https://doi.org/10.1016/j.arr.2020.101021

Roles of the actin cytoskeleton in aging and age-associated diseases

Wing-Fu Lai[1,2,3*], Wing-Tak Wong[3]

1. School of Pharmaceutical Sciences, Shenzhen University, P. R. China
2. School of Life and Health Sciences, The Chinese University of Hong Kong, Shenzhen, P. R. China
3. Department of Applied Biology and Chemical Technology, Hong Kong Polytechnic University, Hong Kong Special Administrative Region, P. R. China

* E-mail: rori0610@graduate.hku.hk

Abstract

The integrity of the cytoskeleton is essential to diverse cellular processes such as phagocytosis and intracellular trafficking. Disruption in the organization and dynamics of the actin cytoskeleton leads to age-associated symptoms and diseases, ranging from cancer to neurodegeneration. In addition, changes in the integrity of the actin cytoskeleton disrupt the functioning of not only somatic and stem cells but also gametes, resulting in aberrant embryonic development. Strategies to preserve the integrity and dynamics of the cytoskeleton are, therefore, potentially therapeutic to age-related disorders. The objective of this article is to revisit the current understanding of the roles played by the actin cytoskeleton in aging, and to review the opportunities and challenges for transition of basic research to intervention development. It is hoped that, with the snapshot of evidence regarding changes in actin dynamics with advanced age, insights on anti-aging medicine can be attained for future research.

Keywords

Actin; aging; cytoskeleton; longevity; tissue homeostasis

1. Introduction

Actin is a highly conserved protein, and is the major component of the microfilament, which has a diameter of 4-6 nm (Davidson and Wood, 2016; Letort et al., 2015). Upon polymerization of actin monomers, namely G-actin, F-actin is generated. Although G-actin can be polymerized into F-actin in the absence of actin-binding proteins (ABPs) (**Fig. 1**) (Park et al., 2018), the production of thick bundles of actin filaments necessitates the involvement of ABPs (e.g., α-actinin and gelsolin), and is driven by ATP hydrolysis. Apart from this, actin-associated proteins (e.g., ankyrin and spectrin) help anchor actin filaments to cellular organelles or the plasma membrane (Aydin et al., 2018; Percipalle, 2009). In vertebrates, actin exists in α-, β-, and γ-isoforms. These isoforms usually differ by only few amino acids (Lee and Dominguez, 2010). These differences occur largely at around the N terminus (Lee and Dominguez, 2010). Till now, with advances in structural characterization techniques, more than 80 structures of actin have been reported in the literature (Dominguez and Holmes, 2011). Many of these structures have been attained in forms of complexes with either ABPs or small molecules (Dominguez and Holmes, 2011). Structurally, the actin monomer is flat, and can fit into a rectangular prism with dimensions of 55 Å × 55 Å × 35 Å (Cleuren and Boonstra, 2012). The polypeptide chain of the actin monomer, comprising 375 amino acids, is generally folded into two major domains (Cleuren and Boonstra, 2012). These two domains have very different sizes under electron microscopy (Cleuren and

Boonstra, 2012). They are named small and large domains. Due to their different locations with the actin filament, they are also called inner and outer domains.

In cells, actin filament nucleation and elongation factors involve in regulating the *de novo* formation of actin filaments (Campellone and Welch, 2010; Dominguez, 2010). Examples of these factors include the Arp2/3 complex, Spire, VopL/VopF, TARP, and formins. Except formins that use the formin homology 2 (FH2) domain to interact with actin (Goode and Eck, 2007), other factors interact with actin via the WASP-homology 2 (WH2) domain (Paunola et al., 2002). Upon interaction with actin, these factors control the location and time of actin polymerization. Apart from the WH2 domain, another domain commonly found in ABPs is the actin-depolymerizing factor homology (ADF-H) domain. This domain is found in five classes of proteins (Paavilainen et al., 2007). One class of proteins is ADF/cofilin, which possesses a single ADF-H domain. It binds to both monomeric and filamentous actin, and inhibits spontaneous nucleotide exchange (Andrianantoandro and Pollard, 2006). It also causes the disassembly of aged actin filaments in cells (Okreglak and Drubin, 2007). Another class of proteins is twinfilin, which contains two ADF-H domains separated by a short linker region (Paavilainen et al., 2004). It binds to monomeric actin or the barbed end of the actin filament, and can prevent the assembly of monomeric actin into the filament end (Helfer et al., 2006). Apart from ADF/cofilin and twinfilin, other proteins that contain the ADF-H domain include the glia maturation factor, Abp1/drebrin, and coactosin (Davidson and Wood, 2016; Lee and Dominguez, 2010). The functions of these proteins, however, are elusive at the moment.

Physiologically, the actin cytoskeleton is the primary cellular machinery for the generation of protrusive forces (through the use of the energy of actin polymerization (Castellano et al., 2001)) and also contractile forces (through the sliding of bipolar filaments of myosin II along actin filaments (Amberg et al., 2012)). The actin cytoskeleton, therefore, involves in various aspects of cell biology, ranging from whole cell migration and phagocytosis to exocytosis. Apart from this, actin is the target of caspases during apoptosis, and experiences oxidative damage when cellular stress occurs (Davidson and Wood, 2016). Because its maintenance and functioning involve a multitude of proteins, the actin cytoskeleton is highly susceptible to disruption caused by aging. In fact, aging has been found to cause not only changes in the expression of actin but also disruption in the organization and dynamics of the actin cytoskeleton, leading to the occurrence of age-related disorders.

2. Causes of changes in actin expression

Aging can alter the organization and dynamics of the actin cytoskeleton by changing actin expression (Deindl et al., 2002; Moshier et al., 1993). This has been shown by an earlier study (Moshier et al., 1993), which compared the expression of β-actin in rats with different ages (6 months, 12 months, and 24 months). Compared to the expression level in 6-month old rats, the level in 12-month and 24-month old rats reduces by 23% and 37%, respectively. A similar observation of the variation in the level of β-actin expression has been found in Kuruma shrimp at different developmental life stages (Sellars et al., 2007). One possible mechanism that mediates age-associated changes in actin expression is the alternation in the hormonal status caused by aging (**Fig. 2**). Examples of hormones known to affect actin expression include tumor necrosis factor-α (TNF-α), insulin, 17β-estradiol, angiotensin II, hydrocortisone, triiodothyronine, and sex-dependent hormones (Gorzelniak et al., 2001; Verma and Shapiro, 2006). Many of

these hormones are changed, in terms of secretion and clearance, with advanced age. For instance, insulin secretory defects occur in aged people (Bruunsgaard et al., 2000), and are attributed to the increase in the rate of glucose intolerance. In addition, compared to that in the young counterparts, the circulating level of TNF-α in elderly subjects is often higher (Chang and Halter, 2003). These alternations in hormonal secretion may lead to changes in action expression.

