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Branching out in different directions: Emerging cellular functions for the Arp2/3 complex and WASP-family actin nucleation factors

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Abstract

The actin cytoskeleton impacts practically every function of a eukaryotic cell. Historically, the best-characterized cytoskeletal activities are in cell morphogenesis, motility, and division. The structural and dynamic properties of the actin cytoskeleton are also crucial for establishing, maintaining, and changing the organization of membrane-bound organelles and other intracellular structures. Such activities are important in nearly all animal cells and tissues, although distinct anatomical regions and physiological systems rely on different regulatory factors. Recent work indicates that the Arp2/3 complex, a broadly expressed actin nucleator, drives actin assembly during several intracellular stress response pathways. These newly described Arp2/3-mediated cytoskeletal rearrangements are coordinated by members of the Wiskott-Aldrich Syndrome Protein (WASP) family of actin nucleation-promoting factors. Thus, the Arp2/3 complex and WASP-family proteins are emerging as crucial players in cytoplasmic and nuclear activities including autophagy, apoptosis, chromatin dynamics, and DNA repair. Characterizations of the functions of the actin assembly machinery in such stress response mechanisms are advancing our understanding of both normal and pathogenic processes, and hold great promise for providing insights into organismal development and interventions for disease.

Keywords

Actin; Arp2/3 complex; Apoptosome; Apoptosis; Autophagy; Caspase; Cytoskeleton; DNA repair; JMY; Macropinocytosis; Mitochondria; N-WASP; Proteostasis; Transcription; WASH complex; WASP; WAVE complex; WHAMM; WHIMP; Wiskott-Aldrich Syndrome

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

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1. Introduction

The basic mechanics underlying actin-associated cellular behaviors are simple: globular (G-) actin monomers assemble into filamentous (F-) actin polymers that can disassemble back into monomers. Actin polymerization generates protrusive forces, while the filaments themselves provide physical structure, serve as scaffolds, and act as tracks for motor proteins. To ensure that actin assembles when and where it is needed, sophisticated regulatory mechanisms control the formation of dimeric, trimeric, or tetrameric actin 'nuclei' that elongate into filaments (Pollard, 2016). Efficient initiation of polymer assembly *de novo* occurs through the actions of proteins called nucleators. Mammals encode 3 main classes of actin nucleators. One class consists of ≥ 8 monomer-aligning proteins that instigate linear actin assembly (Dominguez, 2016; Shekhar et al., 2016). The second is composed of ~15 Formin-family proteins that stabilize actin dimers and elongate linear filaments (Breitsprecher and Goode, 2013; Courtemanche, 2018). The third comprises a 7-subunit macromolecular nucleator called the Arp2/3 complex and its ~12 activators, termed the nucleation-promoting factors (Alekhina et al., 2017; Campellone and Welch, 2010). The Arp2/3 complex cooperates with these factors at the sides of existing actin filaments to nucleate new branched networks that direct diverse cellular activities.

Most mammalian Arp2/3 activators are members of the Wiskott-Aldrich Syndrome Protein (WASP) family: WASP, N-WASP, WAVE1, WAVE2, WAVE3, WASH, WHAMM, JMY, and WHIMP (Campellone et al., 2008b; Derry et al., 1994; Kabrawala et al., 2020; Linardopoulou et al., 2007; Machesky and Insall, 1998; Miki et al., 1998b, 1996; Shikama et al., 1999; Suetsugu et al., 1999; Symons et al., 1996; Zuchero et al., 2009). Other Arp2/3-binding factors include Cortactin and HS1, which stabilize F-actin branchpoints (Helgeson and Nolen, 2013; Schnoor et al., 2018), and WISH/DIP1/SPIN90, which cooperates with Arp2/3 to assemble linear instead of branched filaments (Cao et al., 2020; Wagner et al., 2013). The structural and biochemical mechanisms of Arp2/3 activation by nucleation-promoting factors have been reviewed elsewhere (Gautreau et al., 2022; Kadzik et al., 2020; Lappalainen et al., 2022) and recently described at higher resolution (Shaaban et al., 2020; Zimmet et al., 2020; et al., 2022; Ding et al., 2022). The current review provides a more cell biological perspective on the functions of the Arp2/3 complex and its WASP-family activators. We first summarize the plasma membrane remodeling and endocytic trafficking activities in which the Arp2/3 complex and WASP-family members are well characterized before focusing on newly emerging functions for these nucleation factors in homeostatic and stress response pathways including autophagy, apoptosis, chromatin dynamics, and DNA repair.

2. Cell morphogenesis and movement

Cell motility and directional migration are integral to organismal development, responses to extracellular stimuli, and execution of immune system functions (Pollard, 2018; SenGupta et al., 2021; Swaney and Li, 2016). Morphological changes that allow for the cell to effectively control its movement rely on the coordinated assembly and disassembly of actin filaments beneath the plasma membrane at sites of protrusion and adhesion (Schaks et al., 2019; Svitkina, 2018). This polymerization is dictated by the Arp2/3 complex, originally purified

from *Acanthamoeba castellanii* and shown to localize to the cell cortex (Machesky et al., 1994). The complex is composed of 7 subunits: Arp2, Arp3, ArpC1, ArpC2, ArpC3, ArpC4, and ArpC5, and is highly conserved across eukaryotes (Machesky et al., 1997; Welch et al., 1997). The ability of the Arp2/3 complex to nucleate actin was realized upon the discovery of proteins that activate the complex – the nucleation-promoting factors. Notably, the first Arp2/3 activator to be identified was not of human origin but was bacterial. ActA, uncovered due to its requirement in actin 'comet tail' assembly by pathogenic *Listeria monocytogenes* (Kocks et al., 1992), was shown to promote Arp2/3 complex-mediated actin nucleation in vitro (Welch et al., 1998).

The number of known Arp2/3-activating factors, both bacterial and endogenous mammalian, has since greatly increased (Campellone and Welch, 2010; Rotty et al., 2013). The founding member of the human nucleation-promoting factor family, WASP, was originally identified as the protein product of the *WAS* gene, which is mutated in patients with the immune disorder Wiskott-Aldrich Syndrome (Derry et al., 1994). Soon thereafter, WASP was observed to regulate the actin cytoskeleton (Symons et al., 1996). The crucial link to Arp2/3 was then made when WASP and a homologous protein, WAVE1 (related to the *Dictyostelium* protein SCAR (Bear et al., 1998)), were shown to interact with the Arp2/3 complex (Machesky and Insall, 1998). The key shared feature of WASP, WAVE1, and all subsequently-identified mammalian WASP-family members is their possession of a conserved C-terminal 'WCA' domain, consisting of one or more WASP-homology 2 (WH2) motifs that bind actin monomers, and connector (C) and acidic (A) sequences responsible for engaging the Arp2/3 complex during branched actin nucleation (Machesky and Insall, 1998; Mullins et al., 1998).

The next major advances in our understanding of the Arp2/3 complex and its WASP-family activators came when investigators began to explore the functions of these actin assembly factors at the plasma membrane. The greatest depth of work characterizing the cellular functions of the Arp2/3 complex and WASP-family proteins has been related to their roles in protrusive structures (Fig. 1A). Similar to how the polymerization of actin filaments into comet tails can physically propel bacterial pathogens through the cytosol, the force of actin assembly also drives the plasma membrane forward during protrusion and cell motility.

Two major types of plasma membrane protrusions are filopodia and lamellipodia [Fig. 1A–C]. Filopodia are narrow structures utilized for environmental exploration, sensing, and adhesion (Fischer et al., 2019; Gallop, 2020). A network of branched actin filaments at the cell periphery often underlies the filopodial base, whereas linear bundled filaments comprise the filopodial shaft [Fig. 1B]. Because WASP expression is restricted to hematopoietic cells (Massaad et al., 2013), several filopodia models have utilized its closest relative, the ubiquitously-expressed N-WASP. In fact, the initial characterizations of N-WASP described how its overexpression can induce filopodia biogenesis (Miki et al., 1998a, 1996).

Studies on both WASP and N-WASP, in addition to providing insights into filopodia, have revealed key mechanisms governing the inhibition and activation of actin nucleation factors. WASP and N-WASP can adopt inactive auto-inhibited conformations, where intramolecular interactions physically sequester the C-terminal WCA domain, preventing

it from activating the Arp2/3 complex (Padrick and Rosen, 2010). The N-termini of WASP and N-WASP also form stable complexes with actin-binding proteins from the WIP family (Sokolik et al., 2020). Conformational changes stemming from interactions between several internal domains of WASP/N-WASP with signaling molecules such as small GTPases, phosphoinositides, SH3 domain-containing adaptor proteins, and tyrosine kinases can relieve the auto-inhibited arrangements of these proteins and enable potent Arp2/3 activation (Alekhina et al., 2017). Moreover, oligomerization of WASP and N-WASP stimulates their nucleation-promoting activities (Campellone et al., 2008a; Cheng et al., 2008; Padrick et al., 2008; Sallee et al., 2008). Multivalent complexes formed with receptors and adaptors also control their phase separation into biomolecular condensates, which regulates actin polymerization kinetics (Banani et al., 2017). Among these signaling mechanisms, the G-protein-based regulation of N-WASP may be indirectly relevant to filopodial biogenesis.

In one model for filopodia assembly, termed convergent elongation, small Rho-family GTPases such as Cdc42 bind and activate N-WASP to stimulate the Arp2/3 complex to generate a dendritic actin network, from which some filaments can be bundled and elongated by other actin-binding proteins (Fischer et al., 2019). While overexpression and reconstituted in vitro systems are compatible with a foundational Cdc42-N-WASP-Arp2/3-based model for actin assembly (Dobramysl et al., 2021; Lee et al., 2010; Lim et al., 2008; Snapper et al., 2001), this pathway may not be the quintessential driver of filopodial biogenesis because filopodia can form in some cells lacking Cdc42, N-WASP, or Arp2/3 complex functions (Czuchra et al., 2005; Lommel et al., 2001; Steffen et al., 2006). In the distinct tip nucleation model for filopodia assembly, Cdc42 and other G-proteins relieve the auto-inhibition of actin nucleators belonging to the Formin family, such as mDia1/2/3 and FMNL2/3, which directly polymerize and elongate filaments at the growing tip (Dimchev et al., 2021; Young et al., 2015). Actin polymerases from the Ena/VASP family also function in filament elongation (Faix and Rottner, 2022). Heterogeneity in the factors capable of promoting filopodia formation is further exhibited in reconstitutions of filopodia-like structures using a variety of combinations of actin nucleation factors and regulators (Dobramysl et al., 2021; Jarsch et al., 2020). Given the existence of multiple mechanisms for actin polymerization within filopodia, these models may reflect the fact that different populations of filopodia are capable of forming under distinct conditions or in diverse cell types.

In contrast to filopodia, lamellipodia are broad, flat cellular protrusions driven forward by the polymerization of branched and short, rather than linear and long, actin filaments (Alexandrova et al., 2020; Innocenti, 2018). The Arp2/3 complex is crucial for generating lamellipodia, and within these structures it is activated by members of the SCAR/WAVE sub-group (WAVE1, WAVE2, or WAVE3) of nucleation factors (Fig. 1C). Each WAVE protein acts within a heteropentameric complex consisting of WAVE1, 2, or 3 with the canonical subunits Sra1 (Cyfip1), Nap1 (Hem2), Abi1, and Brk1 (Hspc300) (Eden et al., 2002; Gautreau et al., 2004). Instead of an auto-inhibitory regulatory mechanism, the basal inactivity of the WAVEs is maintained in *trans*, as structural studies show that the WH2 and C regions of the WCA domain are bound to Sra1, thus blocking Arp2/3 interaction (Chen et al., 2010; Ismail et al., 2009). Several of the subunits (WAVE1/2/3 themselves, Cyfip1/2, Hem1/2, Abi1/2/3) also exist in multiple isoforms, giving rise to a variety of

WAVE regulatory complexes with potentially different activities and functional properties (Dubielecka et al., 2011; Pathania et al., 2014; Polesskaya et al., 2022; Suetsugu et al., 2003; Tang et al., 2020).

Like WASP and N-WASP, the localization and activation of the WAVE complexes are regulated by numerous signaling molecules like G-proteins, phospholipids, and protein kinases. This extensive repertoire of WAVE regulatory complex binding partners is detailed elsewhere (Kramer et al., 2022). In the simplest model for WAVE complex activation during lamellipodial protrusion, the G-protein Rac1 binds to two sites on Sra1, promoting reorganization of the complex, exposing the WCA domain, and thus allowing it to stimulate the Arp2/3 complex (Chen et al., 2017, 2014, 2010). The G-protein Arf1 can cooperate with Rac1 in activating the WAVE complex (Koronakis et al., 2011; Singh et al., 2019), and was recently shown to interact with Sra1 at a site distinct from where Rac1 binds (Yang et al., 2022).

