J Med Dent Sci 2001; 48: 1–6

Review

Wiskott-Aldrich syndrome (role of WASP)

Shigeaki Nonoyama, M.D., Ph.D.

Department of Pediatrics, School of Medicine, Tokyo Medical and Dental University, 1-5-45, Yushima, Bunkyo-ku, Tokyo, 113-8519, Japan

Wiskott-Aldrich syndrome (WAS) is an X-linked disorder characterized by thrombocytopenia, eczema and immunodeficiency. WASP, the gene responsible for WAS, has been identified by positional cloning, contains a PH domain, a GBD domain, a proline rich region, and a verprolin/ cofilin homology domain. Subsequent studies suggest that WASP is involved in signal transduction and in the regulation of the cytoskeleton.

Key words: Wiskott-Aldrich syndrome, signal transduction, cytoskeleton

Introduction

The Wiskott-Aldrich syndrome (WAS) is an X-linked recessive disorder characterized by immunodeficiency, eczema, thrombocytopenia and increased risk of autoimmune disorders and malignancies[1]. The gene responsible for WAS (WASP) has been identified by positional cloning, and various mutations of WASP have been reported in patients with WAS. X-linked thrombocytopenia (XLT), characterized by thrombocytopenia and small platelets but without the other clinical findings associated with WAS, is caused by mutations of the same gene[2,3,4].

Although the precise function of WASP is unknown, several unique binding domains have been identified. Considering the function of these domains, WASP appears to play a critical role in signal transduction by interacting with SH3 containing molecules, and in the regulation of the cytoskeletal reorganization.

In this review, we describe the structure and presumed function of WASP, and use this insight to explain the molecular basis of WAS.

Corresponding Author: Shigeaki Nonoyama, M.D., Ph.D.
Department of Pediatrics, School of Medicine, Tokyo Medical and Dental University, 1-5-45, Yushima, Bunkyo-ku, Tokyo, 113-8519, Japan.
Phone: 81-3-5803-5248
Fax: 81-3-5803-5247
e-mail: snonoyama.ped@tmd.ac.jp
Received August 31; Accepted September 25, 2001

Clinical Manifestations of WAS

Immune Defect

The severity of the immune deficiency may vary; in most cases, both the cellular and humoral immune systems are affected. Lymphopenia due to a net loss of T lymphocytes is usually present by age six to eight years[5]. Serum IgG levels are often normal, IgM levels are moderately depressed, and IgA and IgE are elevated. Low isohemagglutinin titers are persistent findings and antibody responses to polysaccharides and to many protein antigens are depressed[1,5]. Abnormal T cell function is suggested by diminished but not absent lymphocyte responses to mitogens[6], depressed proliferative responses to allogenic cells[5] and immobilized anti-CD3 monoclonal antibody[7]. The surface of peripheral blood lymphocytes from WAS patients is void of microvillous projections when compared with normal lymphocytes[8,9]. Although the number of circulating neutrophils and monocytes are normal, in vitro chemotaxis of WAS neutrophils and monocytes has been deficient[5,10].

Platelet Abnormalities

The platelet defect, thrombocytopenia and small platelet volume, is a consistent finding in patients with mutations of the *WASP* gene. Several mechanisms responsible for the platelet abnormalities were proposed, including reduced survival[11], abnormal metabo-

lism[12] and ineffective thrombocytopoiesis[13]. Characteristically, platelet counts and volume increase after splenectomy, but not in response to prednisone or high dose intravenous immunoglobulin[14].

Other Manifestations

Eczema is a characteristic finding in WAS patients but is very mild or absent in XLT patients[2]. Autoimmune disorders are frequent and the incidence of malignancies especially lymphoma is high and increases with age[1].