The nutritional and activity status of an individual may affect the level of actin expression, too. The relevance of the nutritional status to actin expression has been observed in rats (Yamada et al., 1997), in which the expression of β-actin in the pancreas and upper digestive tract has been found to be altered upon fasting. The effect of physical activity on actin expression has also been reported by Jemiolo and Trappe (2004), who examined the expression level of β-actin in muscle biopsies taken from the gastrocnemius of human subjects before and after treadmill running. Because the nutritional and activity status is known to be changed with advanced age, this causes changes in actin expression in the elderly population, ultimately disrupting the functioning and integrity of the actin cytoskeleton.

3. Actin cytoskeleton as a mediator of aging and associated diseases

Apart from actin expression, age-associated disruption has been reported on the actin cytoskeleton *per se* (Franklin-Tong and Gourlay, 2008). In the past, studies on the organization and dynamics of the actin cytoskeleton were predominately performed on yeasts (Mishra et al., 2014). This is partly because *ACT1* is the single actin gene in yeasts (Amberg et al., 2012). It can be easily mutated to enable the generation of diverse actin mutants for research purposes (Amberg et al., 2012). In addition, yeasts can grow in either the fermentative or non-fermentative state. Mutations that disrupt the mitochondrial function, and hence are lethal to other eukaryotic cells, can be possibly studied in yeast cells (Amberg et al., 2012). The dominion of the use of yeast cells in actin research has, however, been changed over the last several decades, with an increasing number of studies on actin carried out in mammalian cells or even stem cells. This has extended our understanding of the roles of the actin cytoskeleton in aging at the cellular level.

Since the multifunctionality of actin is based predominately on three pillars: chaperonin-assisted folding (Balchin et al., 2018), interactions with actin-binding proteins (ABPs) (Pollard, 2016), and post-translational modifications (PTMs) (Terman and Kashina, 2013). Disruption in any of them during the aging process may hamper the proper functioning of the cell. Besides somatic cells, changes in the integrity of the actin cytoskeleton may disrupt the functioning of stem cells and progenitor cells (Sharpless and Depinho, 2007). The underlying mechanism has been elucidated by Kasper *et al.* (2009), who studied the functional and proteomic alternations in mesenchymal stem cells (MSCs) derived from young and old Sprague-Dawley rats. The concentration of MSCs in bone marrow was observed to be reduced with age (Kasper et al., 2009), with the expression of actin cytoskeleton-associated proteins (e.g., calponin-1, transgelin, vinculin, caldesmon-1, myosin light chain regulatory B, and β-actin) in MSCs affected by aging (Kasper et al., 2009). By using functional annotation clustering, age-affected molecular functions were found to be partly associated with the organization of the cytoskeleton (Kasper et al., 2009). These findings point to the fact that actin turnover declines in aged MSCs (Kasper et al., 2009). Such a decline was confirmed upon treatment of the MSCs with an actin-stabilizing drug, Jasplakinolide

(Kasper et al., 2009). Compared to those collected from young rats, the mean ratio of MSCs responding with a fully collapsed actin cytoskeleton is lower in those collected from the aged counterparts (Kasper et al., 2009). This decline in the rate of actin cytoskeleton remodeling may reduce the migratory capacity of aged MSCs and may increase the susceptibility of the cells to senescence (Kasper et al., 2009), leading to a reduction in the responsiveness of those cells to biological and mechanical signals. Actin involves not only in cell maintenance but also in tissue homeostasis. In *Caenorhabditis elegans*, the organization and morphology of the actin cytoskeleton deteriorate in muscles, intestine, and hypodermis during aging (Higuchi-Sanabria et al., 2018). To combat the deterioration, *hsf-1*, which helps regulate the cytoskeletal integrity during aging and whose knockdown leads to premature aging of actin (Higuchi-Sanabria et al., 2018), may function as a feasible target. Overexpression of this gene protects the integrity of the actin cytoskeleton in muscles, intestine, and hypodermis of *C. elegans* (Higuchi-Sanabria et al., 2018). The important role played by the heat shock protein in maintaining the proper functioning of the actin cytoskeleton has also been verified in cultured human cells (Doshi et al., 2010), in which HSPB1 forms a complex with actin and is required for cell motility.

Regarding the roles played by actin in cell maintenance and tissue homeostasis, it is not difficult to see that disruption in the actin cytoskeleton has a strong link with cancer (Table 1). The relevance of actin dynamics to cancer can be attributed to the involvement of the actin cytoskeleton in cell motility (and hence cancer invasion) and also to the importance of the cytoskeleton to cell growth. The need of the actin cytoskeleton in cell cycle control has been suggested by the observation that toxins (e.g., latrunculin B and cytochalasin D) that cause depolymerization of actin filaments can delay the progression of mitosis in fission yeast (Gachet et al., 2001) and primary cells (Lee and Song, 2007). Moreover, disruption in actin filaments results in G1 arrest, which is linked to cyclin expression and cyclin-dependent kinase (CDK) activation (Reshetnikova et al., 2000). In recent years, some actin-binding proteins (e.g., cortactin (Wang et al., 2008), LIMK1 (Sumi et al., 2006), PAK1 (Zhao et al., 2005), integrin-linked kinase (Fielding et al., 2008), focal adhesion kinase (Rodriguez-Fernandez et al., 1999), Pyk2 (Rodriguez-Fernandez et al., 1999), and paxillin (Herreros et al., 2000)) have been found to localize in centromeres during the M phase of the cell cycle, participating in a multitude of processes (ranging from mitotic spindle orientation to centrosome maturation and separation) during mitosis.

In addition to cell growth, apoptosis is regulated by the actin dynamics. This has been suggested by an earlier study which investigated the actin distribution pattern in leukemia cells treated with etoposide (Grzanka, 2001). Upon treatment, reorganization of the actin cytoskeleton occurred, accompanying with the formation of apoptotic bodies (Grzanka, 2001). During apoptosis induced by cytostatic drugs in K-562 and HL-60 leukemia cells, actin was also found to localize in chromatin compaction, and to participate in chromatin remodeling during apoptosis (Grzanka et al., 2003). Because of the importance of the actin cytoskeleton to cell division and apoptosis, age-related actin dysfunction is one of the important mechanisms underlying uncontrolled cell proliferation and hence tumorigenesis. In fact, changes in the dynamics of the actin cytoskeleton can lead to age-associated decline and symptoms in virtually all tissues and organs (**Fig. 3**). In the following parts of this section, few systems (including cardiovascular system, nervous system, immune system, reproductive system, and locomotor system) that have drawn particular attention in aging research will be used

as examples to delineate the relevance of actin dynamics to aging and associated diseases.