Lamellipodia-like membrane ruffles also form following activation of other WASP-family members including N-WASP (Legg et al., 2007), JMY (Coutts et al., 2009; Zuchero et al., 2009), and WHIMP (Kabrawala et al., 2020). These factors may work in experimental context-, stimulus-, cell type-, and/or organism-specific manners. Among such WASP-family members, WHIMP is the most recently discovered and is related to the WAVEs, but is only present in a subset of animals and appears to be the least potent Arp2/3 activator (Kabrawala et al., 2020). In mouse cells, WHIMP can promote motility and hyper-ruffling phenotypes through an additional ability to stimulate Src-family kinase signaling, which may amplify Arp2/3 activation via the other WAVEs (Fig. 1C). Although *WHIMP* appears to be absent from the most recent assembly of the human genome (Nurk et al., 2022), its existence in other animals reinvigorates questions regarding how organisms can evolutionarily lose members of the actin regulatory machinery yet maintain finely-tuned processes like membrane protrusion and movement (Kollmar et al., 2012; Veltman and Insall, 2010).

While protrusion is one necessary step in cell motility, adhesion using substrate contacts embedded within lamellipodia is often crucial as well. The ultrastructure and function of focal adhesions are reviewed in greater depth elsewhere (Burridge and Guilluy, 2016; Case and Waterman, 2015). Briefly, nascent adhesions form near the leading edge in many cell types, where the force of actin polymerization and retrograde actin flow activates integrins that simultaneously associate with intracellular F-actin-binding proteins like talin and α-actinin and the extracellular matrix (ECM) (Gardel et al., 2010; Romero et al., 2020). As adhesions mature, so do the pools of factors that are organized in layers to coordinate signaling and force transduction (Kanchanawong et al., 2010). Force can be further modulated by actin arcs connected to focal adhesions by dorsal stress fibers (Burnette et al., 2014). Phosphotyrosine signal transduction during adhesion is carried out by kinases like FAK and Src-family members, the same molecules that phosphorylate and interact with N-WASP and the WAVEs during Arp2/3 complex-mediated protrusion (Ardern et al., 2006; Cory et al., 2002; LeClaire et al., 2008; Padrick and Rosen, 2010; Suetsugu et al., 2002; Torres and Rosen, 2006; Wu et al., 2004). Furthermore, depletion of WASP, the WAVE complex, or the Arp2/3 complex in phagocytes or N-WASP in fibroblasts impairs

cell adherence (Kumar et al., 2012; Misra et al., 2007; Rotty et al., 2017; Stahnke et al., 2021).

Actin assembly in adhesions can also be modulated by variations of the core nucleation machinery, as non-canonical Arp2/3 complexes consisting of Arp2, Arp3, ArpC2/3, and vinculin can be formed (Chorev et al., 2014; Pizarro-Cerdá et al., 2017). These observations not only bring to light the potential relevance of hybrid Arp2/3 complexes containing specialized factors but serve as a reminder that the canonical Arp2/3 complex subunits themselves exhibit diversity that may affect activity. In recent years, the functional consequences of isoform diversity within the Arp2/3 complex have begun to emerge.

Using Vaccinia virus-infected cells as a model system, different isoforms of ArpC1 and ArpC5 were analyzed. Strikingly, Vaccinia actin tails are longer when cells are depleted of ArpC5 or ArpC1A, and are shorter after depletion of the ArpC5L or ArpC1B isoforms (Abella et al., 2016). Complexes containing distinct ArpC1 and ArpC5 isoforms also show differences in actin nucleation activity in vitro (Abella et al., 2016). These results suggest that Vaccinia, which utilizes an N-WASP-dependent mechanism of Arp2/3 activation, may have a molecular preference for a particular composition of Arp2/3 complex during actin-based motility. Subsequent studies have examined how the structure of Arp2/3 complex isoforms can influence nucleation activity, filament elongation, filament disassembly, branch junction stability, and cell cycle progression (Fäßler et al., 2023; Galloni et al., 2021; Molinie et al., 2019; von Loeffelholz et al., 2020). Future avenues of exploration may reveal how the many possible Arp2/3 complex isoforms behave in cell- or tissue-specific manners, respond to distinct WASP-family members, or act in different pathological situations.

Given that the Arp2/3 complex and WASP-family members are so important for protrusion, adhesion, and motility, it is not surprising that genetic mutations or epigenetic alterations that change the molecular activities or expression levels of such nucleation factors are associated with diseases (Kramer et al., 2022). For the Arp2/3 complex, frameshift mutations in *ARPC1B* result in immunodeficiency phenotypes such as vasculitis and poor wound healing (Kahr et al., 2017; Kuijpers et al., 2017; Volpi et al., 2019). Lack of a functional ArpC1B subunit leads to deficiencies in T-cell spreading, synapse formation, and proliferation (Brigida et al., 2018; Randzavola et al., 2019; Somech et al., 2017). These studies describe a role for the Arp2/3 complex in immune disorders and emphasize the importance of the ArpC1B isoform in particular. Changes in expression and mutations in Arp2/3 complex subunits, as well as WASP-family members, have additionally been observed in a variety of cancers, as reviewed elsewhere (Biber et al., 2020; Molinie and Gautreau, 2018) and discussed further below.

Disruptions of plasma membrane remodeling, signaling, and motility arising from mutations in WASP-family genes have also been associated with immunodeficiencies. Loss-of-function point mutations and microdeletions in the X-linked gene encoding WASP were the first to be connected to disease and found to cause Wiskott-Aldrich Syndrome, related immune system disorders, and bleeding conditions (Bouma et al., 2009; Thrasher, 2009). Such mutations may result in the absence of functional WASP, as is historically the case with the most severe cases of Wiskott-Aldrich Syndrome (Thrasher and Burns, 2010). In contrast, pseudo-gain-

of-function mutations that disrupt WASP auto-inhibition lead to neutropenia. Since WASP is important for so many hematopoietic cell processes, including T-cell maturation and signaling, phagocytosis, and the formation of invadosomal protrusions that allow for invasive migration and degradation of the ECM (Linder, 2009; Murphy and Courtneidge, 2011), WASP mutants have pleiotropic effects in patients. Given that pathogenic *WAS* mutations are so well catalogued and are X-linked, it is unsurprising that they are prime candidates for gene therapy (Aiuti et al., 2013; Rai et al., 2020), leading to the possibility that patient prognoses may eventually be greatly improved.

More recent work indicates that mutations in the autosomal WASP-family genes may give rise to illnesses beyond immune disorders. For example, neurodevelopmental diseases have been attributed to autosomal dominant *de novo* mutations in the gene encoding WAVE1 (Ito et al., 2018; Srivastava et al., 2021). Taken together with the observations that numerous *CYFIP1/2* variants are associated with other neurological conditions (Kramer et al., 2022), these new results suggest that additional alterations in the WAVE complexes which adversely affect brain function will likely be revealed by more genomic testing.

As ongoing research clarifies human disease phenotypes and clinical outcomes concerning the functions of different WASP-family members, it seems likely that the parallel use of animal models deficient in one or more of these proteins, both globally and in a tissue-specific manner (Aloisio and Barber, 2022; Gligorijevic et al., 2012; Juin et al., 2019; Kim et al., 2020; Liu et al., 2021; Morris et al., 2018; Papalazarou et al., 2020; Gruenbaum-Cohen et al., 2012; Zhou et al., 2015), would provide a great benefit. Such models could allow for the visualization of pathogenesis and the effects of potential therapeutic interventions at the organismal level. Furthermore, the study of cell morphogenesis and migration in animal models continues to expand beyond immune responses and cancers, as deletion of either Arp3 or N-WASP in conditional knockout mice negatively influences kidney function through disrupted development, adhesion, and protrusion of podocytes, cells which are crucial for forming the filtration barrier in the glomerulus (Schell et al., 2018, 2013). With the body of work on nucleation factor-deficient mouse models becoming more prevalent, so too will the connections between the actin assembly machinery, tissue-specific processes, development, and disease.

3. Macropinocytosis, endocytosis, and endocytic trafficking

Plasma membrane protrusions, in addition to their key roles in cell movement and exploration of the environment, also allow cells to internalize extracellular materials (Fig. 1D). Protrusions in the form of membrane ruffles can sample the surroundings and engulf microbes, nutrients, or other molecules. In one type of ingestion, termed macropinocytosis, actin-driven ruffles project out into the milieu, enclose, and internalize, creating a fluid-filled vacuole known as a macropinosome (Kay, 2021; Swanson and King, 2019). N-WASP, WAVE1, WAVE2, and WHIMP have all been localized to peripheral, dorsal, or pathogen-induced membrane ruffles or analogous sites of macropinocytosis (Fig. 1D). N-WASP localizes to dorsal ruffles, and some N-WASP-deficient mouse embryonic fibroblasts exhibit aberrant ruffle formation (Legg et al., 2007). Distinct WAVE subfamily members are also enriched at ruffle structures in fibroblasts, with WAVE1 important dorsally, and WAVE2

more prominent in peripheral ruffling (Suetsugu et al., 2003), although dorsal ruffles can form in some cells lacking WAVE1 (Legg et al., 2007). In any case, internalization of fluid-phase molecules appears to be more dependent on components of the WAVE complex than N-WASP (Innocenti et al., 2005). As with WAVE complex-mediated lamellipodial protrusion, macropinocytic protrusion is positively regulated by G-proteins from the Rac and Arf sub-families. Finally, murine WHIMP localizes to dorsal and peripheral ruffles, and its expression increases macropinocytosis (Kabrawala et al., 2020). Collectively, these observations underscore the idea that cells from different tissues or organisms are versatile in their capacity to form ruffles and undergo macropinocytosis.

While macropinocytic protrusions are one way in which the actin assembly machinery can contribute to the internalization of extracellular material, the Arp2/3 complex and WASP-family members are also key players in membrane invagination processes including receptor- and clathrin-mediated endocytosis (Fig. 1E). During these processes, actin is assembled in an Arp2/3- and N-WASP-dependent manner as the membrane deformation turns inward to the cytoplasm to form the endocytic pit (Chakrabarti et al., 2021; Kaksonen and Roux, 2018). Multiple loss-of-function approaches including dominant negative proteins, gene knockouts, and RNA interference indicate that N-WASP is important for the internalization of several receptors and cargo (Benesch et al., 2005; Bu et al., 2010; Innocenti et al., 2005; Merrifield et al., 2004). Branched filaments appear at the neck of the pit and can also surround the pit itself. More recent high-resolution imaging and modeling reveals that N-WASP- and Arp2/3-mediated actin networks can create asymmetric forces for internalization of some endocytic vesicles (Akamatsu et al., 2020; Jin et al., 2022; Serwas et al., 2022).

Actin dynamics are not only important for the internalization step of endocytosis, but also for the subsequent movement and trafficking of endocytic vesicles and their cargo (Fig. 1F). Internalized vesicles associated with N-WASP and the Arp2/3 complex move via actin tail rocketing motility (Benesch et al., 2002; Southwick et al., 2003; Taunton et al., 2000). Once endosomes are within the cell, encapsulated cargo must be properly sorted and directed through the endomembrane system. The destination of endocytic components is initially determined at an early or sorting endosome, from which tubules emerge to form different endosomal compartments, where some receptors can be directed back to the plasma membrane through recycling endosomes. Other receptors and ligands may proceed to the Golgi or distinct organelles for further modification and sorting, or develop into late endosomes that mature and acidify into lysosomes (MacDonald et al., 2020; Wang et al., 2018). Within the WASP-family, WASH is the central figure in endocytic trafficking.

Originally discovered to be encoded by numerous human subtelomeric genes (Linardopoulou et al., 2007), WASH is evolutionarily conserved in many animals and protists, but not fungi (Kollmar et al., 2012; Velle and Fritz-Laylin, 2019; Veltman and Insall, 2010). The relevance of the human WASH paralogs is unclear, as most mammalian studies have focused on mouse WASH or human WASH1 (both referred to simply as WASH here) and have been reviewed elsewhere (Alekhina et al., 2017; Fokin and Gautreau, 2021). WASH is part of a heteropentameric protein complex that is structurally and functionally similar to that of the WAVE regulatory complex (Derivery et al., 2009; Gomez

and Billadeau, 2009; Jia et al., 2010). The core subunits are Fam21 (WashC2), Ccdc53 (WashC3), Swip (WashC4), and Strumpellin (WashC5). Several early papers demonstrated that WASH localizes to multiple endosomal populations (Derivery et al., 2009; Duleh and Welch, 2010; Gomez and Billadeau, 2009; Park et al., 2013; Zech et al., 2011). WASH is essential in mice (Gomez et al., 2012; Xia et al., 2013), and at the cellular level, WASH inactivation or depletion disrupts numerous endosomal cargo sorting events. Furthermore, WASH maintains the integrity, distribution, and size of the lysosome population (Gomez et al., 2012; Park et al., 2013), extending WASH's influence over the entire endolysosomal system.