Identification of the WASP Gene

The *WASP* gene, which is responsible for WAS, was identified by positional cloning (gene bank accession number U12707)[15]. The gene consists of 12 exons spanning 9 Kb of genomic DNA (Fig. 1). The 1,821 basepair cDNA contains an open reading frame of 502 amino acids and generates a protein with a predicted molecular weight of 54 kDa. A mouse homologue of the *WASP* gene has been isolated[16], and a neural homologue of WASP was cloned by purifying Ash/Grb2-binding proteins from bovine brain[17]. A human and rat N-WASP has been recently identified[18]. WASP is constitutively expressed in all hematopoietic stem cell-derived lineages whereas N-WASP is present in various non-hematopoietic tissue extracts[15,17]. Bee1, a protein that is critical for the assembly of cortical actin skeleton in yeast, was found to be a homologue of WASP[19].

Structure of WASP

A number of investigators have identified functional domains within WASP including a WH1 (WASP-Homology 1) domain /PH (pleckstrin homology) domain, a GBD (GTPase binding domain)/CRIB (cdc42 or Rac-interactive binding) motif, a proline-rich region, a verprolin homology domain, and a cofilin homology domain (Fig. 1)[17,20].

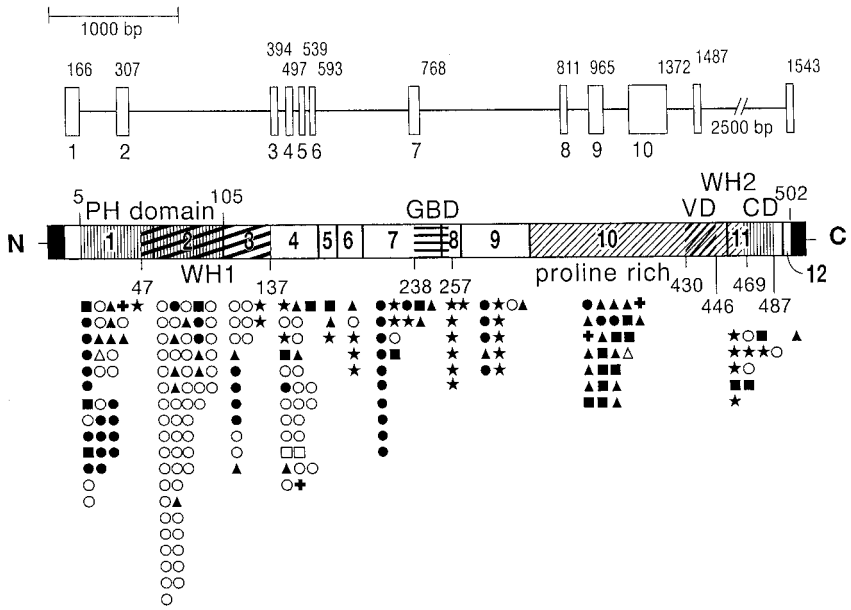
Pleckstrin homology domain/WH1 domain

Computer analysis identified pleckstrin homology (PH)-like domain within the N terminal region (a.a. 6-105) of WASP and N-WASP, and binding of PIP2 to the PH domain of N-WASP was demonstrated[17]. The WASP homology 1 (WH1) domain (a.a. 47-137), which overlaps with the PH-domain, was found by homology search[20]. Proteins containing a WH1 domain include the vasodilator-stimulated phosphoprotein (VASP), dena (Drosophila ena, enabled) and homer, which are involved in actin cytoskeleton regulation[20,21]. The WH1/PH-domain of WASP must be functionally important, since most of the missense mutations described to date are located in this domain (Fig. 1)[22]. Functionally, the PH domain is of importance for the localization of proteins through the interactions with other proteins or lipids, and may play a role in the binding of cytoplasmic proteins to membranes[23]. Ligands for PH domains reported to date include PKC, the $\beta\gamma$ subunit of G proteins, and PIP2[17]. Since the level of homology between individual PH domains is low, the recognition of PH domains based on structure is difficult[17] and will ultimately require crystallography. Because N-WASP regulates actin polymerization in a PIP2-dependent manner [17], it is possible that binding of PIP2 to the PH domain of WASP has a similar effect. An alternative function of the WH1/PH domain of WASP is that of anchoring WASP to the membrane through PIP2, as has been recently demonstrated for other molecules[24].

