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Wiskott-Aldrich syndrome protein: emerging mechanisms in immunity

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Summary
The Wiskott Aldrich syndrome protein (WASP) participates in innate and adaptive immunity through regulation of actin cytoskeleton-dependent cellular processes, including immune synapse formation, cell signaling, migration and cytokine release. There is also emerging evidence for a direct role in nuclear transcription programmes uncoupled from actin polymerization. A deeper understanding of some of the more complex features of Wiskott Aldrich syndrome (WAS) itself, such as the associated autoimmunity and inflammation, has come from identification of defects in the number and function of anti-inflammatory myeloid cells and regulatory T and B cells, as well as defects in positive and negative B-cell selection. In this review we outline the cellular defects that have been characterized in both human WAS patients and murine models of the disease. We will emphasize in particular recent discoveries that provide a mechanistic insight into disease pathology, including lymphoid and myeloid cell homeostasis, immune synapse assembly and immune cell signaling.

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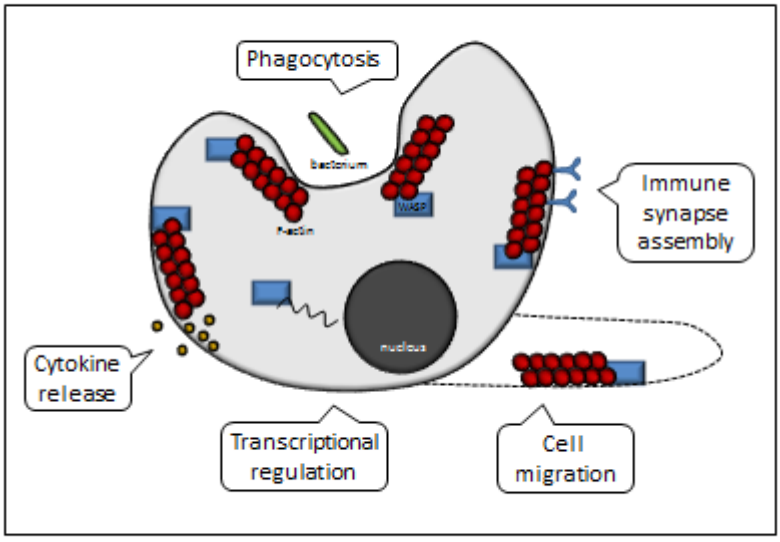
Graphical abstract text

WASP is an important regulator of the actin cytoskeleton with roles in immune cell functions such as cell migration, immune synapse assembly, phagocytosis and cytokine release. Cytoskeleton-independent roles in nuclear transcription are also described. Review of WASP research in human and murine models provides valuable insight into WAS disease pathology.

F-actin, filamentous actin; WAS, Wiskott Aldrich syndrome; WASP, Wiskott Aldrich syndrome protein



Introduction

Wiskott Aldrich syndrome protein (WASP) is ubiquitously expressed in non-erythroid haematopoietic cells. Since identification of the WAS gene more than 20 years ago (1), there have been approximately 300 different mutations described, leading to a remarkably varied clinical phenotype including immunodeficiency, inflammatory symptoms, bleeding diathesis, autoimmunity and malignant potential. The clinical aspects of WAS and emerging treatments have been reviewed in detail recently (2) and will not be discussed here.