The importance of WASH appears to lie in its ability to promote Arp2/3-mediated actin assembly, whereby the actin filaments enable endosomal tubule scission (Derivery et al., 2009; Gomez and Billadeau, 2009). The recruitment of WASH to endosomal membranes is primarily achieved through interactions of Fam21 with the retromer complex, a key constituent of the endosomal sorting apparatus (Seaman, 2021; Simonetti and Cullen, 2019). Newer studies have further revealed a connection between WASH and the retromer-related retriever complex, which is recruited to endosomal membranes through interactions with subunits of yet another multi-protein complex, the CCC complex (McNally et al., 2017; Phillips-Krawczak et al., 2015; Singla et al., 2019). The WASH complex also coordinates with the F-actin capping machinery and microtubule-associated factors, as Fam21 interacts with CapZ to perform an anti-capping function and create seed filaments based on remodeling of the dynactin complex (Fokin et al., 2021; Jia et al., 2010). In contrast to the many studies on how WASH complex binding partners regulate its recruitment to endosomal membranes, the activation of the complex by signaling molecules is less understood. Mammalian WASH does not appear to be activated by Cdc42 or Rac1, but it is ubiquitinated, which appears to be important for Arp2/3-mediated actin assembly on endosomes (Hao et al., 2013). More work is needed to elucidate the other molecular mechanisms underlying WASH complex activation.

It is also notable that endocytic trafficking pathways can intersect with biosynthetic pathways, and several WASP-family members influence ER-to-Golgi transport, membrane tubulation, *trans*-Golgi dynamics, and other secretory remodeling events (Fig. 1G). These nucleation factors and topics have been discussed elsewhere (Blom et al., 2015; Campellone et al., 2008b; Chakrabarti et al., 2021; Luna et al., 2002; Matas et al., 2004; Russo et al., 2016; Schlüter et al., 2014).

Disruption of the endolysosomal network has long been connected to disease, but our understanding of the contribution of WASP-family members is now beginning to come into play (Kramer et al., 2022). In pancreatic cancer, N-WASP may enable ductal adenocarcinoma cell migration via its role in endocytic recycling of a chemotaxis-related receptor (Juin et al., 2019). Mutant forms of WASH complex subunits can disrupt endolysosomal integrity and cargo sorting in the context of neurological disorders (Courtland et al., 2021; Ropers et al., 2011; Valdmanis et al., 2007). The importance of WASH in membrane trafficking processes that affect protein homeostasis or turnover is also particularly relevant to neurodegenerative diseases, as explained below. While characterizing phenotypic alterations in cellular processes like endosomal trafficking are

crucial to understanding many aspects of disease, in cases involving nucleation factors like N-WASP and WASH that have numerous functions, it remains challenging to identify which defective processes are the primary drivers of pathogenesis. As our ability to more precisely sort out the molecular basis of cellular dysfunction improves, the paths for designing therapeutic interventions will likely become clearer.

4. Proteostasis and autophagy

Following the discovery of WASH and two other WASP-family members, WHAMM and JMY, cellular studies on the functions of the Arp2/3 complex and its nucleation-promoting factors began to branch out in new directions. In particular, investigations into how the actin assembly machinery contributes to maintaining several aspects of cellular homeostasis have emerged [Table 1]. Protein homeostasis, termed proteostasis, is the maintenance of appropriate protein concentrations within the cell amidst changing conditions (Hipp et al., 2019; Yerbury et al., 2016). Proteostasis is sustained through several coordinated processes [Fig. 2A], including protein synthesis, folding, trafficking, and degradation [Fig. 2B–E]. Disruption of one or more of these activities can impair multiple intracellular behaviors and reduce cell viability. Among the different arms of the proteostasis network, those pertaining to protein trafficking and degradation currently have the strongest connections to the actin cytoskeleton.

Targeted protein degradation in cells takes place via two primary mechanisms: the ubiquitin-proteasome system (UPS) and the autophagosome-lysosome system (ALS) (Fig. 2E). Both pathways operate constitutively, but can be upregulated in response to several stimuli (Korolchuk et al., 2010; Yin et al., 2020). Though these pathways differ in their targets and steps leading to degradation, both involve the process of ubiquitination. Ubiquitin is a 76 amino acid polypeptide containing several lysine (K) residues that can be conjugated to other protein substrates at their lysines, either as a single moiety rendering the substrate monoubiquitinated or as a polyubiquitin chain. These modifications designate targets for degradation or promote other non-proteolytic processes (Ji and Kwon, 2017). The fates of the target proteins are influenced by the types of ubiquitin-lysine linkages. For example, K48 linkages commonly lead to proteasomal degradation, while K63 linkages can be detected by autophagy receptors (Yau and Rape, 2016). The K48 polyubiquitin chains are recognized by the 26S proteasome, composed of a 19S regulatory particle acting as a lid to the proteolytic 20S core, where degradation of the unfolded proteins takes place (Livneh et al., 2016). The relationship between the UPS and the actin cytoskeleton is not well understood, although actin and actin-binding proteins can be degraded by the proteasome, and actin filaments have been shown to interact with proteasomes in yeast (Haarer et al., 2011).

In contrast to UPS-mediated cytosolic digestion of proteins, the ALS degrades and recycles cellular components through delivery of protein and other macromolecular cargo to lysosomes (Ballabio and Bonifacino, 2020). Autophagy is formally categorized into 3 distinct degradation processes: microautophagy, chaperone-mediated autophagy, and macroautophagy. Microautophagy involves the direct uptake of cytosolic cargo into lysosomes via membrane invagination (Park and Cuervo, 2013). Chaperone-mediated autophagy targets proteins possessing KFERQ-like motifs for transport by the chaperone

HSC70 to lysosomes, where they dock at the membrane receptor LAMP2A and are translocated into the lysosomal lumen (Kaushik and Cuervo, 2018). Macroautophagy (often and hereafter referred to simply as autophagy) is defined by the sequestration of cytosolic components within double-membrane-bound vesicles known as autophagosomes followed by autophagosomal fusion with and digestion by lysosomes (Morishita and Mizushima, 2019; Zhao and Zhang, 2019). It is also the degradation pathway in which the actin cytoskeleton has been most studied (Fig. 3A–D).

Autophagy is a fundamental mechanism for catabolizing and recycling intracellular components in response to multiple stressors, including nutrient starvation (Ohsumi, 2014). Autophagosomes can envelop bulk cytoplasm in a nonselective process, or they can isolate specific, often ubiquitinated, cargo in processes collectively called selective autophagy (Gatica et al., 2018; Hansen et al., 2018). Autophagosome biogenesis is frequently initiated by the ULK1 (ATG1) protein kinase complex that phosphorylates key factors which participate in the autophagy pathway, such as components of the Beclin- and Vps34-based PI3 kinase complex that produce the phospholipid PI(3)P at sites of nascent autophagosome, or phagophore, formation (Palamiuc et al., 2020; Sridharan et al., 2011). A significant number of these isolation membranes are formed in association with endoplasmic reticulum (ER) structures known as omegasomes (Roberts and Ktistakis, 2013). The formation of PI(3)P-binding complexes allows for the assembly of the core ATG machinery, a ubiquitin-like conjugation system that incorporates autophagosomal membrane proteins from the ATG8 family into the developing phagophore, which elongates, matures, and eventually closes to form an autophagosome surrounding the cargo (Carlsson and Simonsen, 2015; Nakatogawa, 2020).

In mammals, the ATG8 family consists of the LC3 (LC3A/B/C) and GABARAP (GABARAP, GABARAP-L1/L2) subfamilies, which exist in cytosolic forms (e.g., LC3-I or GABARAP-I) that can be lipidated with phosphatidylethanolamine to create their autophagosomal membrane-associated forms (e.g., LC3-II or GABARAP-II) (Nguyen and Lazarou, 2022). For completion of autophagy, autophagosomes fuse with lysosomes to create autolysosomes, where the contents are degraded and/or recycled to meet the metabolic and biosynthetic needs of the cell (Nakamura and Yoshimori, 2017). Autolysosomes may then undergo tubulation and scission to form protolysosomes in the process of lysosome regeneration. The protolysosomes mature into lysosomes, serving to maintain the intracellular lysosomal population (Yang and Wang, 2021).

Selective autophagy, as the name implies, targets specific cargo for degradation. Autophagy receptors act as the link between the target and the autophagosome, utilizing a ubiquitin-binding domain to recognize the ubiquitinated cargo, and an LC3 Interacting Region (LIR) to bind LC3 embedded in the autophagosomal membrane (Morishita and Mizushima, 2019). Forms of selective autophagy are typically named for their intended targets: aggrephagy for protein aggregates, mitophagy for mitochondria, xenophagy for microbes, and several others (Lamark and Johansen, 2021). Some autophagy receptors, including SQSTM1/p62, can participate broadly in several types of selective autophagy, while others such as OPTN, NDP52, NBR1, and TAX1BP1 may be used preferentially with different cargoes (Kirkin et

al., 2009; Lazarou et al., 2015; Pankiv et al., 2007; Sarraf et al., 2020; Thurston et al., 2009; Wild et al., 2011; Wong and Holzbaur, 2014).

Selective autophagy is especially relevant to neurodegenerative disorders like Huntington's, Alzheimer's, and Parkinson's Disease, in which proteins aggregate and proteostasis is disrupted. More specifically, changes in mitophagy significantly impact neurodegeneration, as the hallmark players in neuronal mitophagy – the protein kinase PINK1, phosphorylated ubiquitin, and the ubiquitin ligase Parkin – are often dysregulated in Parkinson's Disease patients (Killackey et al., 2020; Kitada et al., 1998; Pickrell and Youle, 2015; Valente et al., 2004). PINK/Parkin-mediated mitophagy is coordinated with mitochondrial remodeling, as mitochondria cluster into mitoaggregates until they can be disassembled in an actin-associated fashion to allow for encapsulation by an autophagosome (Hsieh and Yang, 2019). Irrespective of the particular molecular cargo, the actin cytoskeleton then appears to play multiple roles in the pathway of autophagosome biogenesis, transport, and turnover (Fig. 3A–D).

For a long time, little was known about how the actin cytoskeleton might impact autophagic processes. Many years ago, actin filaments were found to be necessary for autophagosome formation in mammalian cells during nutrient starvation, as blocking polymerization with cytochalasin D reduced the number of autophagic vacuoles (Aplin et al., 1992). It was later shown that the branching factor Cortactin is recruited to ubiquitinated protein aggregates destined for autophagic degradation, and that Cortactin depletion results in less actin at these aggregates, a decrease in autophagosome-lysosome fusion, and an increased accumulation of autophagosomes (Lee et al., 2010). The connections between various forms of autophagy and the actin nucleation machinery then began to come into focus.

While the Arp2/3 complex had previously been localized to autophagosomal structures in yeast (Monastyrska et al., 2008), it was several years until the mammalian complex, namely the ArpC1B subunit, was observed to localize to LC3-positive autophagosomes in rat kidney epithelial cells (Mi et al., 2015). In the latter system, an autophagosomal membrane remodeling pathway is dependent on the phospholipid PI(3) P and the F-actin capping protein CapZ to stimulate actin assembly within developing phagophores and positively control their size and shape (Mi et al., 2015). Several subsequent studies revealed that multiple nucleation-promoting factors can also affect the autophagosome biogenesis process.

Among WASP-family members, WASP itself is important for multiple aspects of non-selective autophagy in some types of myeloid cells (Lee et al., 2017; Rivers et al., 2020), but much of what we know about the cytoskeletal mechanisms that govern several forms of autophagy in diverse cell types come from studies on WHAMM, JMY, and WASH (Fig. 3A–D). Early in the constitutive and starvation-induced autophagic pathways, WHAMM localizes to omegasomes and sites of autophagosome biogenesis, in part through its ability to bind PI(3)P (Kast et al., 2015; Mathiowetz et al., 2017). Deletion of WHAMM or removal of its WCA domain results in decreases in LC3-I to LC3-II conversion and autophagosome abundance, and mutation of a PI(3)P-binding motif within its PX-like domain abrogates WHAMM localization to autophagosomes (Mathiowetz et al., 2017). The expression of WHAMM positively correlates with autophagosome size and number, and this relationship

requires its capacity to activate the Arp2/3 complex (Kast et al., 2015). WHAMM can also be recruited to endomembranes by the small G-protein Rab1 (Russo et al., 2016), a known regulator of autophagy (Huang et al., 2011; Kakuta et al., 2017; Thomas et al., 2014; Tremel et al., 2021; Zoppino et al., 2010), but it is not known if Rab1 controls WHAMM localization or activity during autophagosome formation.