3.1 Cardiovascular system

Cardiac muscle in an adult heart consists of the conduction system (CS) as well as the working myocardium. The former includes the peripheral Purkinje fibers (PF), the bundle branches (BB), the atrioventricular bundle (AVB), the atrioventricular node (AVN), the internodal tract or bundle (IB), and the sinoatrial node (SAN). While cardiomyocytes in the IB and SAN contain α-cardiac (α-CA) and α-smooth muscle (α-SMA) actin isoforms (Orlandi et al., 2009); those in the PF, BB, AVB and AVN are α-CA and α-skeletal (α-SKA) positive (Orlandi et al., 2009). The wide distribution of actin isoforms in cardiac muscle suggests the importance of the actin cytoskeleton in cardiac functioning. This is supported partly by the roles played by actin dynamics in heart development and functional maintenance. For instance, HSPB7, whose mutations may lead to dilated cardiomyopathy and heart failure, functions by binding with monomeric actin to repress actin polymerization so as to modulate the actin thin filament length in cardiac muscle (Wu et al., 2017). Functional maintenance of the adult heart in mice also necessitates the actin-organizing formin protein Fhod3 (Ushijima et al., 2018). Regarding its involvement in the development and functioning of the heart, the actin cytoskeleton may potentially be adopted as a target for heart regeneration and repair. The technical possibility of this has been illuminated by Morikawa *et al.* (2015), who, by blocking the Hippo signaling (which inhibits the expression of the transcriptional coactivator Yap to prevent the regeneration of cardiomyocytes in mammals, and contributes to the poor regenerative capacity of the mammalian heart), have successfully resumed the response of Yap to mechanical signaling associated with heart injury to lead to the remodeling of the actin cytoskeleton with protrusion formation, resulting in heart repair.

Apart from the heart, the growth of blood vessels involves actin. This has been suggested by the remarkable upregulation of β-actin during vessel growth in a rabbit model, in which collateral artery growth has been induced by femoral artery ligation (Deindl et al., 2002). Actin dysfunction in the vascular system may lead to microvascular remodeling, which contributes to elevated systemic vascular resistance in hypertension and is related to the rearrangement of the actin cytoskeleton in the vascular wall (Feihl et al., 2008). Prolonged vasoconstriction of resistance arteries and resistance artery remodeling in hypertension are, in fact, attributed to improper control of actin polymerization (Nakamura et al., 2000; Staiculescu et al., 2013). Cytoskeletal actin polymerization is also involved in force generation during PKC-mediated vasoconstriction in cerebral arteries (El-Yazbi et al., 2015). In the medial layer of human atherosclerotic coronary arteries, signs of actin disorganization as well as a decline in the level of actin binding proteins (e.g., gelsolin and vinculin) have been observed (de la Cuesta et al., 2013; Itoh et al., 2002). The association between actin and vascular functioning has been further confirmed by using a hypercholesterolemic rabbit model, in which alterations in actin microfilaments have led to dysfunctional endothelial-substratum adhesion and the formation of atherosclerotic plaques (Colangelo et al., 1998). All these point to the close relationship between actin dynamics and vascular functioning.

3.2 Nervous system

To maintain the proper functioning of the nervous system, tight control of the dynamic

reorganization of the actin cytoskeleton in response to extracellular and intrinsic stimuli is required as it affects the morphological and functional plasticity of neurons and glial cells (Seixas et al., 2019). Oligodendrocytes are one type of glial cells, whose cytoskeleton consists of mainly microtubules and actin filaments (Kachar et al., 1986; Wilson and Brophy, 1989). The cytoplasmic protrusions of these cells have growing tips with actin-rich filopodia, and also have long bundles of actin filaments (Fox et al., 2006). These actin-based protrusions form a multilayered myelin membrane to wrap around axons spirally to promote long-term axonal integrity and to enhance the speed of conduction of action potential (Barateiro et al., 2016). Myelination is initiated during development when oligodendrocyte progenitor cells (OPCs) migrate toward the vicinity of neurons to undergo differentiation to ensheath axons (Domingues et al., 2018; Emery, 2010). The differentiation program of oligodendrocytes involves the morphological change of the cells from a simple spindle-like shape to an arborized morphology, as well as the expression of myelin genes that lead to the production of structural components of mature sheaths (Seixas et al., 2019). Compared to microtubules, actin filaments display a higher turnover rate and higher reorganization potential. They provide morphological plasticity to oligodendrocytes (Simpson and Armstrong, 1999; Song et al., 2001). Regarding the fact that the disruption and loss of myelin in the white matter often occur in an aged brain (Duce et al., 2006), along with the close relationship between the actin cytoskeleton and the process of myelination (Seixas et al., 2019), disruption in actin dynamics is one of the factors to be considered when the mechanism of age-associate changes in an aged brain is elucidated in future research.

As a matter of fact, the role played by actin in establishing the polarized morphology of neurons has already been shown by a recent study (van de Willige et al., 2019), which examined the neuronal function of growth arrest-specific 2-like 1 (Gas2L1). Results have revealed that Gas2L1, which can bind to different components (including actin, microtubules and microtubule plus-end-tracking end binding proteins) of the cytoskeleton, can promote axon branching while restricting axon elongation in cultured rat hippocampal neurons (van de Willige et al., 2019). A similar observation of the involvement of actin in axon growth has been demonstrated in *Drosophila melanogaster*, in which the function of the transcription factor Lola has been found to mediate axon growth partly by suppressing the expression of the actin nucleation factor Spire (Gates et al., 2011). Apart from axons, dendrite formation and branching are affected by actin dynamics (Georges et al., 2008; Nithianandam and Chien, 2018; Yoo et al., 2019). For instance, Tmod1 and Tmod2 have been shown to regulate dendritic morphology and dendritic spine shape by actin binding (Gray et al., 2018). Phosphatidylinositol 3,4-bisphosphate has also been found to regulate neurite initiation and dendrite morphogenesis via actin aggregation (Zhang et al., 2017). Based on the evidence presented above, it is not difficult to see that proteins involved in regulating the actin dynamics may turn out to be feasible targets for the future development of regenerative interventions to combat age-associated neurological degeneration.

Because neurological functioning tightly relies on proper control of actin dynamics, disruption in actin regulation may lead to diseases in the nervous system (Spears et al., 2014). For example, Hirano bodies, which are rod-shaped intraneuronal inclusions containing diverse proteins (including actin, α-actinin, vinculin, and tropomyosin), are commonly found in patients with various degenerative diseases (Davis et al., 2008; Fechheimer et al., 2002). An increase in the expression of β-actin has also been found

in brain tissues of patients suffering from Alzheimer's disease (AD) (Gutala and Reddy, 2004). Recently, by examining the isolated brain vessel extract and cortex from a mouse model with strong β-amyloid plaque deposition, the protein and mRNA levels of α-smooth muscle actin, which is a protein prominently expressed on brain vessels and is thought to influence the blood vessel contraction (Hutter-Schmid and Humpel, 2016), have been shown to be increased (Hutter-Schmid and Humpel, 2016). This finding seems to be contradictory to the finding reported by Ervin *et al.* (2004), who observed a decrease in the vascular smooth muscle actin density in arachnoid, grey matter, and white matter blood vessels in patients with late-stage AD. Such a discrepancy may be partly due to the difference in the stage of the disease examined by the two studies, although more follow-up studies are required before the mechanism linking the actin cytoskeleton to the pathogenesis of AD and other neurodegenerative diseases can be fully elucidated.