GTPase binding domain/CRIB motif

Several investigators have independently reported the interaction of WASP with the small GTPase, Cdc42[20,25,26]. Cdc42, Rac, and other Rho-like GTPases are key elements in the dynamic organization of the actin cytoskeleton[27]. A GTPase binding domain (GBD), also referred to as CRIB motif, located in exons 7 and 8 of the WASP gene, has been identified. WASP, like other proteins containing a CRIB motif, recognizes the GTP but not the GDP-bound form of Cdc42. A functional role of the CRIB motif by its interaction with Cdc42 is suggested by the observation that over-expression of WASP in transfected cells causes a clustering of polymerized actin that can be inhibited by simultaneous over-expression of a dominant negative mutant form of Cdc42; and by the observation that micro-injections of WASP into different cell types consistently causes a profound effect on actin polymerization[20]. However, a subsequent study demonstrated that Y40C mutant of Cdc42, which does not bind to WASP, still induces filopodium formation, suggesting that interaction of Cdc42 with WASP may not be essential for cytoskeletal organization[27]. Consistent with this observation, it was demonstrated that the Y40C mutant of Cdc42 binds to N-WASP GBD/CRIB motif but not to WASP GBD/CRIB motif[28]. N-WASP induces long actin microspikes if co-expressed with Cdc42, while WASP fails to induce filopodium formation, despite the structural similarities. In addition, the binding affinity of WASP with Cdc42 is low[29]. Thus, the precise role of the interaction between WASP and

Fig. 1. Schematic representation of the genomic organization of the *WASP* gene (top), and a schematic representation of the WAS protein representing 12 exons and the major functional domains (bottom).



PH=pleckstrin homology; GBD=GTPase binding domain (or CRIB motif); VD=verprolin domain; CD=cofilin domain;

Distribution of known mutations of the WASP gene/protein:
○ point mutation, nonsense; ● point mutation, missense; ■ insertion, frameshift; □ insertion, inframe; ▲ deletion, frameshift; △ deletion, inframe; ★ splice site mutation; + complex mutation.

Cdc42 remains unclear.

Proline-rich region

WASP is unusually rich in proline motifs derived from exon 10, and in motifs corresponding to the PXXP binding consensus for SH3 domains. Several groups have demonstrated that WASP interacts with the SH3 domains of selected signaling molecules, including cytosolic adapter proteins, Grb2 and P47^{nck}[30,31,32]; Fyn[33,34]; cFgr[33,35]; Lck[33,34]; c-Src and p47^{phox}[35]; the Tec family cytoplasmic tyrosine kinases, Btk, Tec[36]; PLCγ1[2,35,36]; and Itk[36,37]. Peptides that correspond to proline-rich regions within WASP inhibit binding between WASP and several SH3-containing proteins, e.g., Src, Fyn, PLCγ1, Btk. The most effective peptides included two PPPPXXRG-based SH3 binding motifs[37]. These data suggest that WASP, through its interaction with the SH3 domain of selected molecules, plays an important role in intracellular signaling of hematopoietic cells.

In a recent study, Wu, et al. have demonstrated that the cytoskeletal-associated protein PSTPIP binds with its SH3 domain to the proline-rich region of WASP. Phosphorylation of a tyrosine residue in the SH3 domain of PSTPIP results in decreased binding of WASP[38]. Furthermore, co-expression of PSTPIP with WASP results in a loss of WASP-induced actin bundling activity, suggesting that the interaction of PSTPIP with WASP, which is regulated by tyrosine phosphorylation, is involved in cytoskeletal organization.