JMY additionally promotes autophagosome formation (Fig. 3A), as JMY physically interacts with LC3 via a LIR motif, and depletion of JMY results in decreases in LC3-I and LC3-II levels (Coutts and La Thangue, 2015). The physical motility of mature autophagosomes is also influenced by both WHAMM and JMY [Fig. 3B], as these two WASP-family members can promote Arp2/3-mediated actin-based rocketing of autophagosomes (Hu and Mullins, 2019; Kast et al., 2015). LC3 binding activates JMY-driven actin assembly during this process (Hu and Mullins, 2019). While WHAMM possesses an N-terminal LIR homologous to the one found in JMY, the mechanisms of WHAMM activation and the biological purposes of autophagosomal rocketing are unclear.

Actin assembly is also important later in the canonical autophagy pathway (Fig. 3C–D), as WHAMM possesses two PI(4,5)P_2-binding motifs that mediate localization to autolysosomes, where WHAMM promotes Arp2/3-dependent actin assembly during membrane tubulation for lysosomal regeneration (Dai et al., 2019). WHAMM is further capable of interacting with BLOC1S1, a component of the BLOC-1 lysosome biogenesis complex, which is thought to participate in recruiting WHAMM during lysosomal tubule formation (Wu et al., 2021). This membrane remodeling activity of WHAMM is analogous to that of WHAMM in driving actin assembly to tubulate membranes that transport cargo through the ER-Golgi secretory pathway (Campellone et al., 2008b; Russo et al., 2016; Shen et al., 2012). The molecular similarities and differences underlying WHAMM-mediated tubulation of secretory versus autophagic organelles remain to be determined.

Apart from WHAMM and JMY, WASH is another WASP-family member that participates in autophagy. Given its role in the sorting of cargo through the multiple endocytic trafficking pathways mentioned earlier (Figs. 1F, 2 D), it is not surprising that depletion or disruption of the WASH regulatory complex impacts the lysosomal functions that enable autophagic flux and turnover of autolysosomal cargo [Fig. 3D]. Like WHAMM, WASH appears to interact with the BLOC-1 lysosome biogenesis complex (Monfregola et al., 2010; Ryder et al., 2013). However, conflicting findings have led to debate on the net positive versus negative effects that WASH has on autophagy. Mouse fibroblasts lacking WASH show an increased conversion of LC3-I to LC3-II and degradation of p62, while cells overexpressing WASH show decreased Beclin-1 ubiquitination, which diminishes its association with Vps34, suggesting that WASH may normally suppress autophagy (Xia et al., 2013). On the other hand, depletion of WASH in HeLa or neuronal cells decreases LC3-II levels and alters the localization of ATG9 to LC3-positive membranes, suggesting that WASH positively influences autophagosome formation (Zavodszky et al., 2014). WASH-associated autophagy is also impaired in Parkinson’s Disease patients with a D620N mutation in Vps35, a component of the retromer complex. This mutation weakens the association between retromer and WASH, and also results in a decrease of LC3-II (Zavodszky et al., 2014). It seems likely that different populations of WASH act in different steps of autophagy,

or that its separate functions may be cell or tissue specific. More work is needed to bring the role of WASH in autophagy into focus.

On the topic of proteostasis and disease, especially related to neurodegenerative disorders, the accumulation of protein aggregates and intracellular defects in their removal via the UPS or ALS is undeniable (Mizushima and Levine, 2020). From a cytoskeletal standpoint, disruptions in endolysosomal trafficking and alterations in WASH complex subunits have been implicated in disease. Several mutations in the gene encoding Strumpellin/WashC5 are found in patients with severe hereditary spastic paraplegia (Valdmanis et al., 2007). Moreover, in a form of autosomal recessive intellectual disability, a single amino acid substitution in SWIP/WashC4 diminishes the stability of the WASH complex, leading to impaired lysosome formation and accumulation of lipid-like inclusions in motor cortex neurons (Courtland et al., 2021; Ropers et al., 2011). It is clear that investigating the presence of mutations within WASP-family genes, especially those with functions tied to maintaining proteostasis, is an avenue worth exploring to further understand the effects of the actin assembly machinery on disease.

One such mutation occurs in *WHAMM* in a subset of patients with Galloway-Mowat Syndrome (GMS), an autosomal recessive disorder characterized by neurodevelopmental delay and progressive renal failure. The genetic basis of GMS has been attributed to mutations in many different genes, including *WDR73*, *NUP107*, *PRDM15*, *WDR4*, and subunits comprising the KEOPS complex such as *OSGEP*, *LAGE3*, *TP53RK*, and *TPRKB* (Ben-Omran et al., 2015; Braun et al., 2018, 2017; Colin et al., 2014; Domingo-Gallego et al., 2019; Jinks et al., 2015; Mann et al., 2021; Rosti et al., 2017; Vodopiutz et al., 2015). The underlying relationship between GMS pathogenesis and the functions of the proteins encoded by these genes is unclear, as the proteins participate in numerous cellular processes, including cell proliferation, nucleo-cytoplasmic transport, tRNA modification, and transcriptional activation. Interestingly, a cohort of patients within the Amish community afflicted with this syndrome was found to possess a homozygous loss-of-function mutation in *WHAMM* in addition to a homozygous mutation in *WDR73* (Jinks et al., 2015; Mathiowetz et al., 2017). The GMS-associated *WHAMM* mutation results in altered WHAMM mRNA splicing and the production of frameshifted WHAMM protein variants that lack a WCA domain and are unable to activate the Arp2/3 complex (Mathiowetz et al., 2017). GMS patient fibroblasts expressing these truncated versions of WHAMM show profound defects in autophagosome biogenesis that can be rescued by re-introduction of full-length WHAMM, but not WDR73, highlighting the importance of WHAMM in mammalian autophagy (Mathiowetz et al., 2017). Nevertheless, the specific contributions of each genetic mutation to neuronal or kidney phenotypes remain unresolved.

As we come to understand the roles of WASP-family members in proteostasis and autophagy, there is still much to be learned about their molecular modes of action and how their activities are coordinated. For example, while WHAMM binds phospholipids and Rab1, and JMY binds LC3 and has genetic interactions with the G-protein RhoD, the spatiotemporal relationships between WHAMM and JMY functions are unknown. Moreover, whether these two factors work in multi-subunit complexes or are activated by signaling molecules in ways resembling how the WASP, WAVE, and WASH subfamilies

are regulated has yet to be elucidated. More broadly, the ways in which the UPS and ALS degradation pathways themselves are coordinated, and how they may compensate for one another in cells with defective WASP-family members remains an open area for investigation. Finally, while work in cultured cell lines has been critical for deciphering the basic functions of WASP-family members and linking them to human diseases, future studies utilizing animal models will truly begin to uncover the impact of specific nucleation factors on different physiological systems, tissues, and relevant cell types. Expanding our characterizations of these factors in vivo will be necessary for understanding their influence on development and disease.

5. Apoptosis

In addition to autophagy, another fundamental cellular response to multiple kinds of stress – but in this case lethal stimuli – is apoptosis (Kerr et al., 1972). In contrast to the homeostatic and pro-survival functions of autophagy, apoptosis is a programmed form of cell death regulated by signaling cascades that culminate in organized proteolysis, nuclear and DNA fragmentation, and cytoskeleton-mediated morphogenic changes (Fig. 4A–C). Apoptotic cell suicide can be driven by intrinsic mitochondria-mediated or extrinsic receptor-mediated pathways that involve distinct initial signaling events but converge on a shared terminal execution pathway to cause an irreversible deterioration of intracellular functions and loss of cellular integrity (Tait and Green, 2013; von Karstedt et al., 2017).

Intrinsic apoptosis pathways are triggered in response to developmental programs or intracellular damage and are characterized by mitochondrial outer membrane permeabilization (MOMP), the export of apoptogenic proteins from mitochondria to the cytosol, and the subsequent formation of macromolecular signaling platforms called apoptosomes (Bock and Tait, 2020). In contrast, extrinsic apoptosis pathways are initiated in response to external stimuli when extracellular ligands bind to transmembrane death receptors that promote the intracellular formation of multi-protein complexes called death-inducing signaling complexes (DISCs) (Dickens et al., 2012; Yang, 2015). The key enzymes that orchestrate the apoptotic death signaling cascades are cysteine-dependent aspartate proteases known as caspases (Julien and Wells, 2017). Caspase zymogens, or procaspases, are inactive precursors with limited enzymatic activity that must undergo proteolytic processing to form active caspase enzymes. The 9 mammalian caspases involved in apoptosis are divided into two groups, initiators and executioners. The initiator caspases differ between the intrinsic versus extrinsic pathways, and the executioner caspases are common between both mechanisms. From an actin cytoskeletal perspective, more is understood about intrinsic mitochondrial pathways (Fig. 5).

Mitochondria are dynamic organelles that synthesize ATP but also produce reactive oxygen species and, upon dysfunction or damage, must be isolated from the healthy population to prevent cellular injury and maintain homeostasis. They exist as tubular chains or individual organelles, and their fusion and fission are controlled by several components of the actin assembly machinery (Ji et al., 2015; Korobova et al., 2014, 2013; Li et al., 2015; Liu et al., 2021; Manor et al., 2015). The actin cytoskeleton additionally appears to monitor the health of the mitochondrial network, as actin filaments cyclically associate with subpopulations of

mitochondria (Moore et al., 2016). The Arp2/3 complex and Formin nucleators cause the rapid formation of cytoskeletal cages that surround and segregate damaged mitochondria during interphase and also promote actin tail assembly and mitochondrial mixing in mitotic cells (Kruppa et al., 2018; Moore et al., 2021). Multiple actin nucleation pathways are involved in these processes. After calcium induction, the Formin INF2 polymerizes actin, whereas following acute mitochondrial depolarization, Cdc42-activated FMNL-family Formins trigger linear actin polymerization, and Rac1-activated WAVE complexes stimulate Arp2/3-mediated branched actin assembly (Fung et al., 2022, 2019). A subset of these pathways may segue into mitophagy, as described above.

Mitochondrial-mediated intrinsic apoptosis occurs in response to a variety of internal stressors, including DNA damage, mitotic defects, and mitochondrial injury. The main arbitrator of the cellular fates that follow stress is the transcription factor and tumor suppressor protein p53 (Hafner et al., 2019; Kastenhuber and Lowe, 2017). In unstressed cells, p53 is negatively regulated through interactions with the ubiquitin ligase Mdm2, which binds p53 to block its transcriptional activity and ubiquitinates p53 to promote its degradation via the proteasome (Haupt et al., 1997; Kubbutat et al., 1997). In response to stressors, p53 is stabilized and activated by stimulus-dependent cofactor-mediated post-translational modifications including serine/threonine phosphorylation and acetylation (Fig. 5). Once stimulated, p53 then behaves as a decision-maker by integrating these signals and orchestrating transcriptional programs that govern a variety of cellular responses like cell cycle arrest, DNA repair, senescence, or apoptosis (Andrysik et al., 2017; Sullivan et al., 2018). Genes that are upregulated by p53 include cell cycle inhibitors and mitochondrial permeabilization factors.

Upon initiation of intrinsic apoptotic signaling, MOMP is driven by pro-apoptotic Bcl-2 family proteins such as Bax and Bak (Fig. 5). In a process coordinated by other Bcl-2 family members, these factors oligomerize into pores in the mitochondrial outer membrane to enable the export of pro-apoptotic proteins from the intermembrane space into the cytosol (Kale et al., 2018; Kalkavan and Green, 2018). Some evidence indicates that pores initially form in only a few mitochondria, and that permeabilization propagates in a wave-like fashion across the mitochondrial network (Bhola et al., 2009; Lartigue et al., 2008; Rehm et al., 2009). However, it is unclear what signals determine the initial area of pore formation.

Cytochrome *c* (cyto *c*) is a key mitochondrial protein that is released into the cytosol through the apoptotic pores (Fig. 5). Once cytosolic, cyto *c* instigates the assembly of apoptosomes, wheel-like macromolecular structures that contain the scaffolding protein Apaf-1 and serve as platforms to mediate the multimerization and activation of initiator procaspase-9 (Dorstyn et al., 2018; Kim et al., 2005; Yuan et al., 2010; Zhou et al., 2015; Zou et al., 1999). Active caspase-9 can interact with apoptosomes, forming holo-apoptosomes that process executioner procaspase-3 and -7 and release them as cleaved caspases (Hu et al., 2014; Li et al., 2017; Rodriguez and Lazebnik, 1999; Yin et al., 2006; Yuan et al., 2011). Those enzymatically active executioner caspases then drive the terminal death pathway by targeting numerous cellular substrates for proteolytic cleavage (Fuentes-Prior and Salvesen, 2004).