3.3 Immune system

Macrophages help repair damaged tissues, eliminate infectious agents, and mediate inflammatory responses (Murray and Wynn, 2011). These functions are mainly performed via chemotaxis and phagocytosis, during which macrophages undergo actin cytoskeletal remodeling to produce various F-actin rich membrane structures (including lamellipodia and phagocytic cups) (Rougerie et al., 2013). For instance, Fcγ receptor (FcγR)-triggered phagocytosis involves the recruitment and activation of actin-regulating proteins such as WASp and Arp2/3 (Rougerie et al., 2013). Chemotaxis induced by colony-stimulating factor-1 (CSF-1) signaling also involves actin cytoskeleton rearrangement mediated by nucleation-promoting factors that belong to the WASP/WAVE family (Rougerie et al., 2013). Because the functioning of macrophages relies largely on proper control of actin dynamics, disruption in actin regulation during aging may lead to an age-associated decline in phagocytic ability and in the capacity of generating reactive oxygen species (ROS) (Li et al., 2017). This has been demonstrated by the case of alveolar macrophages. When bacterial infection occurs in the respiratory system, cytoskeleton remodeling is initiated in alveolar macrophages, stimulating the expression of the bacterial scavenger receptor MARCO and executing phagocytosis (Li et al., 2017). The initiation of this remodeling process necessitates the involvement of Rac1-GTP, which activates Arp2/3 to induce filopodia formation, to stimulate F-actin polymerization, and to increase the cell surface expression of MARCO (Li et al., 2017). The expression of Rac1, however, is reduced with advanced age (Li et al., 2017). This impairs the initiation of phagocytosis in alveolar macrophages, rendering elderly subjects susceptible to sepsis led by respiratory infection. This evidences the close link between age-associated changes in the cytoskeletal integrity and the functional loss of macrophages during aging.

Similar to the case of macrophages, an age-associated decline in the ability of ROS production occur in polymorphonuclear leukocytes (PMNs). Compared to young PMNs, the aged counterparts in general show impaired capacity of generating the superoxide anion (O_2^-) in response to treatment with formyl-methionyl-leucine-phenylalanine (FMLP). The changes in the cytoskeleton assembly capacity with advanced age may account for this impaired capacity (Piazzolla et al., 1998), and also for the failure of proper exocytosis of appropriate cell-surface receptors to the cell membrane of PMNs in aged subjects (Noble et al., 1999; Plackett et al., 2004; Rao et al., 1992). These changes have been observed by Rao (1986), who detected a reduction in the extent of actin polymerization in aged PMNs upon incubation with FMLP and phorbol myristate

acetate. A similar reduction has also been noted in aged palettes treated with thrombin (Rao, 1986). As actin polymerization is vital to the success of cellular activation, the reduction in the extent of ligand-induced actin polymerization may partly account for the deteriorated functioning of PMNs in aged subjects.

Finally, interactions of T-cell receptors (TCR) with major histocompatability complex–peptide complexes on antigen-presenting cells can activate signaling cascades, resulting in the formation and stabilization of an immune synapse required for modulating T-cell responses (Billadeau and Burkhardt, 2006). During this process, reorganization of the actin cytoskeleton is involved. Some of the actin regulatory proteins involved in the functioning of T cells include the WAVE complex (Nolz et al., 2006; Zipfel et al., 2006), WASp (Zhang et al., 1999), WASp-interacting protein (WIP) (Ramesh et al., 1997; Sasahara et al., 2002), cofilin (Eibert et al., 2004), HS1 (Taniuchi et al., 1995), and Ena/VASP proteins (Krause et al., 2000; Lafuente et al., 2004). Because aged lymphocytes display impaired cytoskeletal actin filament functions (Brock and Chrest, 1993) and a lower polymeric actin content (Cheung et al., 1987), this reduces the surface receptor motility and subsequent lymphocyte proliferation, contributing to the declined function of the immune system.

3.4 Reproductive system

Due to the deterioration in oocyte quality with advanced age, aged oocytes are often compromised in competence in fertilization. The connection between alternations in subcellular structures and the performance in fertilization has been reported by an earlier study (Limatola et al., 2019), which simulated the aging process experienced by oocytes of *Astropecten aranciacus* by treating the freshly collected oocytes directly with 1-methyladenine, or by removing the oocytes from the gonad and maintaining them in seawater for a substantial period with or without subsequent treatment with 1-methyladenine. In the inner cytoplasm of the oocyte, random distribution of thick actin filaments has been identified in the oocyte at the germinal vesicle (GV)-stage but not in the one treated directly with 1-methyladenine (Limatola et al., 2019). Apart from this, oocytes aged by maintenance in seawater, with or without further treatment with 1-methyladenine, have displayed substantial changes in the structural organization of cortical actin filaments as compared to those at the GV-stage (Limatola et al., 2019). Taking the different rates of polyspermy and the variations in fertilization envelope (FE) elevation as experienced by the oocytes into account (Limatola et al., 2019), polyspermy in aged oocytes is thought to be partly due to changes in the structural integrity of the actin cytoskeleton.

Besides starfish, oogenesis in *Drosophila melanogaster* requires tight control of actin dynamics. This has been reported by Sokolova *et al.* (2018), who generated a mutant of RanBP9 (which is a nuclear actin import receptor) and observed that the mutant not only shows a lower nuclear actin level (**Fig. 4**) but the eggs laid by the mutant also display abnormal morphology and short dorsal appendages. Because manipulation of nuclear transport factors of actin leads to a decline in the expression of eggshell genes, it is possible that actin involves in gene regulation. This has been verified in NIH3T3 cells, in which disruption in the actin cytoskeleton alters the transcription activity mediated by the myocardin-related transcription factor and the serum response factor (MAL/SRF) (Miralles et al., 2003). The regulation of the actin cytoskeleton and that of gene expression appear to be connected, the nature of their functional integration is, however, not well understood till now. Nevertheless, based on the cases described above,

actin dysfunction seriously compromises embryonic development. This, in fact, has already been corroborated in various species, spanning from mice (Mackenzie et al., 2016) and horses (Ruggeri et al., 2015) to sea urchins (Chun et al., 2014). Changes in the integrity of the actin cytoskeleton, therefore, disrupt the functioning of not only somatic and stem cells but also gametes. This may explain the failure of some assisted reproductive technologies in aged eggs. Further research in this direction is needed in order to obtain a more comprehensive view of the relevance of actin dynamics to reproductive aging.