Profilin, an actin-binding protein that promotes actin polymerization, was shown to bind with N-WASP[28,39]. Since WASP contains Gly(Pro)5, the putative profilin binding motif, it is likely that WASP through its proline-rich region associates similarly with profilin.

Verprolin/cofilin homology domain

The C-terminal region of WASP and N-WASP contain a verprolin homology domain (a.a.430-446) and a cofilin homology domain (a.a.469-487) [17]*. Verprolin, a yeast protein, is involved in the regulation and maintenance of actin cytoskeletal organization[40]. Cofilin, an actin binding protein, has been shown to depolymerize actin filaments[17,41].

Over-expression of wild-type WASP in COS-7 cells results in the formation of large cytoplasmic clusters of WASP and polymerized F-actin[20]. However, if COS-7 cells were transfected with a mutated WASP cDNA lacking the C-terminal 59 amino acids that include a verprolin and cofilin homology domain, clustering of WASP and F-actin did not occur[20]. The clustering of F-

actin observed in WASP over-expressing cells is dependent on actin polymerization, suggesting that the C-terminal portion of WASP is important for actin polymerizing activity. This interpretation is further supported by the observation that the cofilin homology and verprolin homology domains in N-WASP bind to actin and regulate actin polymerization[17,28,39].

WASP Interactive Protein (WIP)

Using a yeast two-hybrid system, a proline rich WASP Interactive Protein (WIP), which co-immunoprecipitated with WASP from lymphocyte extracts, was identified[42]. The WIP gene encodes a 503 amino acid proline-rich protein with a calculated molecular mass of approximately 52 kDa. The N-terminal region contains two stretches that are highly homologous to corresponding amino acid sequences in the N-terminal region of the yeast protein verprolin and contains the actin binding KLKK motif. In addition, WIP contains two APPPPP sequences which have been shown to bind to profilin known to regulate actin polymerization. WIP binds to WASP in vivo and in vitro at a site distinct from the Cdc42 binding site. Unlike WASP, which is only found in hematopoietic cell lineages, WIP is widely expressed in many cells and may interact with N-WASP which is also widely expressed in non-blood cells. Overexpression of WIP in human B cells increased polymerized actin content similar to cells overexpressing WASP, and induced the appearance of actin-containing cerebriform projections on the cell surface. It appears that WIP acts downstream of WASP and plays an important role in linking WASP to the actin cytoskeleton.

The Function of WASP

The complex clinical phenotype of classic WAS is difficult to explain by a single gene mutation. The gene product, WASP, has a number of unique domains that suggest a “multifaceted” function. Accumulating observations indicate that WASP is involved both in the cytoskeleton and the cytoplasmic signaling system of hematopoietic cell lineages.

Several signaling molecules including tyrosine kinases bind to WASP, suggesting that WASP plays a role in signal transduction pathways. A consistent finding has been the defective proliferative response of WAS-T cells if stimulated with anti-CD3 mAb[7]. It was also found that WASP co-immunoprecipitates with the activated epidermal growth factor receptor (EGFR) after EGF stimulation, and that Grb2 enhances the association of WASP with EGFR[32], suggesting that WASP may be located downstream of the EGF receptor. The finding that carrier females show non-random X inactivation in $CD34^+$ cells[43], in addition to non-random X-inactivation in T cells, B cells, neutrophil, and monocytes indicates that WASP provides a growth advantage for these cells, suggesting that WASP is involved in the growth and survival of $CD34^+$ hematopoietic stem cells.