Early cytoskeletal studies of apoptosis focused primarily on the actin filament rearrangements and disassembly that take place during the late execution phase and contribute to changes in cell adherence and morphology (Desouza et al., 2012; Gourlay and Ayscough, 2005). Unsurprisingly, manipulating actin dynamics by treating cells with drugs that stabilize (Cioca and Kitano, 2002; Odaka et al., 2000; Posey and Bierer, 1999; Rao et al., 1999; White et al., 2001) or depolymerize (Genescà et al., 2006; Martin and Leder, 2001; Morley et al., 2003; Paul et al., 2002; Suria et al., 1999) actin filaments cause the appearance of many morphological and some biochemical hallmarks of apoptosis. While these studies suggest that alterations in actin dynamics can influence apoptotic signaling cascades, the broadly disruptive nature of such drugs makes it difficult to interpret specific mechanisms of action for the actin cytoskeleton in cell death pathways. Some of the first investigations on actin dynamics in intrinsic apoptosis therefore focused on the roles of the actin turnover machinery, eventually including several proteins with specific activities at mitochondria.

Dying cells undergo dramatic morphological alterations during the execution phase of the apoptotic process (Fig. 4B–C). Actin-binding proteins have been identified as targets for caspase processing, and caspase-mediated cleavage of such structural proteins instigates a loss of focal adhesions and the formation of contractile Myosin-F-actin rings, causing cells to adopt a rounded and shrunken morphology (Charras et al., 2006; Levkau et al., 1998; Rosenblatt et al., 2001). The actin-severing protein Gelsolin is also a caspase target, and full-length Gelsolin may play a pro-survival role under normal circumstances (Ahn et al., 2003; Kusano et al., 2000; Ohtsu et al., 1997). However, Gelsolin cleavage by caspases yields an N-terminal fragment with unregulated F-actin severing activity that reduces the overall stability of the actin cytoskeleton and contributes to the morphological features of apoptosis (Chhabra et al., 2005; Kothakota et al., 1997). Earlier in the intrinsic apoptosis pathway, at around the time of mitochondrial permeabilization, actin and the actin depolymerizing protein Cofilin are recruited to mitochondria (Rehklau et al., 2012; Tang et al., 2006; Wang et al., 2008). Cofilin interacts with the GTPase Drp1 to promote both mitochondrial fission and cyto *c* release (Chua et al., 2003; Hoffmann et al., 2021; Hu et al., 2020; Klamt et al., 2009; Rehklau et al., 2012; Zhu et al., 2006). Taken together, such studies on Gelsolin and Cofilin indicate that the actin disassembly machinery is important for multiple apoptotic events which take place between the time of mitochondrial permeabilization and the overall collapse of the cell.

While actin turnover proteins partake in apoptosis, it eventually became apparent that some actin assembly proteins also function at mitochondria during apoptosis (Fig. 5). WAVE1 has effects on apoptosis and was the first WASP-family protein shown to influence the localization or modification of Bcl-2-family proteins. In hepatocytes, WAVE1 associates with the pro-apoptotic sensitizer protein Bad to promote mitochondrial pore formation (Danial et al., 2003), and in neuronal cells WAVE1 engages the anti-apoptotic protein Bcl-xL to allow mitochondrial recruitment of the pro-apoptotic family member Bax (Cheng et al., 2007). In contrast, in leukemia cells exposed to chemotherapeutic stimuli, WAVE1 interacts with pro-survival Bcl-2 members to reduce apoptotic signaling (Kang et al., 2010). In yet another cell type, fibroblasts, a permanent knockout of WAVE1 does not significantly affect the number of cells that undergo apoptosis following acute DNA damage (King et al., 2021). Why WAVE1, but not other members of the WAVE subfamily, modulates apoptotic

signaling in certain contexts is not understood. Thus, defining the mechanisms by which WAVE1 imparts its cell type-specific effects on Bcl-2 family protein homeostasis requires further investigation.

Another WASP-family protein that functions in apoptosis is JMY. In fact, JMY was discovered to participate in apoptosis a full decade before it was realized to be an actin nucleation factor (Shikama et al., 1999; Zuchero et al., 2009). Under normal cellular growth conditions, JMY can be found in both the cytoplasm and nucleus (Fig. 5). It is regulated in the cytoplasm through interactions with Mdm2, the same ubiquitin ligase that controls p53 (Coutts et al., 2007). Upon genotoxic stress, JMY binds importins and accumulates in the nucleus (Coutts et al., 2009; Zuchero et al., 2012), where it associates with p53, the acetyltransferase p300, and stress response protein STRAP (Demonacos et al., 2001; Shikama et al., 1999). There, JMY can promote pro-apoptotic signaling by enhancing the transcription of *BAX* (Coutts et al., 2009; Shikama et al., 1999).

To systematically evaluate the impact of actin nucleation factors on apoptosis, a panel of human fibroblasts genetically lacking each Arp2/3 complex activator was created and exposed to etoposide, an acute genotoxic agent (King et al., 2021). All of the cell lines underwent rapid p53-dependent apoptosis with two exceptions – JMY knockouts and WHAMM knockouts (King et al., 2021). Given the findings on p53-mediated transcription a decade earlier, the identification of JMY as an important player in apoptosis was not surprising. The recognition of WHAMM also makes sense, since it is the WASP-family member with the greatest homology to JMY. Unexpectedly, however, the effect of JMY as a transcriptional modulator in the nucleus was minimal in these studies. By comparison, the capacity of JMY to act as an Arp2/3-activating factor in the cytoplasm was crucial for its pro-apoptotic function (King et al., 2021). Both JMY and WHAMM likely play multiple roles in intrinsic apoptotic signaling within the cytoplasm, because the propagation of mitochondrial cyto *c* release, processing of initiator caspase-9, and cleavage/activation of executioner caspase-3 are all delayed or blocked in cells lacking JMY, WHAMM, or both family members (King et al., 2021).

The specific functions of JMY and WHAMM became clearer when their localizations in relation to actin filaments, cyto *c*, and the caspases were examined (King and Campellone, 2023). At a single juxtanuclear cluster of permeabilized mitochondria, actin is polymerized and reorganized into a structure called an F-actin-rich territory (Figs. 4 and 5). JMY, WHAMM, and the Arp2/3 complex localize throughout the territory, while the branchpoint stabilizer Cortactin is found at the territory perimeter (King and Campellone, 2023). In contrast, STRAP, a known inhibitor of JMY-mediated actin assembly (Hu and Mullins, 2019), and microtubules, which can repress WHAMM-mediated Arp2/3 activation (Shen et al., 2012), are excluded from the apoptotic F-actin-rich regions. Mechanistically, JMY and WHAMM polymerize actin into dense filamentous territories to mediate the early sequestration of permeabilized mitochondria and cyto *c*, and to create microenvironments that are conducive to apoptosome assembly (King and Campellone, 2023).

The F-actin-rich territories also provide a temporary physical barrier against caspase inhibitors to allow for an efficient activation of the caspase cascade, thus coordinating the

spatiotemporal progression of intrinsic apoptotic signaling (King and Campellone, 2023). By compartmentalizing the transitions from cyto *c* release to apoptosome assembly to caspase activation, the actin cytoskeleton provides a cytoprotective function until active executioner caspases accumulate to levels sufficient to escape the territory and cause a sudden demolition of the rest of the cell (Figs. 4 and 5). The caspases transmit the cell death signal by cleaving a multitude of cytosolic and nuclear proteins including other caspases, kinases, endonucleases, nuclear lamins, and structural proteins. These cleavage events create proteins with gain- or loss-of-function activities that cause the characteristic morphological and molecular features of apoptosis such as cell shrinkage, membrane blebbing, and nuclear fragmentation.

While the roles of actin nucleation factors in intrinsic apoptosis are beginning to emerge, the influence of actin rearrangements on extrinsic pathways is less well understood. Actin filaments affect the aggregation of death receptors and DISC formation (Algeciras-Schimnich et al., 2002; Fais et al., 2005; Luciani et al., 2004), but it is unclear specifically how the actin cytoskeleton regulates signaling progression. Interestingly, the extrinsic and intrinsic pathways appear to be interconnected, as canonical extrinsic caspases can translocate to mitochondria where they promote permeabilization events, release of apoptogenic proteins, and apoptosome-mediated activation of intrinsic caspases (Jost et al., 2009; Li et al., 1998; Luo et al., 1998). This apoptotic amplification loop results in more caspase activation and rapid progression to cell death. It has not been determined how the actin cytoskeleton may modulate this process either.

It is also important to note that the cytoskeleton itself is a target of caspases, as actin has been identified as a substrate for caspase processing. Caspases cleave actin monomers, resulting in two fragments that are incapable of polymerizing into filaments (Mashima et al., 1997, 1995). Transient transfection of the smaller actin fragment can promote the appearance of apoptotic morphologies (Kayalar et al., 1996; Mashima et al., 1999; Utsumi et al., 2003). In the future, it would be interesting to define the relationship between caspase-mediated actin cleavage and F-actin-rich territory breakdown.

Since apoptosis plays pivotal roles in tissue organization, turnover, and homeostasis, further studies on how WAVE1, JMY, WHAMM, and the Arp2/3 complex impact programmed cell death will deepen our understanding of actin nucleation factors in organismal development. Furthermore, the importance of apoptosis in human health and disease is highlighted by the fact that the improper regulation of cell suicide pathways is an underlying contributor to, or even cause of, many pathological conditions, such as tumorigenesis, autoimmunity, and neurodegeneration. Many anti-cancer therapeutics are designed to target various aspects of apoptosis pathways, including transcriptional regulation, Bcl-2-family homeostasis, and caspase activation (Boice and Bouchier-Hayes, 2020; Carneiro and El-Deiry, 2020; Diepstraten et al., 2022). As mentioned above, genes encoding regulators of actin dynamics also frequently exhibit expression changes in cancerous cells (Molinie and Gautreau, 2018). Thus, whereas the functions of WASP-family proteins in cell motility fit with proto-oncogenic or pro-metastasis roles, the findings that some components of the actin nucleation machinery can promote cell death hold promise for their potential as mediators of tumor suppression.

6. The nuclear options

All of the previously discussed functions for the Arp2/3 complex and WASP-family members take place in the cytoplasm, either beneath the inner leaflet of the plasma membrane, at the surface of an organelle, or elsewhere in the cytosol to create a novel cytoskeletal compartment. However, other work in recent years has revealed that the most understudied location of actin – the nucleus – is ripe for new discoveries of cytoskeletal functions. For a long time, the mere presence of actin, as well as its polymerization and organization in the nucleus, were debated (Pederson, 2008). Now, functions for actin in the nucleus are not only accepted, but studies on nucleation factors around and inside the nucleus have become more common.

The nucleus is a dynamic organelle, and the actin cytoskeleton influences multiple nuclear processes (Fig. 6). On the cytoplasmic side, the actin cytoskeleton is mechanically connected to the nucleus through transmembrane complexes that allow it to transfer forces across the nuclear envelope, resulting in changes in morphology and positioning, as well as alterations in chromatin organization and gene expression (Davidson and Cadot, 2021; Lusk and King, 2017; Makhija et al., 2016; Mishra and Levy, 2022; Seirin-Lee et al., 2019; Ulferts et al., 2021). Actin and actin-binding proteins also shuttle between the cytosol and nucleus, where they participate in several functions such as transcription, repair of damaged DNA, and chromatin dynamics, the latter of which takes place during both interphase and mitosis. While Arp2/3 complex subunits and WASP-family members can be found in the nucleus and contain nuclear localization and export signals (Suetsugu and Takenawa, 2003; Taylor et al., 2010; Verboon et al., 2015; Zuchero et al., 2012), their specific roles in these diverse nuclear processes are just beginning to be uncovered.

Nuclear actin contributes to transcriptional regulation by interacting with chromatin remodeling complexes, RNA polymerases, and transcription factors (Hofmann et al., 2004; Hu et al., 2004; Kapoor and Shen, 2014; Miralles and Visa, 2006; Percipalle, 2013; Philimonenko et al., 2004; Vartiainen et al., 2007). WASP, the titular member of the WASP-family, accumulates in the nuclei of differentiating T-helper cells, where it associates with chromatin remodeling complexes to influence histone modifications and transcription through apparently Arp2/3-independent mechanisms (Sarkar et al., 2014; Taylor et al., 2010). Alterations in chromatin organization and gene expression are also found in cells from patients with Wiskott-Aldrich Syndrome (Sadhukhan et al., 2014; Sarkar et al., 2014).