WASP is a cytosolic protein comprising 502 amino acids. It consists of an Ena-VASP homology domain (EVH1, also known as WH1) at the amino terminal, a short basic domain (B), a guanosine triphosphatase-binding domain (GBD), a large polyproline (PP) domain and verprolin homology/ central/ acidic (VCA) domain at the carboxyl terminal (Figure 1). WASP is established as a key regulator of the actin cytoskeleton in haematopoietic cells, with important functional roles in lymphoid and myeloid cell migration, receptor signaling, cytotoxicity, and phagocytosis. More recently, cytoskeleton-independent functions of WASP have been identified at the level of nuclear transcription (Table 1). At rest, WASP exists in an autoinhibited state, in which the VCA domain associates with a hydrophobic pocket in the GBD domain (3) (Figure 1, top). Binding of WASP with partners, such as the Rho family GTPase cell division cycle 42 (CDC42), and/or phosphorylation of a tyrosine residue (Y291 in human WASP) within the GBD hydrophobic region destabilizes the autoinhibited conformation (Figure 1, bottom). This exposes the VCA region, thereby allowing actin related protein (ARP) 2/3 binding (4-6). Subsequent localization and nucleation of actin filaments results in the formation of actin branches (7). Several other proteins, particularly the SRC homology 3 (SH3) domain adaptor NCK, and a number of defined tyrosine kinases, also promote the activation of WASP through interaction with the basic or polyproline domains (8-11). Phosphorylation of two serine residues in the VCA domain further regulate WASP activation through enhanced affinity to the ARP 2/3 complex (3, 5, 12, 13). Evidence also exists for regulation of WASP activity through oligomerization, where active WASP proteins form complexes through VCA dimers or higher order oligomers, with much greater potency for ARP 2/3 stimulation (14, 15). In addition to activation, phosphorylation of Y291 in the GBD domain is thought to mark WASP for degradation by calpain and proteasome proteolysis (6, 16-18). WASP-interacting protein (WIP) stabilizes WASP by binding to the EVH1 domain, and protecting it from calpain and proteasomal degradation (16, 19) (Figure 1, top), but also is important for localizing WASP to areas of actin polymerization (16, 20).

The role of WASP in lymphoid lineages

WASP in T cells

WASP has been implicated in a number of intrinsic T-cell functions including cell proliferation, differentiation and survival, through both actin-dependent and -independent mechanisms (Table 1). In lymphoid lineages the development of early progenitors proceeds normally in both humans and mice bearing a WASP deficiency, but WASP is required for the survival and homeostasis of terminally differentiated cells (21-23). Abnormal thymopoiesis in the absence of WASP has been suggested by evaluation of lymphocyte counts in WAS patients (24, 25), and by the observation of thymic

hypoplasia at post mortem (26). Evidence for a role of WASP in thymopoiesis has also been identified in murine models, in which subtle abnormalities such as a possible block in progression from double negative ($CD4^-$ $CD8^-$) to double positive ($CD4^+$ $CD8^+$) T cells (22, 23) have been shown. The numbers of circulating naïve $CD4^+$ T cells in human WAS are usually within the normal range, but the proportion of $CD8^+$ T cells is usually low (2), often accompanied by an abundance of γδ T cells (27). Age-dependent clonal skewing of T-cell receptor (TCR) β-chain repertoires has been found in human peripheral blood of WAS patients (28). Interestingly, WASP has been found to be present in the T-cell nucleus and may play an important actin-independent role in regulating histone methylation at the TBX21 promoter (29) and in transcription of cytokines required for T_H1 differentiation (30, 31). The absence of WASP in human T helper (T_H) cells is associated with detrimental effects on cytokine gene transcription required for T_H1 differentiation resulting in skewing towards T_H2 dominance (Figure 2a). Additionally, WASP may play a role in lymphocyte survival. Activated T cells can undergo apoptosis in response to TCR stimulation in order to eliminate T cells responding to chronically expressed antigens, including autoantigens, through interactions with the tumour necrosis factor (TNF) family member Fas ligand (FasL). Murine wasp deficiency is associated with impaired TCR-induced FasL secretion in $CD4^+$ T cells and reduced apoptosis with increased autoantibody production (32), which may go some way to explain the predisposition to autoimmunity. In contrast, attenuated B-cell lymphoma 2 (BCL2) and abnormal CD95 expression in human WAS have been associated with increased lymphocyte apoptosis (33, 34). It is unclear whether this process is a result of dysregulated transcription or secondary to intracellular cytoskeletal events, but may reflect a compensatory mechanism in response to increased autoantigen expressing T cells.