3.5 Locomotor system

The locomotor system is a complex leverage apparatus composed of muscles, ligaments, bones, joints, and various soft tissues. Its deterioration may impair locomotion and the performance of coordinated movements. For example, the age-associated loss of the muscle force and contractile speed will impede balance maintenance, leading to a higher rate of falls and related injuries among aged subjects (Cuevas-Trisan, 2019). To elucidate the effects of aging on the motor functions of muscle, the contractile speed in skinned muscle fibers expressing different isoforms of the myosin heavy chain (MHC) have been investigated in the literature (Degens et al., 1998; Larsson et al., 1997; Li and Larsson, 1996; Yu et al., 1998). In skeletal muscle cells from both rats and humans, an age-related reduction in the maximum velocity of unloaded shortening has been reported (Degens et al., 1998; Larsson et al., 1997; Li and Larsson, 1996; Yu et al., 1998). In muscle fibers collected from various species (including humans, rats and mice) and expressing the slow (type I) β-myosin heavy chain isoform, an age-associated decrease in the actin sliding speed on myosin has also been observed (Hook et al., 2001). All these link actin dysfunction to the functional decline of the locomotor system.

In addition, muscle growth and repair require satellite cells, which are a self-renewing population of myogenic progenitors. The involvement of the actin cytoskeleton in the functioning of satellite cells is partly evidenced by the expression of the actin binding protein Xin during skeletal muscle regeneration and also the involvement of that protein in regulating myoblast function (Hawke et al., 2007). By controlling the organization of the actin cytoskeleton and actin-based protrusions, Srf, which help regulate myoblast fusion in mammals, has also been found to regulate hypertrophic myofiber growth (Randrianarison-Huetz et al., 2018). Because the integrity of the actin cytoskeleton is disrupted with advanced age, changes in the actin dynamics in satellite cells is one of the possible mechanisms accounting for the aging of myocytes. Apart from this, changes in the expression pattern of the actin isoform may link with the age-associated decline in the contractile function of muscle fibers. This has been shown by Lancioni *et al.* (2007), who, by examining the satellite cells isolated from skeletal muscle biopsies from subjects with different ages, observed that the expression level of the α-smooth muscle actin isoform (α-SMA) in satellite cells isolated from the newborn is substantially lower than the aged counterpart. The persistently high expression of α-SMA in satellite cells in elderly subjects may partially account for the age-associated decline in contractile function due to its possible effects on cell fusion and on the differentiation of myotubes into myofibers (Lancioni et al., 2007).

4. Links between actin dynamics and life span determination

Apart from the aging process *per se*, the life span of an individual may be affected by actin dynamics, though at the moment evidence on life span determination has been collected mainly from *Saccharomyces cerevisiae* (Amberg et al., 2011). The actin

cytoskeleton in yeast cells consists of three dynamic structures. One is the actomyosin ring, which is important to cytokinesis (Amberg et al., 2011). The other one is the cortical actin patch, which is thought to be the site of endocytosis and is polarized to the buds of a growing cell (Kaksonen et al., 2003). The last one is the actin cable, which is a bundle of long actin filaments that extend from the bud tip or neck to the mother cell tip, guiding bidirectional cargo transport and regulating the movement of organelles (e.g., peroxisomes and mitochondria) and secretory vesicles (Pruyne et al., 2004). By examining the actin cytoskeleton in yeast cells, stationary-phase cultures of *Saccharomyces cerevisiae* have been found to consist of two cell subpopulations (Vasicova et al., 2015). One possesses a dynamic actin cytoskeleton, and the other one has static actin bodies. The impact of aging on the actin cytoskeleton has been reported by an earlier study (Vasicova et al., 2015), which used a GTP-fused actin binding protein (Abp140-GFP) to analyze the dynamics of cables in yeast cells. Compared to exponentially growing cultures that comprise only cells with dynamic actin cables (Vasicova et al., 2015), aged cultures possess cells with actin bodies and cells with no specific Abp140-GFP fluorescence (Vasicova et al., 2015). The number of cells containing actin cables and bodies decreases during chronological aging, but the number of non-fluorescent cells increases (Vasicova et al., 2015). Taking the age-associated changes in the dynamics and organization of the actin cytoskeleton into consideration, actin manipulation may turn out to be a route of life span extension in the future.

In addition, the target of rapamycin (TOR) pathway is one of the pathways that have drawn attention in aging research. This pathway helps regulate mitochondrial respiration and ROS production, and hence determines the chronological life span in yeast cells (Bonawitz et al., 2007; Pan and Shadel, 2009). Some of the important regulators of aging in the TOR pathway include Tor1, Sch9, and Ras2 (Liu et al., 2015). These proteins control carbon source substitution and mediate the effect of caloric restriction on life span prolongation (Wei et al., 2009). In a recent study, yeast cells with mutations on genes for these proteins have been generated (Liu et al., 2015). Microscopy examination has revealed that the actin structure is more dynamic in those mutants than in wild-type cells (Liu et al., 2015). Compared to the chronological life span of DBY746 wild-type cells, that of the mutants has been shown to be longer (Liu et al., 2015). This has consolidated the validity of extending the life span via actin manipulation. What remains is to translate the validity into practice from the yeast model to the mammalian model.

5. Opportunities and challenges for intervention development

Regarding the biological importance of actin dynamics as delineated in preceding sections, actin manipulation has practical potential in biomedicine. For instance, thymosin β_4, which contains an actin-binding domain and is a major actin-sequestering molecule in eukaryotic cells, has been found to accelerate the healing of full-thickness dermal wounds in aged mice by increasing keratinocyte migration, wound contracture, and collagen deposition (Philp et al., 2003). By over-expressing cofilin to disrupt the actin filaments in H1299 lung carcinoma cells, over 90% of the cells have been arrested at the G1 phase (Lee and Keng, 2005). These studies suggest the feasibility of taking the actin cytoskeleton as a target for tissue regeneration and for treatment of age-associated diseases (such as cancer). More recently, Higuchi and co-workers (2013) have discovered that the fitness of mitochondria inherited by buds, and hence the health span of yeast cells, can be enhanced by increasing the retrograde actin cable flow

(RACF). This discovery points to the possibility of manipulating RACF for health span prolongation during aging. Over the years, different agents have been discovered to modulate the functioning and organization of the actin cytoskeleton. Some of them are listed in Table 2. These agents may have the potential to be candidates for drug development to manipulate the actin cytoskeleton in the future.