The interaction of WASP with the small GTPase Cdc42, a key element in the dynamic organization of the actin/cytoskeleton has been interpreted that WASP plays an important role in the regulation of the actin/cytoskeletal system. It is presently unknown whether WASP interacts directly with actin or through actin-binding proteins, and if mutations of WASP result in a transmembrane signaling defect. Using WAS T cell lines immortalized by Herpesvirus Saimiri, it was demonstrated that WAS T cells failed to polymerize and reorganize actin in response to anti-CD3 stimulation[44]. The observation that actin bundling is necessary for T cell activation by anti-CD3 antibody[45] and that Cdc42 is required for the polarization of T cells toward antigen-presenting cells[46] suggests that the abnormal antibody responses characteristic for classical WAS patients are a direct consequence of defective T/B cell interaction: in the absence of functional WASP, T cells fail to provide adequate help to B cells, resulting in impaired B cell function. Recently, Miki et al. reported that megakaryocyte differentiation and microvesicle formation is dependent upon the interaction of WASP with actin filaments, a process in which WASP associates with tyrosine phosphorylated Shc, suggesting that WASP controls the assembly of actin filaments required for microvesicle and pro-platelet formation[30].

These observations suggest that WASP may play a role in linking tyrosine kinases to the actin cytoskeleton probably by associating with the active form of Cdc42.

Mutation Analysis, Genotype/Phenotype Correlation

The scoring system, described in Table 1, is based on the postulate that patients with WAS/XLT have in common thrombocytopenia and small sized platelets and that most, if not all, develop some form of immunodeficiency, although to a different degree. The extent of eczema may be difficult to assess. Lack of a history of eczema or mild, transient eczema responding well to treatment, indicated by (+) in Table 1, and mild, infrequent infections not resulting in sequalae (+) are consistent with XLT (score 1 or 2). Severe, treatment resis-

Table 1. Scoring system to define the phenotypes of WAS

	XLT		WAS CLASSIC		
SCORE	1	2	3	4	5
Thrombocytopenia	+	+	+	+	+
Small platelets	+	+	+	+	+
Eczema	-	(+)	+	++	+/++
Immunodeficiency	-/(+)	(+)	+	+	+
Infections	-	(+)	+	+/++	+/++
Autoimmunity and/or malignancy	-	-	-	-	+

-/(+) absent or mild

(+) mild, transient eczema, or mild, infrequent infections, not resulting in sequalae

++ eczema that is difficult to control and severe, life-threatening infections

tant eczema, recurrent infections in spite of optimal therapy, autoimmune diseases, and malignancies are characteristic for classic WAS and are scored as “mild” (score of 3), “moderate” (score of 4), or “severe” (score of 5).

Using these criteria, patients with missense mutations affecting exons 1, 2, and 3 (WH1/PH domain) (Fig. 1) have mild disease. Other mutations observed in patients with mild disease include splice anomalies resulting in multiple splicing products. All mutations associated with a mild phenotype have in common the expression of a normal sized or truncated protein in various quantities[34]. Thus, missense mutations that affect the WH1/PH domain (exons 1-3) and leave intact the 3' regions containing the Cdc42 binding site, the SH3 binding motifs, and the WH2 domain, are associated with a mild phenotype (XLT). Most other mutations result in a classic WAS phenotype[34].

Conclusions

The clinical phenotype of WAS is complex and varies from mild to severe. Although all hematopoietic cell lineages express WASP and are affected by mutations of the WASP gene, the most prominent symptoms are related to defective lymphocyte, especially T cell, function, and thrombocytopenia. WASP has unique domains that support a number of crucial cell functions including signal transduction and interaction with the cytoskeleton. Mutations affecting certain domains of the WASP gene may result in two characteristic clinical phenotypes, classic WAS and XLT. Future research will focus on the better understanding of the function of WASP and the identification and functional analysis of the multiple “scaffolding” molecules known to interact with WASP. Transgenic and WASP knockout mice may provide experimental tools to better understand the in vivo function of WASP.