The immunological synapse (IS) is a highly dynamic interface between communicating immune cells. It is organized so that optimal antigen recognition and signal transduction may occur and relies on remodeling of the actin cytoskeleton to distribute proteins accordingly (35). In wild-type cells, TCR ligation leads to IS assembly by clustering of receptor and signaling molecules into lipid rafts. Subsequent IS maturation results in a central concentration of TCRs and costimulatory molecules surrounded by a peripheral ring of adhesion molecules including lymphocyte function-associated antigen (LFA)-1 (36). WASP is rapidly recruited to the TCR upon ligation and is required for efficient endocytic TCR internalization, which is impaired in WASP-deficient human and murine T cells (37-39). WASP is recruited to the IS by WIP and is activated by CDC42 (40), but also through CD2 stimulation (41). Murine and human WASP-deficient T cells have impaired actin polymerization at the T cell-antigen-presenting cell (APC) contact site, resulting in inefficient recruitment of other IS proteins in response to TCR stimulation (40-42), and lower numbers of lipid rafts that fail to cluster (42). Disrupted formation of actin foci is found in murine wasp-deficient T cells upon T cell activation, with subsequent impaired calcium signaling, and may be critically important for focused signal integration and amplification of downstream signals (35, 43, 44). Murine wasp-deficient T cells also demonstrate failure to polarize cytokines (45, 46), and exhibit abrogated chemokine-induced migration in transwell migration assays, with impaired homing to Peyer's patches following adoptive T cell transfer (45-48).

The number and development of regulatory T (Treg) cells in WASP deficiency have been shown to be normal (49-51), but the peripheral homeostasis and function of these cells are disturbed (32, 49),

and may therefore contribute to the predisposition of WAS patients to autoimmunity. A role for WASP in granzyme B-mediated B cell killing has been identified, with murine wasp-deficient Treg cells showing defective B-cell suppression (52). Murine wasp-deficient Treg cells lack tissue-homing markers, including integrin α4β7 and chemokine receptors CCR4 and P and E selectin ligands, which may explain why they are almost entirely absent in inflamed peripheral tissues and found in decreased numbers in secondary lymphoid tissues (53). Both human and murine WASP-deficient Treg cells exhibit impaired ability to suppress the proliferation of activated T effector cells (49-51), with relatively unrestrained T_H2 effector responses driving inflammation in a mouse model of intestinal allergy (54) (Figure 2a). WASP-deficient Treg cells also secrete less of the anti-inflammatory cytokine IL-10 (53), which may further predispose to pathological inflammation.

WASP in B cells

WASP plays a critical B-cell-specific role in immune homeostasis involved in development of the splenic marginal zone, regulation of lymph node germinal center interactions and prevention of autoimmunity by negative selection of autoreactive B-cell progenitors (55-57). Murine wasp-deficient B cells demonstrate hyperproliferation associated with autoantibody production and enhanced differentiation into class switched plasmoblasts (55). WAS patients, however, have normal or slightly reduced absolute numbers of circulating B cells, and normal numbers of class switched memory B cells (56). In both humans and mice, transitional B cells exhibit enhanced proliferation in response to stimulation by antigen or myeloid differentiation primary response protein 88 (MYD88) (56, 58, 59), which, in addition to relaxed peripheral tolerance (59-61), results in the enrichment of autoreactive cells at the naïve B-cell stage .

Memory B-cell activation is disrupted in murine wasp deficiency by reduced transcription of the B-cell receptor (BCR) co-receptor CD19, and enhanced recruitment of the BCR's negative regulators FcγIIB and SH2 inositol 5-phosphatase (SHIP) (62-65). Impaired BCR and integrin signaling in human and murine WASP-deficient B cells also results in poorly formed immunological synapses, which may further impair B-cell activation, chemotaxis and subsequent signaling in memory B cells, but is not known to compromise class-switching (66). Murine wasp-deficient immature B cells, however, appear to have enhanced BCR responsiveness, which promotes egress from the splenic marginal zone (57, 65) and may provide an explanation for the suboptimal T-independent antibody responses observed in WAS patients (55, 66). Altered antibody production in WAS likely results from intrinsic B-cell dysfunction, but also through defective activity of follicular T (Tfh) cells, which proliferate poorly, and exhibit defective differentiation with increased apoptosis (67).