The more ubiquitously-expressed family members N-WASP, WAVE1, WASH, and JMY also participate in transcriptional regulation (Fig. 6). N-WASP was the first to be directly associated with transcription, as it interacts with RNA polymerase II to affect gene expression, and the Arp2/3-activating capacity of N-WASP appears to be important for its function in transcriptional regulation (Suetsugu and Takenawa, 2003; Wu et al., 2006). More recently, N-WASP was found to be required for RNA polymerase II and nuclear actin clustering, which drives serum-induced transcriptional programs (Wei et al., 2020). In *Xenopus*, WAVE1 localizes to nuclei and impacts the expression of developmental genes during nuclear reprogramming and embryogenesis (Miyamoto et al., 2013, 2011). Whether WAVE1 or the other WAVEs play similar roles in mammals is unclear. In mouse

hematopoietic stem cells, WASH interacts with nucleosome remodeling complexes to affect chromatin accessibility and gene expression (Xia et al., 2014). JMY, as stated above, was discovered as a p53 and p300 cofactor that increases transcription of the pro-apoptotic gene *BAX* (Shikama et al., 1999). To further define the connection between the actin nucleation machinery and transcriptional regulation, it would be interesting to decipher which WASP-family members associate with different RNA polymerase complexes during promoter-specific gene expression under distinct experimental conditions.

The actin cytoskeleton may also alter gene expression indirectly by controlling intranuclear organization (Fig. 6). Evidence from *Drosophila* indicates that WASH interacts with nuclear lamins to govern the global architecture of the nucleus, with the depletion or expression of mutant forms of WASH leading to a multitude of nuclear deformation phenotypes (Verboon et al., 2015). The observation that WASH depletion also changes histone modification patterns suggests that chromatin accessibility may be altered, opening new avenues of investigation into how actin assembly factors control gene expression via several distinct mechanisms. It also remains to be seen if the actions of WASH in nuclear organization involve the actin cytoskeleton and whether the findings in flies are echoed in mammalian systems.

One of the most exciting new nuclear functions for actin nucleators, nucleation-promoting factors, and even myosin motor proteins has come from studies of DNA damage and repair (Caridi et al., 2019). Technical advances using fluorescent fusion proteins to visualize nuclear G- and F-actin spurred the discovery of actin filament formation inside the nucleus in response to several types of stress (Belin et al., 2014; Melak et al., 2017). Following DNA damage, the nucleators Formin-2, Spire1, and Spire2 assemble nuclear actin filaments (Belin et al., 2015), suggesting an important role for nucleoplasmic actin polymerization in recognizing, reorganizing, and/or repairing damaged DNA. Studies in *Drosophila* and mammalian cells next showed that nuclear DNA damage responses also rely on the Arp2/3 complex (Fig. 6).

Chemical inhibition, transient depletion, or permanent deletion of the Arp2/3 complex leads to significant defects in the cellular reactions to DNA damage, such as the apoptotic responses described above and DNA repair pathways (Caridi et al., 2018; Schrank et al., 2018). To enable DNA repair in both insect and mammalian cells following ionizing radiation, endonuclease activation, or exposure to other genotoxic agents, the Arp2/3 complex polymerizes actin in the nucleus (Caridi et al., 2018; Schrank et al., 2018). In *Drosophila* cells, the Arp2/3 complex assembles actin in the vicinity of heterochromatic double-stranded DNA (dsDNA) break sites to provide tracks for their myosin-dependent relocalization to the nuclear periphery where repair takes place (Caridi et al., 2018). This movement appears to involve the *Drosophila* orthologs of WAVE and WASH, but not WASP, and depletion of the former factors or the Arp2/3 complex in larvae causes genomic instability and aneuploidy (Caridi et al., 2018).

In contrast to the clear findings in the fly model, the identities of the WASP-family proteins that enable Arp2/3-dependent DNA repair in mammalian cells are debated. In U2OS osteosarcoma cells, WASP was reported to cooperate with the Arp2/3 complex for clustering

DNA containing double-stranded breaks (Schrank et al., 2018). However, the expression of WASP in non-hematopoietic cells is controversial, and in other human cell lines WASH was found to promote repair of etoposide-induced DNA breaks by interacting with components of the non-homologous end joining machinery (Wang et al., 2022).

Despite this uncertainty upstream of Arp2/3, it is noteworthy that the complex is not only important for repair of the severe damage that is created by acute experimental manipulations like radiation exposures or chemical treatments. The Arp2/3 complex is also crucial for repair of endogenously-generated DNA breaks in mouse fibroblasts (Haarer et al., 2023). This function of the Arp2/3 complex in preventing the accumulation of damaged DNA in mammalian cells is emphasized by the findings that deletion of the complex from mouse fibroblasts results in dsDNA breaks, chromosome segregation abnormalities, chromatin fragments that incorporate into micronuclei, and ultimately cellular senescence (Haarer et al., 2023).

Some of the latter observations are reminders that the Arp2/3 complex has key functions not just during interphase, but throughout the cell cycle. For example, complexes containing the ArpC1B isoform are important for the progression of G1 to S phase (Molinie et al., 2019). This transition appears to be dependent on the WAVE complex, although other WASP-family members may also contribute (Molinie et al., 2019). Actin and Arp2/3 influence chromosome dynamics during meiosis and mitosis as well. Actin filaments are found at meiotic spindles in mouse oocytes where they control spindle migration and affect chromosome alignment and segregation (Azoury et al., 2008; Mogessie and Schuh, 2017). The Arp2/3 complex directs microtubule spindle positioning in mouse oocytes via actin filament-dependent cytoplasmic streaming (Sun et al., 2011b; Yi et al., 2011). WAVE2, JMY, and WHAMM seem to be important in this system, as depletion of each factor leads to changes in Arp2/3 localization as well as alterations in spindle positioning, stability, and migration (Huang et al., 2013; Jo et al., 2021; Liu et al., 2012; Sun et al., 2011a, 2011c). The Arp2/3 complex also localizes to F-actin structures at centrosomes in multiple mammalian cell types, and inhibition of the complex reduces centrosomal actin levels and perturbs microtubule spindle assembly (Farina et al., 2019, 2016; Inoue et al., 2019; Plessner et al., 2019). Further, deletion of the complex causes chromosome segregation defects and increased micronucleus formation (Caridi et al., 2018; Haarer et al., 2023). While it appears that the Arp2/3 complex is a major player in multiple aspects of meiosis and mitosis, the mechanisms underlying how the specific WASP-family members and their upstream regulators coordinate these processes remain less understood. The pathways of nucleation factor recruitment and activation that drive proper chromatin dynamics and nuclear division will hopefully be uncovered in the future.

When considering the functions of actin dynamics in health and disease, it goes without saying that the inability to repair damaged DNA or to properly segregate chromosomes would expectedly have major deleterious effects on cells and, consequently, organisms. The relationships between aneuploidy and cancer are well discussed (Gordon et al., 2012; Li and Zhu, 2022), as are the connections between senescence and the pathologies of organismal aging (Di Micco et al., 2021; Gasek et al., 2021; Gorgoulis et al., 2019; McHugh and Gil, 2018). Furthermore, alterations in the concentration and organization of nuclear actin

have been linked to cancers, neurodegenerative diseases, and myopathies. Shifts in the balance between cytosolic and nuclear actin pools can affect tumorigenesis, where increased levels of nuclear actin contribute to the ability to escape quiescence and acquire cancerous characteristics (Fiore et al., 2017; Spencer et al., 2011). In addition, the accumulation of F-actin rods in the nuclei of neurons or muscle cells is a common cell stress response and has been observed in samples from patients with neurodegenerative and muscle disorders (Bamburg et al., 2010; Bathe et al., 2007; Clarkson et al., 2004; Costa et al., 2004; Domazetovska et al., 2007; Minamide et al., 2000; Munsie et al., 2011).

The discoveries of actin cytoskeletal functions in the nucleus provide important contributions to discussions about the potentially opposing roles of actin nucleation factors in pro-metastasis (motility) and pro-survival (autophagy) mechanisms versus anti-proliferative (apoptosis, senescence) processes. The observations that DNA repair pathways and proper transcriptional responses to environmental insults can safeguard cells against the mutations and genomic instability that lead to cancer further support the tumor suppressive perspective. Therefore, continuing to define the activities of the actin assembly machinery in aspects of nuclear biology like chromatin dynamics, gene expression, and DNA repair could offer new insights into tumorigenesis and provide innovative means for understanding and modulating cellular stress response mechanisms.

7. Conclusion

The Arp2/3 complex and WASP-family proteins are well-established players in driving cell motility and shaping the endolysosome system. The more recent emergence of their functions in autophagy, apoptosis, and chromatin dynamics has created new branching-off points for experimental exploration. Undoubtedly, there is still much to be learned about the molecular, cellular, and organismal functions of the nucleation factors. By characterizing the intersections between the actin assembly machinery and the diverse macromolecular complexes that govern proteostasis, apoptotic pathways, and nuclear organization, we will gain a more complete picture of the mechanisms underlying such fundamental cellular activities. Finally, the study of natural variants, pathogenic mutations, alternatively-spliced isoforms, combinatorial complexity, and post-translational modifications also holds great promise for the future. Deciphering how such structural alterations in the Arp2/3 complex and WASP-family members precisely affect their functions in specific cellular processes will provide great clarity in our understanding of human health and disease.

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Abbreviations:

Arp2/3	Actin-related protein 2/3
ALS	Autophagosome-Lysosome System

Cyto *c*	Cytochrome *c*
DISC	Death-Inducing Signaling Complex
JMY	Junction Mediating and regulatorY protein
MOMP	Mitochondrial Outer Membrane Permeabilization
N-WASP	Neuronal Wiskott-Aldrich Syndrome Protein
UPS	Ubiquitin-Proteasome System
WASP	Wiskott-Aldrich Syndrome Protein
WASH	WASP and SCAR Homolog
WAVE	WASP family VErprolin homolog
WHAMM	WASP Homolog associated with Actin, Membranes, and Microtubules
WHIMP	WAVE Homology In Membrane Protrusions

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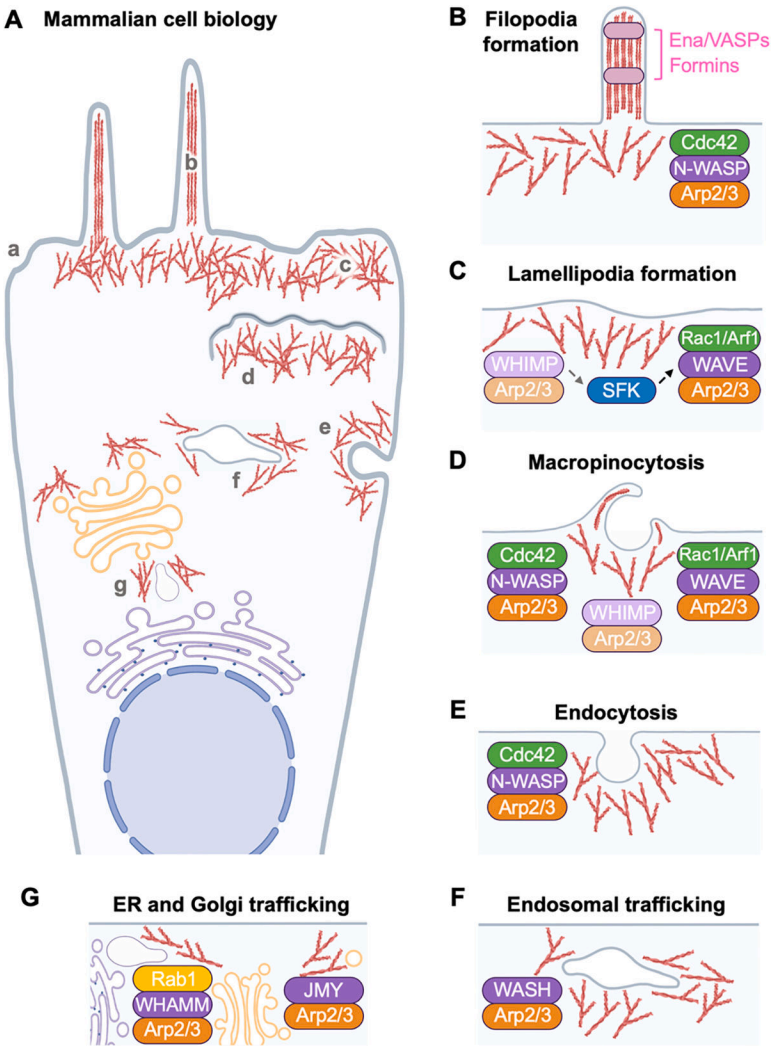

Fig. 1.

