled and organized response to external cues is a survival requirement for cells. Cell interactions with the extracellular matrix (cell–matrix adhesion) and neighboring cells (cell–cell adhesion) contribute to cell fate (proliferation, survival and differentiation) and behavior (polarization, phagocytosis, motility, metastasis, chemotaxis, and cytokinesis among others, see Penninger and Crabtree, 1999). Following the realization that cell motility is a major player in human health because of its involvement in the immune response, cancer invasion and metastasis, and wound healing (Franz et al., 2002), our understanding of the molecules and mechanisms that regulate cell motility has received enormous scientific attention. Understanding how cells move entails understanding the dynamics of disassembly, relocation and reassembly of adhesion-associated cytoskeletal structures within the cell since actin reorganization mediates changes in cell shape associated with many essential cellular processes including adhesion, cell motility, migration, and chemotaxis (Ridley et al., 2003). Considerable effort has been directed to linking the cascade of signals from transmembrane receptors to downstream effectors of the actin cytoskeleton. These efforts have shown that the Rho GTPases Cdc42, Rac, and Rho are principal targets that promote distinct cytoskeletal changes leading to the formation of filopodia, lamellipodia or stress fibers, respectively (Hall, 1998; Higgs and Pollard, 1999; Ridley et al., 2003). Some of the specific downstream effectors of each Rho GTPase belong to the Wiskott–Aldrich syndrome protein (WASP) family. For instance, neural WASP (N-WASP) mediates filopodium formation induced by active Cdc42 (Miki et al., 1998a) and WAVE/Scar (WASP family verprolin-homologous protein) mediates membrane ruffling induced through active Rac (Miki et al., 1998b). WASP family members exert their effect by activating the Arp2/3 (actin-related protein) complex that contains seven polypeptides that are essential for actin nucleation and dendritic branching of actin filaments (Higgs and Pollard, 1999; Machesky and Insall, 1998; Svitkina and Borisy, 1999; Welch et al., 1997). It is less appreciated that N-WASP/WASP function can also be modulated by binding to WASP-interacting protein (WIP). WIP is the first identified member of a family of proline-rich proteins that includes CR16 and WICH (WIP- and CR16-homologous protein)/WIRE (WIP-related) (Aspenström, 2002; Kato et al., 2002; Ramesh et al., 1997; Weiler et al., 1996). All the members bind to WASP, N-WASP, and actin and participate in actin cytoskeleton regulation and actin-related cellular functions. Generation of WIP knock-out (KO) mice has contributed to defining a critical role for this protein in the formation of a variety of actin-rich structures in different cellular models. While the functions of WASP/N-WASP have been object of excellent recent reviews (Calle et al., 2004; Millard et al., 2004; Ochs and Notarangelo, 2005) there have been few reviews focusing on WIP. Here we will comment on the WIP family proteins and will summarize WIP function in different cell types.

WIP family proteins

The gene coding for WIP, located on human and murine chromosome 2, was initially described in 1997 (Ramesh et al., 1997). Four years later the WIP family grew when CR16, previously described as a neural protein (Masters et al., 1996), was shown to share a 25% sequence identity with WIP (Ho et al., 2001). In 2002, a new member of the WIP family showing 30–40% identity to WIP and CR16 was simultaneously described as WICH (Kato et al., 2002) and WIRE (Aspenström, 2002). Human WIP is composed of 503 amino acids (aa), human CR16 of 483 aa and human WICH/WIRE of 440 aa. All members of the WIP family contain a high percentage of proline residues (28% in WIP, 32% in CR16, and 27% in WICH/WIRE) which likely contribute to their aberrant electrophoretic migration, for example, WIP has a calculated molecular mass of 52 kDa but migrates as a 63–65-kDa protein.

Their alignment reveals two highly homologous regions (Kato et al., 2002) (Fig. 1): one region, near the N-terminus of the proteins, includes the actin-binding verprolin homology region (V-domain). Verprolin is a yeast actin- and myosin-interacting protein involved in cell polarity and endocytosis (Donnelly et al., 1993). WIP and verprolin are functional homologues because WIP can complement the defects in growth, cytoskeletal organization and non-receptor-mediated endocytosis observed in verprolin-deficient yeasts (Vaduva et al., 1999). The second homologous region is located near the C-terminus of these three proteins and mediates interaction with the WH1 (WASP Homology 1) domain of both WASP and N-WASP. Only WICH/WIRE has been described to bind preferentially N-WASP.

Not all functions of the WIP family of proteins are related directly to N-WASP/WASP interactions. WIP, CR16, and WICH/WIRE contain between three and six potential profiling-binding sites named ABM-2 (actin-based motility homology-2 including the sequence XPPPPP, where X is A, S, L, or G) (Fig. 1). Besides profilin, an actin-regulating protein, they bind to both G- and F-actin (Aspenström, 2004). However, their ability to affect the kinetics of actin polymerization is different. WIP, but not CR16, inhibits in vitro N-WASP induced Arp2/3 complex-mediated actin polymerization (Ho et al., 2001; Martínez-Quiles et al., 2001). WIP and WICH/WIRE also inhibit actin depolymerization rates