Recent studies have suggested that WASP is required for acquisition of normal regulatory B (Breg) cell number and function, which may have an important influence on the balance and recruitment of Treg cells and T_H17 cells during inflammation (68, 69) (Figure 2a). In particular, arthritic WAS knockout (KO) mice were shown to have reduced numbers of IL-10-producing Breg cells in association with reduced Treg cells$_s$ and increased T_H17 cells (68). Interestingly, adoptive transfer of wild-type Breg cells ameliorated arthritis and restored the balance between Treg cells and T_H17 cells, but selective deficiency of wasp in Breg cells did not lead to exacerbated arthritis or increase in T_H17 cells despite reduced numbers of Breg and Treg cells. This suggests an element of compensation by other regulatory cell lineages.

WASP in NK and iNKT cells

WASP has previously been demonstrated to be one of a few cytoskeletal proteins responsible for the regulation of NK-cell killing (70). Enriched human WASP-deficient NK cells demonstrate impaired actin polymerization and perforin accumulation at the NK-target contact point (71), resulting in significantly reduced NK-cell cytolytic activity. Expansion of NK-cell populations is often found in WAS patients (71), which may be compensatory for these functional defects.

WASP has also been implicated in the homeostasis and function of invariant NKT (iNKT) cells, which have roles in microorganism clearance, tumour surveillance and autoimmunity (72-75). Circulating iNKT cells are almost absent in WAS, but interestingly are normal in patients with X-linked thrombocytopaenia (XLT), the milder form of disease where some residual WASP expression and function is retained (73). This suggests that defective iNKT activity may contribute to disease pathology, but the degree to which this is important has not been defined. Murine studies have suggested that wasp is more important for peripheral homeostasis rather than thymic production, though iNKT-cell maturation in the wasp-deficient murine thymus shows retarded progression to mature phenotypes (72). Murine wasp-deficient iNKT cells respond poorly to glycopeptide antigens, with defective activation, homing and retention within peripheral lymphoid tissues (72, 73), but the role of WASP in humans has not been properly explored.

The role of WASP in myeloid lineages

WASP has been shown to have an important role in myeloid cell migration and phagocytosis, with profound abnormalities in actin distribution leading to impaired cell polarization and migration, protrusion activity and phagocytic cup formation in human and murine WASP-deficient monocytes, macrophages, dendritic cells (including Langerhans cells (LC)) and neutrophils (76-81). WASP has also recently been shown to have a role in the transcriptional and epigenetic regulation of myeloid cells (82).

Cell migration requires adhesive interactions with substrata. The β-2 family of integrins is important in this process by linking the extracellular matrix to the actin cytoskeleton, necessary for transducing mechanical force and pulling on neighboring cells. Podosomes are specialized, highly dynamic structures found in many cells including macrophages and DCs. They contain an actin core surrounded by a ring of integrins, scaffold and actin-binding proteins, and are thought to be important for adhesion-dependent migration through digestion of the extracellular matrix (83). There are many similarities between adhesive podosomes observed in myeloid cells and actin foci formed at the IS suggesting that this fundamental structure can be adapted for multiple tasks. In migrating human and murine polymorphonuclear (PMN) cells the absence of WASP leads to failure of integrin clustering at the leading edge (84). Podosomes are completely absent in WASP-deficient human and murine myeloid cells, but are restored when a wild-type copy of the WAS gene is reintroduced, causally linking WASP with their formation (85). Human and murine WASP deficiency results in impaired adhesion to endothelial adhesion molecule intercellular adhesion molecule 1

(ICAM-1), leading to defective migration, poor IS stabilization and degranulation, and abrogated activation of respiratory burst (83, 84, 86).