References

1. Sullivan KE, Mullen CA, Blaese RM, Winkelstein JA: A multi-institutional survey of the Wiskott-Aldrich syndrome. J Pediatr 1994, 125:876-885.
2. Zhu Q, Zhang M, Blaese RM, Derry JMJ, Junker A, Francke U, Chen SH, Ochs HD: The Wiskott-Aldrich syndrome and X-linked congenital thrombocytopenia are caused by mutations of the same gene. Blood 1995, 86:3797-3804.
3. Villa A, Notarangelo L, Macchi P, Mantuano E, Cavagni G, Brugnoni D, Strina D, Patrosso MC, Ramenghi U, Sacco MG, Ugazio A, Vezzoni P: X-linked thrombocytopenia and Wiskott-Aldrich syndrome are allelic diseases with mutations in the WASP gene. Nat Genet 1995, 9:414-417.
4. Kolluri R, Shehabeldin A, Peacocke M, Lamhonwah AM, Teichert-Kuliszewska K, Weissman SM, Siminovitch KA: Identification of WASP mutations in patients with Wiskott-Aldrich syndrome and isolated thrombocytopenia reveals allelic heterogeneity at the WAS locus. Hum Mol Genet 1995, 4:1119-1126.
5. Ochs HD, Slichter SJ, Harker LA, Von Behrens WE, Clark RA, Wedgwood RJ: The Wiskott-Aldrich syndrome: Studies of lymphocytes, granulocytes, and platelets. Blood 1980, 55:243-252.
6. Cooper MD, Chase HP, Lowman JT, Krivit W, Good RA: Wiskott-Aldrich syndrome. An immunologic deficiency disease involving the afferent limb of immunity. Am J Med 1968, 44:499-513.
7. Molina IJ, Sancho J, Terhorst C, Rosen FS, Remold-O’Donnell E: T cells of patients with the Wiskott-Aldrich syndrome have a restricted defect in proliferative responses. J Immunol 1993, 151:4383-4390.
8. Kenney DM, Cairns L, Remold-O’Donnell E, Peterson J, Rosen FS, Parkman R: Morphological abnormalities in the lymphocytes of patients with the Wiskott-Aldrich syndrome. Blood 1986, 68:1329-1332.
9. Molina IJ, Kenney DM, Rosen FS, Remold-O’Donnell E: T cell lines characterize events in the pathogenesis of the Wiskott-Aldrich syndrome. J Exp Med 1992, 176:867-874.
10. Altman A, Cohen IR: The nonspecific helper effect of mixed lymphocyte reactions on the induction of T cell-mediated immunity in vitro. Eur J Immunol 1974, 4:577-580.
11. Gröttum KA, Hovig T, Holmsen H, Abrahamsen AF, Jeremic M, Seip M: Wiskott-Aldrich syndrome: Qualitative platelet defects and short platelet survival. Br J Haematol 1969, 17:373-388.