Despite the technical possibility of actin manipulation, actin dynamics is a complex process, and impairment in the function of one component may lead to dramatic disruption in the cytoskeletal integrity. This has partially been evidenced in $C_3H_{10}T_{1/2}$ cells, in which actin filament-associated protein (AFAP) is distributed along F-actin fibers and is present in both cytosolic and cytoskeletal portions of stress fibers (Xiao et al., 2012). Upon overexpression of AFAP, cytoskeleton reorganization occurs (Xiao et al., 2012). In BEAS2B cells, the morphology of podosomes formed by the phorbol 12,13-dibutyrate (PDBu)-treated cells is different from those in which AFAP is overexpressed (Xiao et al., 2012). This suggests that simply changing the activity of one protein may dramatically change the organization of the actin cytoskeleton. Because of the complexity of actin dynamics, there are a vast number of possibilities for actin dysfunction to occur during aging. This imposes difficulties when attempts are made to reverse actin dysfunction in practice. Solutions may be provided by advances in high-throughput technologies for gene sequencing (Brettmann et al., 2018; de Masson et al., 2018; Kezimana et al., 2018) and for the elucidation of protein structures (Fogg et al., 2006; Hirata et al., 2019; Rames et al., 2014; Shah et al., 2010). These technologies can help identify the malfunctioned proteins to be tackled, and can enhance our understanding of the regulatory network governing proper functioning and maintenance of the actin cytoskeleton.

Finally, while efforts in the literature are largely devoted to deciphering the cytoplasmic functions of actin, the role of actin in the nucleus should not be overlooked. Over the years, an increasing number of evidence has pointed to the importance of nuclear actin to cell physiology. For instance, by using confocal microscopy and the fluorescence recovery after photobleaching (FRAP) assay, the rate of GFP-actin nuclear transport has been shown to be different between NIH 3T3 cells and those undergone different treatments (e.g., serum starvation for cell cycle arrest at the G_0 phase, or treatment with thymidine or hydroxyurea for locking the cells into the late G1/early S phase) (Johnson et al., 2013). More recently, the actin binding cytoskeletal protein moesin has also been found in the nuclei of cultured S2R+ cells and in the salivary glands of third instar larvae, participating in nuclear mRNA export in fruit flies (Kristo et al., 2017). As the physiological roles played by nuclear actin in DNA repair and gene regulation have already been reviewed elsewhere (Bajusz et al., 2018; Hurst et al., 2019; Kapoor and Shen, 2014; Misu et al., 2017; Miyamoto and Gurdon, 2013; Pfisterer et al., 2017), they will not be discussed further here. It is, however, worth highlighting that, even though the relationship between nuclear actin and gene regulation has been shown experimentally, the mechanistic understanding of nuclear actin in aging, or even the extent of changes experienced by nuclear actin during aging, is ill-defined till now, partly due to the lack of research tools that enable nuclear actin to be specifically studied. Solving this not only helps increase the comprehensiveness of our understanding of the actin cytoskeleton in cells, but insights can also be gained into the mechanisms of aging and related diseases.

6. Concluding remarks

Actin plays vital roles in diverse physiological processes, ranging from phagocytosis to intracellular trafficking. In this article, we have reviewed the roles of actin in aging, and have also presented the link between actin dynamics and life span determination. As a matter of fact, research on the organization and dynamics of the actin cytoskeleton is not only relevant to basic aging research, but may also reveal subtle sources of obstacles in the development of antiaging therapies. This has been demonstrated by Grosse *et al.* (2007), who generated plasmid/PEI or plasmid/lactosylated PEI complexes to evaluate the cytoskeletal involvement in the cellular trafficking of polyplexes. The transfection efficiency of the polyplexes was found to be reduced by 90% in cystic fibrosis airway epithelial cells when transfection was performed in the presence of cytochalasin D (which depolymerizes actin filaments) or nocodazole (which disrupts the integrity of microtubules) (Grosse et al., 2007). Owing to the effect of aging on actin dynamics, therapeutics may be more difficult to reach aged cells for action. This partially explains the challenges to the development of effective therapies that target aged cells in general. Regarding the possible biogerontological implications of actin research, age-associated changes in the actin cytoskeleton are anticipated to continue to be an important topic in the forthcoming years, not only for the design of interventions that counteract age-associated changes in cytoskeletal integrity *per se* but also for the enhancement of the performance of other anti-aging therapies in practice.

Declaration of Competing Interest

The authors claim no conflict of interest.

Acknowledgements

The authors would like to thank Wai-Sum Lo, Minjian Huang, Guoxing Deng, and Yau-Foon Tsui for helpful discussions during the writing of this manuscript. This work was supported by Natural Science Foundation of Guangdong Province (2018A030310485), the Shenzhen Science and Technology Innovation Commission (JCYJ20170818102436104, and JCYJ20170302144812937), and the Presidential Fund (PF01001421) from the Chinese University of Hong Kong, Shenzhen.

References

Amberg, D., Leadsham, J.E., Kotiadis, V., Gourlay, C.W., 2011. Cellular ageing and the actin cytoskeleton, in: Breitenbach, M., Jazwinski, S., Laun, P. (Eds.), Aging Research in Yeast. Springer, Dordrecht, pp. 331-352.

Amberg, D., Leadsham, J.E., Kotiadis, V., Gourlay, C.W., 2012. Cellular ageing and the actin cytoskeleton. Subcell. Biochem. 57, 331-352.

Ando, Y., Yasuda, S., Oceguera-Yanez, F., Narumiya, S., 2007. Inactivation of Rho GTPases with Clostridium difficile toxin B impairs centrosomal activation of Aurora-A in G2/M transition of HeLa cells. Mol. Biol. Cell. 18(10), 3752-3763.

Andrianantoandro, E., Pollard, T.D., 2006. Mechanism of actin filament turnover by severing and nucleation at different concentrations of ADF/cofilin. Mol. Cell 24(1), 13-23.

Aydin, F., Katkar, H.H., Voth, G.A., 2018. Multiscale simulation of actin filaments and actin-associated proteins. Biophys. Rev. 10(6), 1521-1535.

Bajusz, C., Borkuti, P., Kristo, I., Kovacs, Z., Abonyi, C., Vilmos, P., 2018. Nuclear actin: ancient clue to evolution in eukaryotes? Histochem. Cell Biol. 150(3), 235-244.

Balchin, D., Milicic, G., Strauss, M., Hayer-Hartl, M., Hartl, F.U., 2018. Pathway of actin folding directed by the eukaryotic chaperonin TRiC. Cell 174(6), 1507-1521.

Barateiro, A., Brites, D., Fernandes, A., 2016. Oligodendrocyte development and myelination in neurodevelopment: molecular mechanisms in health and disease. Curr. Pharm. Des. 22(6), 656-679.

Bhadriraju, K., Hansen, L.K., 2004. Extracellular matrix-dependent myosin dynamics during G1-S phase cell cycle progression in hepatocytes. Exp. Cell Res. 300(2), 259-271.