DC cytoskeletal remodeling by WASP is emerging as a key regulatory component of functional immune synapse formation, and consequently is important for directing T-cell responses (35, 87, 88). Human and murine models have demonstrated that priming of wild-type T cells by WAS KO DCs is diminished (87, 89-91). WASP-deficient DCs appear less able to support IL-12 and type 1 interferon secretion (92, 93) with abrogation of downstream events following TCR signaling. Such events include calcium flux, microtubule organizing center polarization, phosphorylation of zeta chain associated tyrosine kinase (ZAP)-70 and T-cell proliferation (87, 90). WASP is also necessary for cytoskeletal remodeling during formation of the DC-NK cell immunostimulatory synapse and subsequent DC induction of NK-cell interferon gamma production (94).

One hypothesis for skin pathology in WAS is that decreased migration of LCs and DCs results in local potentiation of inflammatory T cells (95) (Figure 2b). A recent study in mice subjected to skin challenge with allergens and parasitic infiltration revealed that in the absence of wasp, and thus impaired cdc42-mediated effector function, ras-related C3 botulinium toxin substrate 2 (rac2) activation was enhanced in DCs (96). This led to enhanced cross-presentation of antigen through NADPH-oxidase mediated maintenance of neutral phagosome pH, and marked expansion of IFNγ producing $CD8^+$ T cells at the expense of $CD4^+$ T cells.

WASP has recently been implicated in the anti-inflammatory functions of macrophages (Figure 2c), with an increased percentage of pro-inflammatory macrophages found in pre-colitic wasp-deficient mice (97). Lipopolysaccharide (LPS) stimulation induced a much higher expression of pro-inflammatory cytokines in addition to enhanced $CD4^+$ T-cell proliferation and decreased generation of Treg cells compared to wild-type mice.

WASP is important for neutrophil development. X-linked congenital neutropenia, resulting from gain of function mutations in the WASP GBD domain, results from destabilization of the autoinhibitory conformation and dysregulated actin polymerization (76). Consequently, cytoplasmic viscosity of neutrophil precursors is increased, which impairs chromosomal separation during mitosis leading to premature apoptosis and relative failure of neutrophil differentiation (98). WASP also plays a key role in neutrophil migration, with murine wasp-deficient PMNs migrating more slowly than wild-type through cell monolayers in parallel plate flow assays (84). Although WASP-deficient PMNs adhered similarly to wild-type at low levels of shear stress in bead binding assays, attachments were lost when shear stress was increased to physiological levels (84), highlighting the additional importance of WASP in neutrophil adhesion.

A possible role of WASP in IgE-mediated mast cell cytoskeletal rearrangement has previously been identified. WASP-deficient mast cells exhibited defects in granule exocytosis and cytokine production, with decreased capacity to degranulate on FcεR1 triggering (99).

Activities of WASP family members and binding partners

WASP family proteins have recently been shown to have a number of important roles, particularly in autophagy, where the role of WASP itself is not yet known. WASH (WASP and SCAR homologue) has been implicated in downregulating autophagy by preventing ubiquitination of beclin 1 in murine embryonic fibroblasts (100). WASH deficiency in *Dictyostelium* species and HeLa cells has more recently been linked with impaired autophagosome formation and lysosomal digestion of both phagocytic and autophagic cargo (101, 102). WASH has additionally been shown to have an important role in ARP2/3-dependent endosomal sorting (101, 103). Similarly, WAVE (WASP verprolin homologous proteins) and WHAMM (WASP homologue associated protein with actin membranes and microtubules) have now also been demonstrated to be important in endo/ exocytosis and autophagosome formation (104) (105).