Cellular functions for the Arp2/3 complex and WASP-family actin nucleation factors. (A) Many aspects of mammalian cell biology are impacted by the actin cytoskeleton. F-actin structures are assembled in (a) a generic mammalian cell at (b) filopodia, (c) lamellipodia, (d) sites of membrane ruffling or macropinocytosis, (e) sites of endocytosis, (f) tubular endosomes, and (g) the ER-Golgi intermediate compartment (ERGIC) and Golgi, among other locations. (B) Filopodia may form following activation of a Cdc42-N-WASP-Arp2/3 pathway in some experimental systems, but filopodial biogenesis generally involves multiple nucleation and elongation factors from the Formin and Ena/VASP protein families. (C) Lamellipodia protrude via a highly conserved Rac1/Arf1-WAVE-Arp2/3 signaling mechanism to allow for cell migration. Protrusions in mice may involve WHIMP-Arp2/3 interactions and Src-family kinase (SFK) activation (dashed arrows). The muted color of WHIMP indicates its presence in only a subset of animals. (D) Macropinocytosis at locations of dorsal membrane ruffling can be stimulated by several WASP-family members and small G-proteins. (E) Endocytosis involves N-WASP-Arp2/3-mediated actin assembly and membrane constriction. (F) Endosomal tubule scission and cargo sorting is

controlled by WASH-Arp2/3-assembled actin filaments. (G) At the ERGIC and *trans*-Golgi network, WHAMM and JMY activate the Arp2/3 complex to promote membrane tubulation or transport. The small G-protein Rab1 recruits WHAMM to membranes but limits its nucleation-promoting activity. Note that other G-proteins and kinases (not shown) can activate the WASP-family members by multiple mechanisms, and organelles/proteins are not drawn to scale.

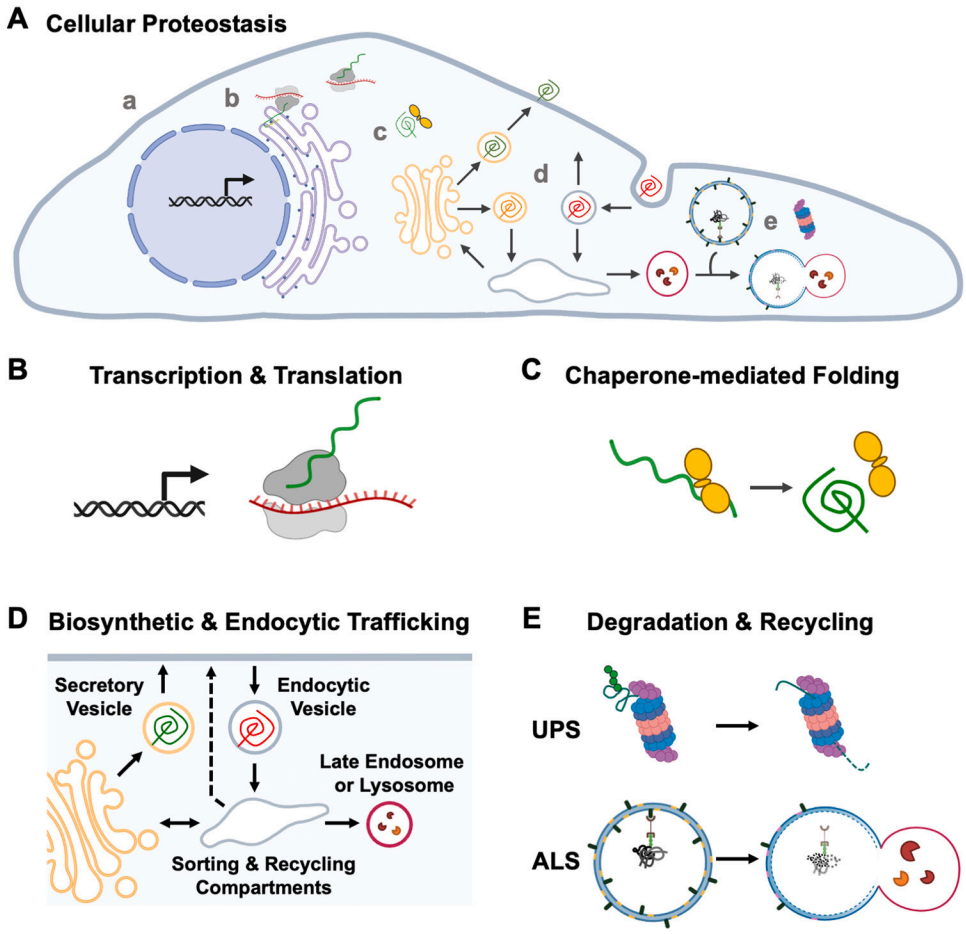

Fig. 2.

Cellular processes that impact proteostasis. (A) Cellular proteostasis is maintained through the coordinated synthesis and turnover of proteins. In (a) a generic mammalian cell, the processes that influence proteostasis include (b) transcription and translation, (c) protein folding, (d) membrane protein trafficking, and (e) protein degradation. (B) Protein production is regulated at the gene expression level in the nucleus, where transcription is modulated by internal and external stimuli. It is also controlled at the polypeptide synthesis level in the cytoplasm, where translation of mRNA by ribosomes in the cytosol or at the ER creates new proteins. Note that co/post-transcriptional regulation (e.g., splicing, nucleo-cytoplasmic transport) and post-translational modifications (e.g., phosphorylation, ubiquitination) are not depicted. (C) During and after synthesis, polypeptide folding may be mediated by chaperone proteins that help the protein achieve its final functional structure. Molecular chaperones are also vital in quality control and preventing the accumulation of toxic protein species, as the chaperones can attempt to refold a misfolded protein, modulate its aggregation, or direct it towards a degradation pathway if it cannot adopt a satisfactory conformation. (D) Proteins are sorted and trafficked to their appropriate destinations through the biosynthetic (e.g., conventional secretory/anterograde) and endolysosome (e.g., endocytic/retrograde) systems. They may be directed to different organelles or structures within the cytoplasm, and to or from the plasma membrane. (E) Proper protein levels are

maintained by degradation pathways that remove proteins which are misfolded, no longer needed, nonfunctional, or targeted for elimination. Degradation occurs through two primary mechanisms: the ubiquitin-proteasome system (UPS) or the autophagosome-lysosome system (ALS). Both systems can be used to degrade ubiquitinated proteins. Proteasome-mediated proteolysis requires protein unfolding, whereas autophagosomes participating in selective autophagy can accommodate larger protein aggregates, defective organelles, or microbial pathogens prior to digestion by lysosomes.

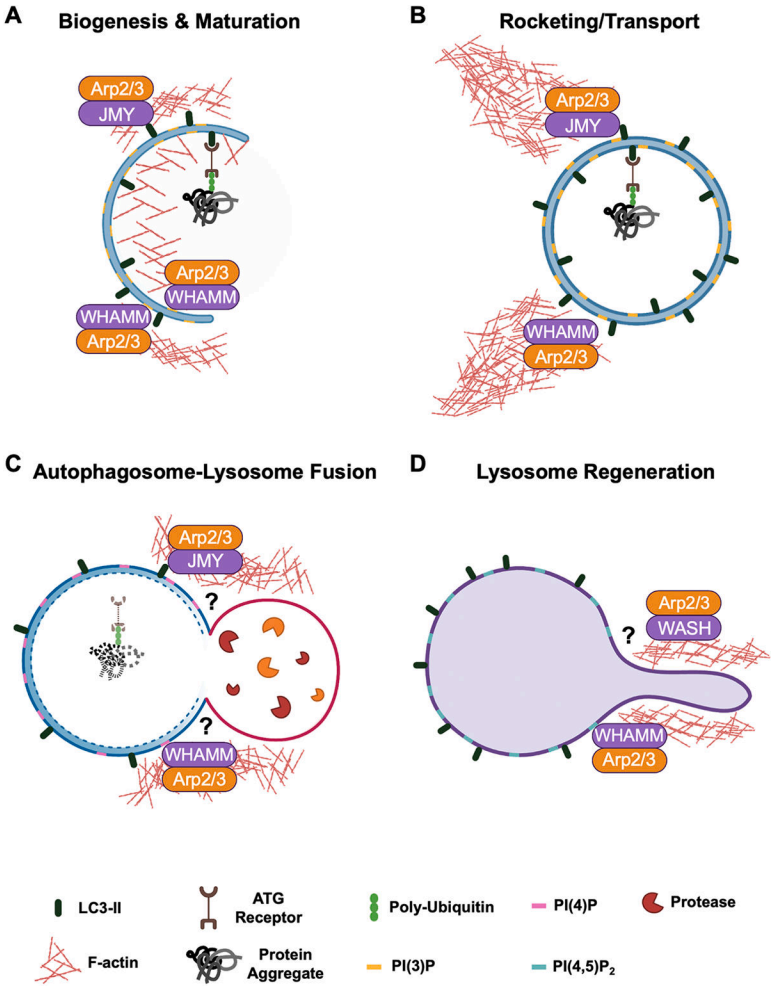

Fig. 3.

Multiple steps of autophagy rely on actin nucleation factors. (A) During autophagosome biogenesis, actin is polymerized inside and outside of the PI(3)P-rich phagophore (nascent autophagosome) to shape the membrane and allow incorporation of lipidated LC3. WHAMM is recruited to forming autophagosomes through its interaction with the phospholipid PI(3)P, while JMY is localized by binding LC3. Both WHAMM and JMY activate the Arp2/3 complex. (B) Autophagosome movement is driven by the force generated by F-actin comet tails derived from JMY- and WHAMM-mediated Arp2/3 complex activation. (C) Autolysosomes contain WHAMM and JMY (and Cortactin; not shown) on their surface, although the extent to which the nucleation factors affect the autophagosome-lysosome membrane fusion step (?) are not well understood. (D) During lysosome regeneration, WHAMM is recruited by $PI(4,5)P_2$ on the autolysosome, where it activates Arp2/3-mediated actin assembly to promote membrane tubulation. WASH is also localized to tubules, although its mechanisms of recruitment to specific autolysosomal membranes (?) is unclear. Collaboration with microtubules, motor proteins, and scission factors (not depicted) enables the reformation of lysosomes.

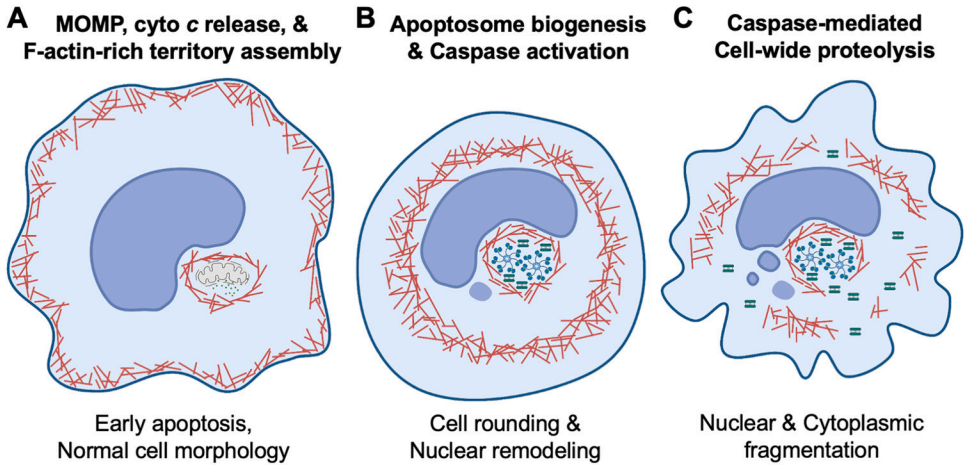

Fig. 4.

F-actin rearrangements and cellular morphogenesis during apoptosis. (A) Early in intrinsic apoptosis, mitochondrial outer membrane permeabilization (MOMP) enables cytochrome *c* (cyto *c*) release into the cytosol, and F-actin is polymerized and reorganized at a juxtanuclear site containing the permeabilized mitochondria. These F-actin-rich territories promote the sequestration of cytosolic cyto *c* and facilitate interactions between apoptosome components. (B) As apoptosis progresses, cell rounding and chromatin condensation occur. The juxtanuclear F-actin-rich territory functions as a subcellular compartment that clusters multiple pro-apoptotic constituents and serves to couple the apoptosome biogenesis process to the activation of the caspase cascade. (C) Executioner caspases clustered within the territories are physically protected from caspase inhibitors and become enzymatically active. They eventually reach quantities that can overcome the inhibitors, escape the territory, and execute a sudden breakdown of the cell leading to the characteristic morphological features of apoptosis such as nuclear fragmentation and cortical membrane collapse. Note that the stoichiometry of organelles and macromolecules shown in the figure (e.g., mitochondria, cyto *c*, apoptosomes, caspases) are not drawn to scale.