Billadeau, D.D., Burkhardt, J.K., 2006. Regulation of cytoskeletal dynamics at the immune synapse: new stars join the actin troupe. Traffic 7(11), 1451-1460.

Bonawitz, N.D., Chatenay-Lapointe, M., Pan, Y., Shadel, G.S., 2007. Reduced TOR signaling extends chronological life span via increased respiration and upregulation of mitochondrial gene expression. Cell Metab. 5(4), 265-277.

Boykin, C., Zhang, G., Chen, Y.H., Zhang, R.W., Fan, X.E., Yang, W.M., Lu, Q., 2011. Cucurbitacin IIa: a novel class of anti-cancer drug inducing non-reversible actin aggregation and inhibiting survivin independent of JAK2/STAT3 phosphorylation. Br. J. Cancer 104(5), 781-789.

Brettmann, E.A., Oh, I.Y., Strong, C.D., 2018. High-throughput identification of gene regulatory sequences using next-generation sequencing of circular chromosome conformation capture (4C-seq). J. Vis. Exp. 140, e58030.

Brock, M.A., Chrest, F., 1993. Differential regulation of actin polymerization following activation of resting T lymphocytes from young and aged mice. J. Cell Physiol. 157(2), 367-378.

Bruunsgaard, H., Pedersen, A.N., Schroll, M., Skinhoj, P., Pedersen, B.K., 2000. TNF-α, leptin, and lymphocyte function in human aging. Life Sci. 67(22), 2721-2731.

Cai, G., Wu, D., Wang, Z., Xu, Z., Wong, K.B., Ng, C.F., Chan, F.L., Yu, S., 2017. Collapsin response mediator protein-1 (CRMP1) acts as an invasion and metastasis suppressor of prostate cancer via its suppression of epithelial-mesenchymal transition and remodeling of actin cytoskeleton organization. Oncogene 36(4), 546-558.

Campellone, K.G., Welch, M.D., 2010. A nucleator arms race: cellular control of actin assembly. Nat. Rev. Mol. Cell Biol. 11(4), 237-251.

Castellano, F., Chavrier, P., Caron, E., 2001. Actin dynamics during phagocytosis. Semin. Immunol. 13(6), 347-355.

Chang, A.M., Halter, J.B., 2003. Aging and insulin secretion. Am. J. Physiol. Endocrinol. Metab. 284(1), E7-E12.

Cheung, H.T., Rehwaldt, C.A., Twu, J.S., Liao, N.S., Richardson, A., 1987. Aging and lymphocyte cytoskeleton: age-related decline in the state of actin polymerization in T lymphocytes from Fischer F344 rats. J. Immunol. 138(1), 32-36.

Chun, J.T., Limatola, N., Vasilev, F., Santella, L., 2014. Early events of fertilization in sea urchin eggs are sensitive to actin-binding organic molecules. Biochem. Biophys. Res. Commun. 450(3), 1166-1174.

Cleuren, Y.T., Boonstra, J., 2012. Actin: structure, function and disease, in: Consuelas, V. A., Minas, D. J. (Eds.), Protein Biochemistry, Synthesis, Structure and Cellular Functions. Nova Science Publishers Inc., New York, pp. 61-96.

Colangelo, S., Langille, B.L., Steiner, G., Gotlieb, A.I., 1998. Alterations in endothelial F-actin microfilaments in rabbit aorta in hypercholesterolemia. Arterioscler. Thromb. Vasc. Biol. 18(1), 52-56.

Cuevas-Trisan, R., 2019. Balance problems and fall risks in the elderly. Clin. Geriatr. Med. 35(2), 173-183.

Davidson, A.J., Wood, W., 2016. Unravelling the actin cytoskeleton: a new competitive edge? Trends Cell Biol. 26(8), 569-576.

Davis, R.C., Furukawa, R., Fechheimer, M., 2008. A cell culture model for investigation of Hirano bodies. Acta Neuropathol. 115(2), 205-217.

de la Cuesta, F., Zubiri, I., Maroto, A.S., Posada, M., Padial, L.R., Vivanco, F., Aluarez-Llamas, G., Barderas, M.G., 2013. Deregulation of smooth muscle cell cytoskeleton within the human atherosclerotic coronary media layer. J. Proteomics 82, 155-165.

de Masson, A., O'Malley, J.T., Elco, C.P., Garcia, S.S., Divito, S.J., Lowry, E.L., Tawa, M., Fisher, D.C., Devlin, P.M., Teague, J.E., Leboeuf, N.R., Kirsch, I.R., Robins, H., Clark, R.A., Kupper, T.S., 2018. High-throughput sequencing of the T cell receptor beta gene identifies aggressive early-stage mycosis fungoides. Sci. Transl. Med. 10(440), eaar5894.

Degens, H., Yu, F., Li, X., Larsson, L., 1998. Effects of age and gender on shortening velocity and myosin isoforms in single rat muscle fibres. Acta Physiol. Scand. 163(1), 33-40.

Deindl, E., Boengler, K., van Royen, N., Schaper, W., 2002. Differential expression of GAPDH and beta3-actin in growing collateral arteries. Mol. Cell Biochem. 236(1-2), 139-146.

Domingues, H.S., Cruz, A., Chan, J.R., Relvas, J.B., Rubinstein, B., Pinto, I.M., 2018. Mechanical plasticity during oligodendrocyte differentiation and myelination. Glia 66(1), 5-14.

Dominguez, R., 2010. Structural insights into de novo actin polymerization. Curr. Opin. Struct. Biol. 20, 217-225.

Dominguez, R., Holmes, K.C., 2011. Actin structure and function. Annu. Rev. Biophys. 40, 169-186.

Doshi, B.M., Hightower, L.E., Lee, J., 2010. HSPB1, actin filament dynamics, and aging cells. Ann. N. Y. Acad. Sci. 1197, 76-84.

Duce, J.A., Hollander, W., Jaffe, R., Abraham, C.R., 2006. Activation of early components of complement targets myelin and oligodendrocytes in the aged rhesus monkey brain. Neurobiol. Aging 27(4), 633-644.

Eibert, S.M., Lee, K.H., Pipkorn, R., Sester, U., Wabnitz, G.H., Giese, T., Meuer, S.C., Samstag, Y., 2004. Cofilin peptide homologs interfere with immunological synapse formation and T cell activation. Proc. Natl. Acad. Sci. U. S. A. 101(7), 1957-1962.

El-Yazbi, A.F., Abd-Elrahman, K.S., Moreno-Dominguez, A., 2015. PKC-mediated cerebral vasoconstriction: role of myosin light chain phosphorylation versus actin cytoskeleton reorganization. Biochem. Pharmacol. 95(4), 263-278.

Emery, B., 2010. Regulation of oligodendrocyte differentiation and myelination. Science 330(6005), 779-782.