Defects in the WASP binding partners WIP (106), ARPC1B, a haematopoietic-restricted component of the ARP2/3 complex (107), and dedicator of cytokinesis 8 (DOCK8) (108-110) have recently been described to result in similar clinical phenotypes to WAS. The increased severity of DOCK8 deficiency may reflect an additional interaction with the WASP family protein neural WASP (N-WASP), which is more widely expressed (111). DOCK8 forms a complex with WIP and WASP linking the TCR to the actin cytoskeleton, with actin polymerization occurring via DOCK8-mediated CDC42 activation of WASP following TCR ligation (112). Combined DOCK8 and WASP deficiencies in mice show attenuated subcortical actin, with reduced filamentous (F) actin content, defective TCR-driven actin foci formation and mechanotransduction, resulting in impaired T-cell transendothelial migration and homing to lymph nodes (112). The cytoskeletal adaptor and fes/ CIP4 homology-bin/ amphiphysin/ rvs (F-BAR) protein proline-serine-threonine phosphatase-interacting protein 1 (PSTPIP1) negatively regulates the transition from podosomes to filopodia in macrophages, through its interaction with WASP. Mutations in PSTPIP1 are causally associated with a number of autoinflammatory diseases, including PAPA syndrome (pyogenic sterile arthritis, pyoderma gangrenosum and acne), which shares some similar inflammatory pathologies to those of WAS. This further highlights the importance of actin cytoskeleton regulation in autoinflammation (113).

Bruton's tyrosine kinase (BTK) has been shown to modulate inflammatory responses in macrophages through its interaction with WASP downstream of toll-like receptors (TLRs) (114, 115). Inhibition of the WASP-BTK interaction in macrophages was shown to result in impaired phosphorylation of inhibitor of κB αβ (IKKαβ) and nuclear factor (NF)-kB with reduced transcription of the inflammatory cytokines TNF-α, IL-6, IL-1β (114, 115). How this plays into the wider picture of inflammation in WAS is not yet known. More recently, an interaction between WASP and BTK has also been demonstrated to be important for neutrophil migration in sterile inflammation (116) (Figure 2b).

Additionally, neutrophil recruitment to sites of inflammation has been found to be dependent on WASP through its binding to SRC kinase-associated phosphoprotein 2 (SKAP 2), which appears to be necessary for regulating actin polymerization and β2 integrin activation (117). Deletion of skap2 in mice results in failure of integrin activation and a leukocyte adhesion deficiency (LAD)-like phenotype.

Conclusion

Over the years, defects in WASP have been identified in many different lineages, but the challenge now is to work out how they operate together to create the complex identity of WAS. Interplay between defects of peripheral and central tolerance, and effector/ regulatory cells that mediate balanced cytokine responses during inflammation is likely to be particularly important. Pursuit of understanding WAS has provided a unique opportunity to explore the role of the cytoskeleton during normal immune function from cellular homeostasis to evasion of infection, cancer and autoimmunity. Future studies may well lead to the emergence of targeted therapies for autoimmunity and inflammation extending beyond the realm of rare monogenic diseases such as WAS.

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Conflict of interest

The authors declare no financial or commercial conflict of interest.

Table 1: Actin cytoskeleton dependent and independent immune functions of WASP.
Early research identified WASP as an important regulator of the actin cytoskeleton. More recently, important cytoskeleton independent functions in nuclear transcription have been identified.

NK, natural killer cell; WASP, Wiskott Aldrich syndrome protein.

Figure legends

Figure 1. Domain structure of WASP in its inactive and active forms.
At rest, WASP exists in an autoinhibited state where the VCA region associates with the GBD region, the conformation of which is stabilised by WIP. WASP becomes activated through binding partners such as the GTPase CDC42 or phosphorylation of a tyrosine residue (Y291), which release the VCA domain and expose the ARP 2/3 binding domain. The ARP 2/3 complex recruits actin monomers resulting in the formation of branched actin filaments.

ARP 2/3, actin-related protein; B, basic domain; CDC42, cell division cycle 42; EVH1, Ena-VASP homology domain; GBD, guanosine triphosphate binding domain; P, phosphate; PP, polyproline domain; VCA, verprolin homology/ central/ acidic domain; WASP, Wiskott Aldrich syndrome protein; WIP, WASP interacting protein.