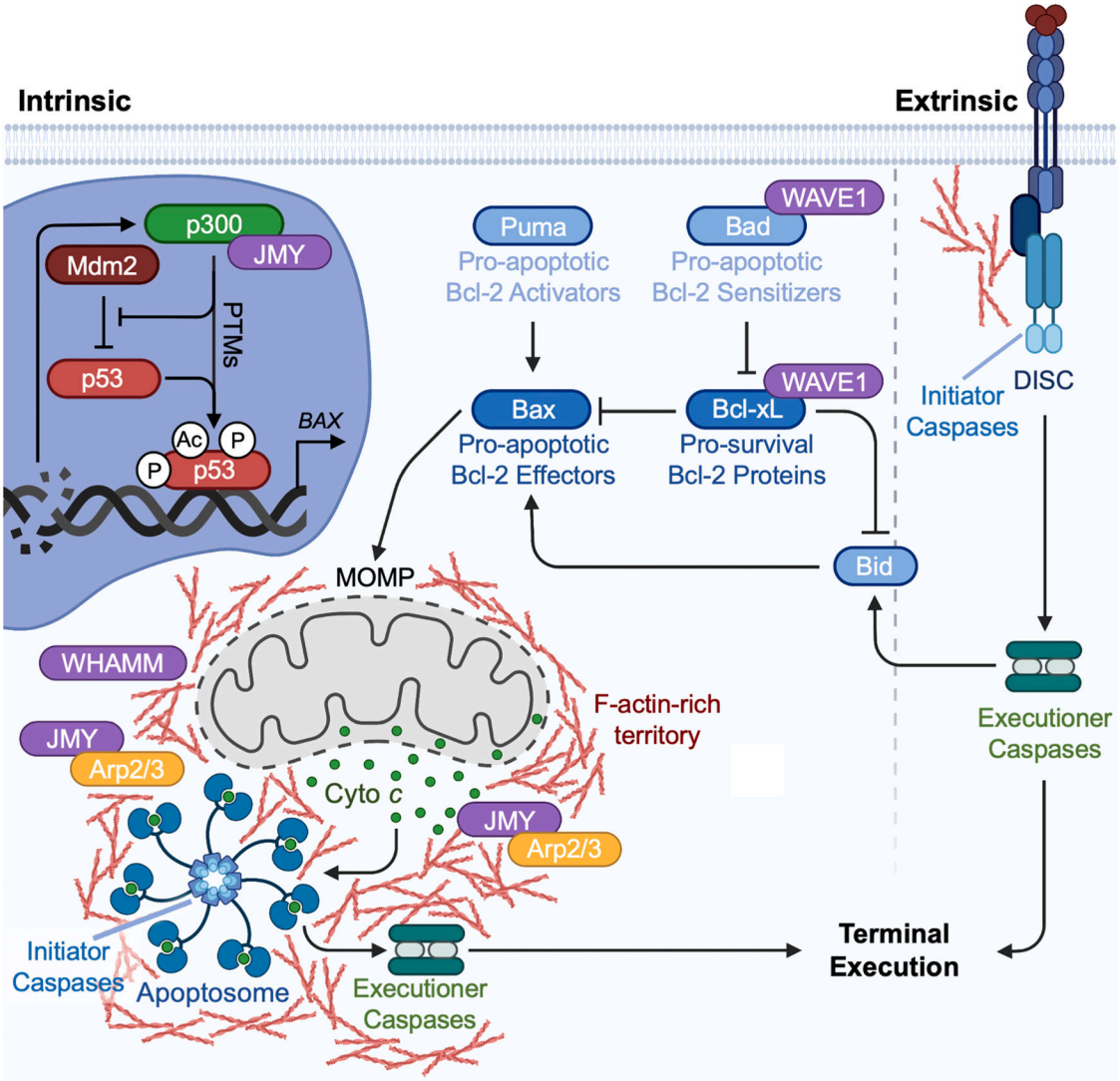

Fig. 5.

Intrinsic and extrinsic apoptosis pathways. Apoptosis is initiated by either intrinsic (left) or extrinsic (right) pathways that converge on a terminal execution program. Under normal conditions, p53 is negatively regulated by Mdm2. Intrinsic stressors, such as DNA damage, are detected by cofactors that promote p53 stabilization and activation through post-translational modifications (PTMs) including phosphorylation (P) and acetylation (Ac). p53 then binds response elements of specific target genes to promote their transcription. JMY can promote cell death by enhancing the p53-mediated transcription of *BAX*, which encodes a pro-apoptotic Bcl-2-family effector protein. The intrinsic pathway is driven by Bcl-2 effector oligomerization, resulting in MOMP and the release of the apoptogenic factor cyto *c* from the mitochondrial intermembrane space. WAVE1 functions in intrinsic apoptosis by influencing the localization or modification of multiple Bcl-2-family proteins. JMY and WHAMM activate the Arp2/3 complex to polymerize actin into a dense F-actin-rich territory surrounding the juxtanuclear site of mitochondrial permeabilization. This territory creates a microenvironment where cytosolic cyto *c* is sequestered and can efficiently

trigger the assembly of Apaf-1 into mature apoptosomes. The apoptosomes bind and activate initiator procaspases, and the resulting active initiator caspases (e.g., caspase-9) process executioner procaspases. The resulting active executioner caspases (e.g., caspase-3) accumulate within the territory, which provides temporary physical protection against caspase inhibitors. The F-actin-rich territory thus coordinates the spatiotemporal progression of intrinsic apoptotic signaling from the step of apoptosome biogenesis to the activation of the caspase cascade. Active executioner caspases eventually escape the territory using an unknown mechanism and go on to cleave many proteins to drive terminal execution. The extrinsic pathway is initiated by death receptor ligation at the plasma membrane, causing the recruitment of adaptor proteins and initiator procaspases to form the death-inducing signaling complex (DISC). Actin influences the aggregation of death receptors and is important for DISC formation. Upon recruitment to the DISC, initiator caspases are activated and can cleave executioner caspases. The intrinsic and extrinsic pathways are interconnected, as active caspases cleave the Bcl-2 effector Bid to an active form that can stimulate MOMP. Note that the stoichiometry of organelles and macromolecules shown in the figure (e.g., mitochondria, apoptosomes, proteins) are not drawn to scale.

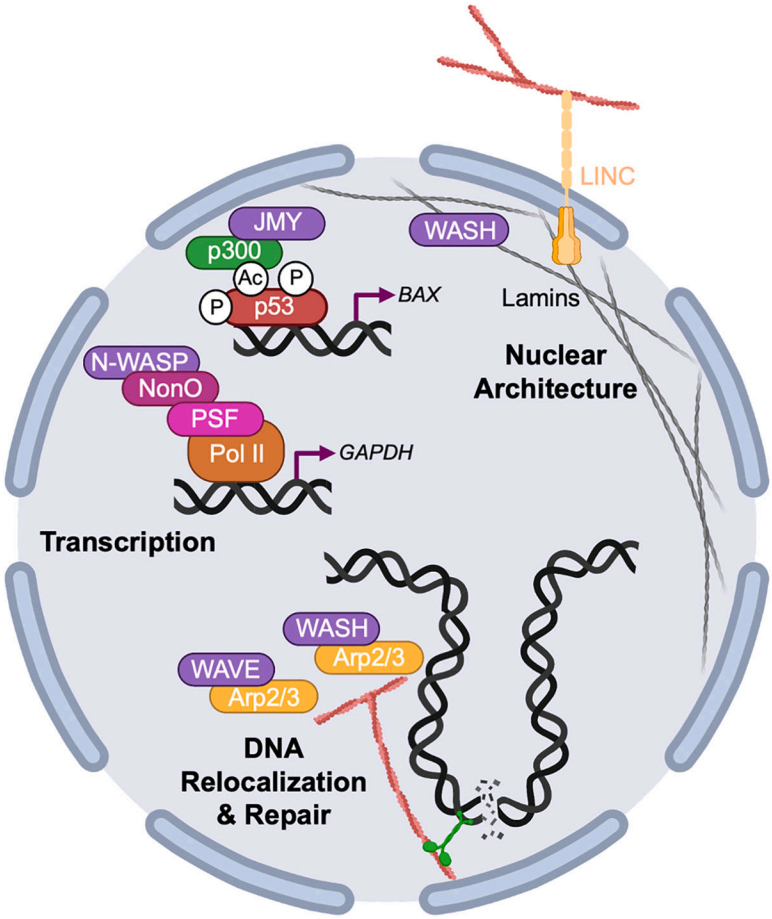

Fig. 6.

Nuclear architecture, transcription, and DNA repair are controlled by actin nucleation factors. The actin cytoskeleton and actin-binding proteins influence nuclear architecture, organization, and function. The cytoplasmic actin cytoskeleton is connected to the nucleus through transmembrane complexes that allow it to transfer mechanical forces to the nuclear envelope, resulting in changes in nuclear morphology and positioning. WASH can interact with nuclear lamins to change nuclear architecture and thereby alter chromatin organization and gene expression. N-WASP and JMY more directly contribute to transcriptional regulation by interacting with chromatin remodeling complexes, RNA polymerases, and transcription factors. WASH and WAVE collaborate with the Arp2/3 complex and myosin motor proteins to drive the relocalization of damaged DNA to sites of repair in the nuclear periphery.

Table 1

Functions for the ubiquitous mammalian WASP-family proteins in cellular homeostasis and stress responses.

Proteostasis		
Autophagy		
Subcellular process	*WASP-Family Member*	*References*
Autophagosome biogenesis	WASH	Xia et al. (2013) Zavodszky et al. (2014)
	WHAMM	Kast et al. (2015) Mathiowetz et al. (2017)
	JMY	Coutts and La Thangue (2015)
Autophagosome rocketing	WHAMM	Kast et al. (2015)
	JMY	Hu and Mullins (2019)
Autolysosome regeneration	WASH	Monfregola et al. (2010) Ryder et al. (2013)
	WHAMM	Dai et al. (2019) Wu et al. (2021)
Mitochondrial homeostasis	WAVE complex(es)	Fung et al. (2022)
Endocytosis		
Endocytic pit formation	N-WASP	Akamatsu et al. (2020) Jin et al. (2022) Serwas et al. (2022)
Cargo internalization	N-WASP	Benesch et al. (2005) Innocenti et al. (2005) Merrifield et al. (2004) Bu et al. (2010)
Endolysosomal Trafficking		
Endocytic vesicle rocketing	N-WASP	Taunton et al. (2000) Benesch et al. (2002) Southwick et al. (2003)
Endosomal cargo sorting	WASH	Derivery et al. (2009) Gomez and Billadeau (2009) Duleh and Welch (2010) Zech et al. (2011) Park et al. (2013)
	N-WASP	Juin et al. (2019)
Lysosomal maintenance	WASH	Gomez et al. (2012) Courtland et al. (2021) Park et al. (2013)
Secretory Trafficking		
Golgi-ER transport	N-WASP	Luna et al. (2002) Matas et al. (2004)
ER-Golgi transport	WHAMM	Campellone et al. (2008b) Russo et al. (2016)
trans-Golgi transport	JMY	Schlüter et al. (2014)
Apoptosis		
Intrinsic Apoptosis		
Pro-apoptotic transcription	JMY	Shikama et al. (1999) Demonacos et al. (2001) Coutts et al. (2009)
Pro-MOMP Bcl-2 functions	WAVE1	Danial et al. (2003) Cheng et al. (2007)
Anti-MOMP Bcl-2 functions	WAVE1	Kang et al. (2010)

Caspase activation	JMY	King et al. (2021) King and Campellone (2023)
	WHAMM	King et al. (2021) King and Campellone (2023)
Nuclear/Chromatin Biology		
Gene Expression		
Pol II-mediated transcription	N-WASP	Suetsugu and Takenawa (2003) Wu et al. (2006) Wei et al. (2020)
Pluripotent reprogramming	WAVE1	Miyamoto et al. (2011) Miyamoto et al. (2013)
Chromatin remodeling	WASH	Xia et al. (2014)
DNA Repair		
dsDNA break relocalization	WASH/WAVE?	Caridi et al. (2018) Schrank et al. (2018)
dsDNA break repair	WASH	Wang et al. (2022)
Chromosome Partitioning		
Spindle organization	JMY	Sun et al. (2011a) Liu et al. (2012)
	WAVE1	Sun et al. (2011c) Liu et al. (2012)
	WHAMM	Huang et al. (2013) Jo et al. (2021)
Centrosomal dynamics	WASH	Farina et al. (2016) Farina et al. (2019)