12. Kuramoto A, Steiner M, Baldini MG: Lack of platelet response to stimulation in the Wiskott-Aldrich syndrome. N Engl J Med 1970, 282:475-479.
13. Slichter SJ, Harker LA: Thrombocytopenia: Mechanisms and management of defects in platelet production. Clin Haematol 1978, 7:523-539.
14. Litzman J, Jones A, Hann I, Chapel H, Strobel S, Morgan G: Intravenous immunoglobulin, splenectomy, and antibiotic prophylaxis in Wiskott-Aldrich syndrome. Arch Dis Child 1996, 75:436-439.
15. Derry JMJ, Ochs HD, Francke U: Isolation of a novel gene mutated in Wiskott-Aldrich syndrome. Published erratum appears in Cell 1994, 79(5):following 922. Cell 1994, 78:635-644.
16. Derry JMJ, Wiedemann P, Blair P, Wang Y, Kerns JA, Lemahieu V, Godfrey VL, Wilkinson JE, Francke U: The mouse homolog of the Wiskott-Aldrich syndrome protein (WASP) gene is highly conserved and maps near the scurfy (sf) mutation on the X chromosome. Genomics 1995, 29:471-477.
17. Miki H, Miura K, Takenawa T: N-WASP, a novel actin-depolymerizing protein, regulates the cortical cytoskeletal rearrangement in a PIP2-dependent manner downstream of tyrosine kinases. EMBO J 1996, 15:5326-5335.
18. Fukuoka M, Miki H, Takenawa T: Identification of N-WASP homologs in human and rat brain. Gene 1997, 196:43-48.
19. Li R: Bee1, a yeast protein with homology to Wiskott-Aldrich syndrome protein, is critical for the assembly of cortical actin cytoskeleton. J Cell Biol 1997, 136:649-658.
20. Symons M, Derry JMJ, Karlak B, Jiang S, Lemahieu V, McCormick F, Francke U, Abo A: Wiskott-Aldrich syndrome protein, a novel effector for the GTPase CDC42Hs, is implicated in actin polymerization. Cell 1996, 84:723-734.
21. Ponting CP, Phillips C: Identification of homer as a homologue of the Wiskott-Aldrich syndrome protein suggests a receptor-binding function for WH1 domains. J Mol Med 1997, 75:769-771.
22. Schwarz K, Nonoyama S, Peitsch MC, de Saint Basile G, Espanol T, Fasth A, Fischer A, Freitag K, Friedrich W, Fugmann S, Hossle H-P, Jones A, Kinnon C, Meindl A, Notarangelo LD, Wechsler A, Weiss M, Ochs HD: WASPbase: A database of WAS- and XLT-causing mutations. Immunol Today 1996, 17:496-502.
23. Rameh LE, Arvidsson AK, Carraway III KL, Couvillon AD, Rathbun G, Crompton A, VanRenterghem B, Czech MP, Ravichandran KS, Burakoff SJ, Wang DS, Chen CS, Cantley LC: A comparative analysis of the phosphoinositide binding specificity of pleckstrin homology domains. J Biol Chem 1997, 272:22059-22066.
24. Lemmon MA, Ferguson KM, Schlessinger J: PH domains: Diverse sequences with a common fold recruit signaling molecules to the cell surface. Cell 1996, 85:621-624.
25. Aspenstrom P, Lindberg U, Hall A: Two GTPases, cdc42 and rac, bind directly to a protein implicated in the immunodeficiency disorder Wiskott-Aldrich Syndrome. Curr Biol 1996, 6:70-75.
26. Kolluri R, Tolias KF, Carpenter CL, Rosen FS, Kirchhausen T: Direct interaction of the Wiskott-Aldrich syndrome protein with the GTPase Cdc42. Proc Natl Acad Sci USA 1996, 93:5615-5618.
27. Lamarche N, Tapon N, Stowers L, Burbelo PD, Aspenstrom P, Bridges T, Chant J, Hall A: Rac and cdc42 induce actin polymerization and G1 cell cycle progression independently of p65PAK and the JNK/SAPK MAP kinase cascade. Cell 1996, 87:519-529.
28. Miki H, Sasaki T, Takai Y, Takenawa T: Induction of filopodium formation by a WASP-related actin-depolymerizing protein N-WASP. Nature 1998, 391:93-96.
29. Zhang B, Wang ZX, Zheng Y: Characterization of the interactions between the small GTPase Cdc42 and its GTPase-activating proteins and putative effectors. Comparison of kinetic properties of Cdc42 binding to the Cdc42-interactive domains. J Biol Chem 1997, 272:21999-22007.