Figure 2: WASP deficiency and inflammation.
Inflammatory symptoms are common in WAS and the role of WASP in inflammation is being increasingly defined. a) $CD4^+$ T cells show impaired gene transcription required for T_H1 differentiation, leading to T_H2 dominance. Treg cells produce less of the anti-inflammatory cytokine IL-10 and fail to regulate T_H2 effector responses, which has been associated with allergic intestinal inflammation. Reduced numbers of IL-10 producing Breg cells are associated with reduced Treg cell recruitment and increased pro-inflammatory T_H17 cells. b) Enhanced cross presentation leads to over activation of $CD8^+$ T cells and is associated with skin inflammation, which is contributed to by allergen-laden Langerhans cells that fail to migrate from the skin to lymph nodes. Neutrophil migration to sites of sterile inflammation is also impaired, particularly through WASP-BTK interaction. c) Increased numbers of pro-inflammatory macrophages are found, with increased production of pro-inflammatory cytokines.

Breg cell, regulatory B cell; BTK, Bruton's Tyrosine Kinase; DC, dendritic cell; LN, lymph node; T_H1/ 2/ 17, T helper cells; Treg cell, regulatory T cell; WAS, Wiskott Aldrich syndrome; WASP, Wiskott Aldrich syndrome protein.

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Figure 1. Domain structure of WASP in its inactive and active forms.

At rest, WASP exists in an autoinhibited state where the VCA region associates with the GBD region, the conformation of which is stabilised by WIP. WASP becomes activated through binding partners such as the GTPase CDC42 or phosphorylation of a tyrosine residue (Y291), which release the VCA domain and expose the ARP 2/3 binding domain. The ARP 2/3 complex recruits actin monomers resulting in the formation of branched actin filaments.

ARP 2/3, actin-related protein; B, basic domain; CDC42, cell division cycle 42; EVH1, Ena-VASP homology domain; GBD, guanosine triphosphate binding domain; P, phosphate; PP, polyproline domain; VCA, verprolin homology/ central/ acidic domain; WASP, Wiskott Aldrich syndrome protein; WIP, WASP interacting protein.

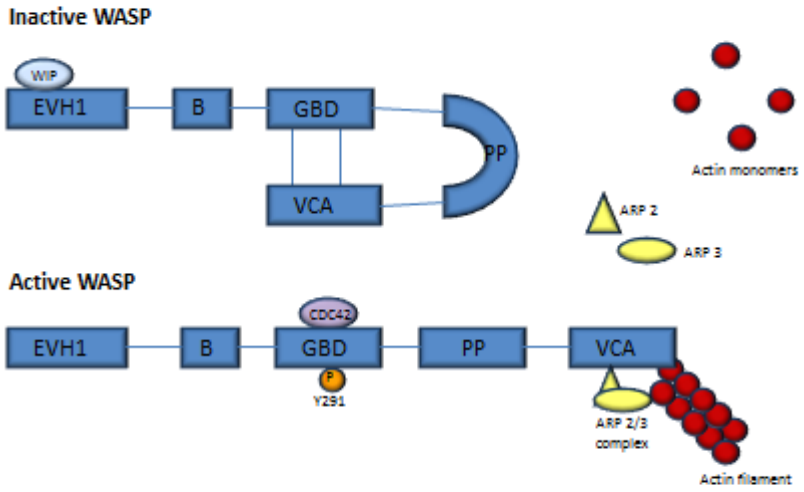

Figure 2: WASP deficiency and inflammation.

Inflammatory symptoms are common in WAS and the role of WASP in inflammation is being increasingly defined. a) $CD4^+$ T cells show impaired gene transcription required for T_H1 differentiation, leading to T_H2 dominance. Treg cells produce less of the anti-inflammatory cytokine IL-10 and fail to regulate T_H2 effector responses, which has been associated with allergic intestinal inflammation. Reduced numbers of IL-10 producing Breg cells are associated with reduced Treg cell recruitment and increased pro-inflammatory T_H17 cells. b) Enhanced cross presentation leads to over activation of $CD8^+$ T cells and is associated with skin inflammation, which is contributed to by allergen-laden Langerhans cells that fail to migrate from the skin to lymph nodes. Neutrophil migration to sites of sterile inflammation is also impaired, particularly through WASP-BTK interaction. c) Increased numbers of pro-inflammatory macrophages are found, with increased production of pro-inflammatory cytokines.

Breg cell, regulatory B cell; BTK, Bruton's Tyrosine Kinase; DC, dendritic cell; LN, lymph node; T_H1/ 2/ 17, T helper cell; Treg cell, regulatory T cell; WAS, Wiskott Aldrich syndrome; WASP, Wiskott Aldrich syndrome protein.

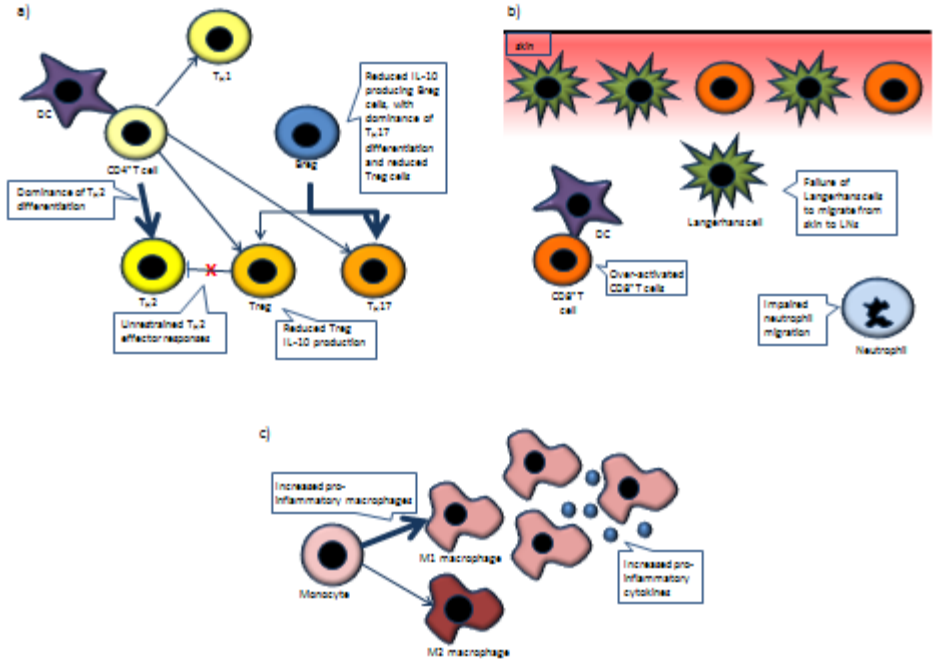

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Table 1: Actin cytoskeleton dependent and independent immune functions of WASP.

Early research identified WASP as an important regulator of the actin cytoskeleton. More recently, important cytoskeleton independent functions in nuclear transcription have been identified.
NK, natural killer cell; WASP, Wiskott Aldrich syndrome protein.

Actin cytoskeleton-dependent functions of WASP	Actin cytoskeleton-independent functions of WASP
Lymphoid cell proliferation and homeostasis	T cell differentiation
Lymphoid and myeloid immune synapse assembly and signaling	Memory B cell activation, through transcription of B cell co-receptor CD19

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Lymphoid and myeloid cell cytokine polarization and release	Transcription of inflammatory cytokines
Myeloid protrusion activity and endothelial adhesion, through podosome formation	Transcriptional regulation of myeloid cells
Lymphoid and myeloid cell migration	
NK cytolytic activity, through perforin accumulation at NK-target cell contact	
Phagocytosis	