30. Miki H, Nonoyama S, Zhu Q, Aruffo A, Ochs HD, Takenawa T: Tyrosine kinase signaling regulates Wiskott-Aldrich syndrome protein function, which is essential for megakaryocyte differentiation. Cell Growth Differ 1997, 8:195-202.
31. Rivero-Lezcano OM, Marcilla A, Sameshima JH, Robbins KC: Wiskott-Aldrich syndrome protein physically associates with Nck through Src homology 3 domains. Mol Cell Biol 1995, 15:5725-5731.
32. She H-Y, Rockow S, Tang J, Nishimura R, Skolink EY, Chen M, Margolis B, Li W: Wiskott-Aldrich syndrome protein is associated with the adapter protein Grb2 and the epidermal growth factor receptor in living cells. Molec Biol Cell 1997, 8:1709-1721.
33. Banin S, Truong O, Katz DR, Waterfield MD, Brickell PM, Gout I: Wiskott-Aldrich syndrome protein (WASp) is a binding partner for c-Src family protein-tyrosine kinases. Curr Biol 1996, 6:981-988.
34. Zhu Q, Watanabe C, Liu T, Hollenbaugh D, Blaese RM, Kanner SB, Aruffo A, Ochs HD: Wiskott-Aldrich Syndrome/X-Linked Thrombocytopenia: WASP Mutations, Protein Expression, and Phenotype. Blood 1997, 90:2680-2689.
35. Finan PM, Soames CJ, Wilson L, Nelson DL, Stewart DM, Truong O, Hsuan JJ, Kellie S: Identification of regions of the Wiskott-Aldrich syndrome protein responsible for association with selected Src homology 3 domains. J Biol Chem 1996, 271:26291-26295.
36. Cory GOC, MacCarthy-Morrogh L, Banin S, Gout I, Brickell PM, Levinsky RJ, Kinnon C, Lovering RC: Evidence that the Wiskott-Aldrich syndrome protein may be involved in lymphoid cell signaling pathways. J Immunol 1996, 157:3791-3795.
37. Bunnell SC, Henry PA, Kolluri R, Kirchhausen T, Rickles RJ, Berg LJ: Identification of Itk/Tsk Src homology 3 domain ligands. J Biol Chem 1996, 271:25646-25656.
38. Wu Y, Spencer SD, Lasky LA: Tyrosine phosphorylation regulates the SH3-mediated binding of the Wiskott-Aldrich syndrome protein to PSTPIP, a cytoskeletal-associated protein. J Biol Chem 1998, 273:5765-5770.
39. Miki H, Takenawa T: Direct binding of the verprolin-homology domain in N-WASP to actin is essential for cytoskeletal reorganization. Biochem Biophys Res Commun 1998 243:73-78.
40. Donnelly SF, Pocklington MJ, Pallotta D, Orr E: A proline-rich protein, verprolin, involved in cytoskeletal organization and cellular growth in the yeast Saccharomyces cerevisiae. Mol Microbiol 1993, 10:585-596.
41. Nishida E, Maekawa S, Sakai H: Cofilin, a protein in porcine brain that binds to actin filaments and inhibits their interactions with myosin and tropomyosin. Biochemistry 1984, 23:5307-5313.
42. Ramesh N, Anton IM, Hartwig JH, Geha RS: WIP, a protein associated with Wiskott-Aldrich syndrome protein, induces actin polymerization and redistribution in lymphoid cells. Proc Natl Acad Sci USA 1997, 94:14671-14676.
43. Wengler G, Gorlin JB, Williamson JM, Rosen FS, Bing DH: Nonrandom inactivation of the X chromosome in early lineage hematopoietic cells in carriers of Wiskott-Aldrich syndrome. Blood 1995, 85:2471-2477.
44. Gallego MD, Santamaria M, Pena J, Molina IJ: Defective actin reorganization and polymerization of Wiskott-Aldrich T cells in response to CD3-mediated stimulation. Blood 1997, 90:3089-3097.
45. Parsey MV, Lewis GK: Actin polymerization and pseudopod reorganization accompany anti-CD3-induced growth arrest in Jurkat T cells. J Immunol 1993, 151:1881-1893.
46. Stowers L, Yelon D, Berg LJ, Chant J: Regulation of the polarization of T cells toward antigen-presenting cells by Ras-related GTPase CDC42. Proc Natl Acad Sci USA 1995, 92:5027-5031.