Ervin, J.F., Pannell, C., Szymanski, M., Welsh-Bohmer, K., Schmechel, D.E., Hulette, C.M., 2004. Vascular smooth muscle actin is reduced in Alzheimer disease brain: a quantitative analysis. J. Neuropathol. Exp. Neurol. 63(7), 735-741.

Fabian, L., Troscianczuk, J., Forer, A., 2007. Calyculin A, an enhancer of myosin, speeds up anaphase chromosome movement. Cell Chromosome 6, 1.

Fechheimer, M., Furukawa, R., Maselli, A., Davis, R.C., 2002. Hirano bodies in health and disease. Trends Mol. Med. 8(12), 590-591.

Feihl, F., Liaudet, L., Levy, B.I., Waeber, B., 2008. Hypertension and microvascular remodelling. Cardiovasc. Res. 78(2), 274-285.

Fielding, A.B., Dobreva, I., McDonald, P.C., Foster, L.J., Dedhar, S., 2008. Integrin-linked kinase localizes to the centrosome and regulates mitotic spindle organization. J. Cell Biol. 180(4), 681-689.

Fogg, M.J., Alzari, P., Bahar, M., Bertini, I., Betton, J.M., Burmeister, W.P., Cambillau, C., Canard, B., Carrondo, M., Coll, M., Daenke, S., Dym, O., Egloff, M.P., Enguita, F.J., Geerlof, A., Haouz, A., Jones, T.A., Ma, Q.J., Manicka, S.N., Migliardi, M., Nordlund, P., Owens, R.J., Peleg, Y., Schneider, G., Schnell, R., Stuart, D.I., Tarbouriech, N., Unge, T., Wilkinson, A.J., Wilmanns, M., Wilson, K.S., Zimhony, O., Grimes, J.M., 2006. Application of the use of high-throughput technologies to the determination of protein structures of bacterial and viral pathogens. Acta Crystallogr. D Biol. Crystallogr. 62, 1196-1207.

Forer, A., Spurck, T., Pickett-Heaps, J.D., 2007. Actin and myosin inhibitors block elongation of kinetochore fibre stubs in metaphase crane-fly spermatocytes. Protoplasma 232(1-2), 79-85.

Fox, M.A., Afshari, F.S., Alexander, J.K., Colello, R.J., Fuss, B., 2006. Growth cone like sensorimotor structures are characteristic features of postmigratory, premyelinating oligodendrocytes. Glia 53, 563–566.

Franklin-Tong, V.E., Gourlay, C.W., 2008. A role for actin in regulating apoptosis/programmed cell death: evidence spanning yeast, plants and animals. Biochem. J. 413(3), 389-404.

Gachet, Y., Tournier, S., Millar, J.B., Hyams, J.S., 2001. A MAP kinase-dependent actin checkpoint ensures proper spindle orientation in fission yeast. Nature 412(6844), 352-355.

Gates, M.A., Kannan, R., Giniger, E., 2011. A genome-wide analysis reveals that the Drosophila transcription factor Lola promotes axon growth in part by suppressing expression of the actin nucleation factor Spire. Neural Dev. 6, 37.

Georges, P.C., Hadzimichalis, N.M., Sweet, E.S., Firestein, B.L., 2008. The yin-yang of dendrite morphology: unity of actin and microtubules. Mol. Neurobiol. 38(3), 270-284.

Goode, B.L., Eck, M.J., 2007. Mechanism and function of formins in the control of actin assembly. Annu. Rev. Biochem. 76, 593-627.

Gorzelniak, K., Janke, J., Engeli, S., Sharma, A.M., 2001. Validation of endogenous

controls for gene expression studies in human adipocytes and preadipocytes. Horm. Metab. Res. 33(10), 625-627.
Gray, K.T., Stefen, H., Ly, T.N.A., Keller, C.J., Colpan, M., Wayman, G.A., Pate, E., Fath, T., Kostyukova, A.S., 2018. Tropomodulin's actin-binding abilities are required to modulate dendrite development. Front. Mol. Neurosci. 11, 357.
Grosse, S., Aron, Y., Thevenot, G., Monsigny, M., Fajac, I., 2007. Cytoskeletal involvement in the cellular trafficking of plasmid/PEI derivative complexes. J. Control. Release 122(1), 111-117.
Grzanka, A., 2001. Actin distribution patterns in HL-60 leukemia cells treated with etoposide. Acta Histochem. 103(4), 453-464.
Grzanka, A., Grzanka, D., Orlikowska, M., 2003. Cytoskeletal reorganization during process of apoptosis induced by cytostatic drugs in K-562 and HL-60 leukemia cell lines. Biochem. Pharmacol. 66(8), 1611-1617.
Gutala, R.V., Reddy, P.H., 2004. The use of real-time PCR analysis in a gene expression study of Alzheimer's disease post-mortem brains. J. Neurosci. Methods 132(1), 101-107.
Hawke, T.J., Atkinson, D.J., Kanatous, S.B., Van der Ven, P.F., Goetsch, S.C., Garry, D.J., 2007. Xin, an actin binding protein, is expressed within muscle satellite cells and newly regenerated skeletal muscle fibers. Am. J. Physiol. Cell Physiol. 293(5), C1636-C1644.
Helfer, E., Nevalainen, E.M., Naumanen, P., Romero, S., Didry, D., Pantaloni, D., Lappalainen, P., Carlier, M.F., 2006. Mammalian twinfilin sequesters ADP-G-actin and caps filament barbed ends: implications in motility. Embo J. 25(6), 1184-1195.
Herreros, L., Rodriguez-Fernandez, J.L., Brown, M.C., Alonso-Lebrero, J.L., Cabanas, C., Sanchez-Madrid, F., Longo, N., Turner, C.E., Sanchez-Mateos, P., 2000. Paxillin localizes to the lymphocyte microtubule organizing center and associates with the microtubule cytoskeleton. J. Biol. Chem. 275(34), 26436-26440.
Higuchi-Sanabria, R., Paul Rd, J.W., Durieux, J., Benitez, C., Frankino, P.A., Tronnes, S.U., Garcia, G., Daniele, J.R., Monshietehadi, S., Dillin, A., 2018. Spatial regulation of the actin cytoskeleton by HSF-1 during aging. Mol. Biol. Cell 29(21), 2522-2527.
Higuchi, R., Vevea, J.D., Swayne, T.C., Chojnowski, R., Hill, V., Boldogh, I.R., Pon, L.A., 2013. Actin dynamics affect mitochondrial quality control and aging in budding yeast. Curr. Biol. 23(23), 2417-2422.
Hirata, K., Yamashita, K., Ueno, G., Kawano, Y., Hasegawa, K., Kumasaka, T., Yamamoto, M., 2019. ZOO: an automatic data-collection system for high-throughput structure analysis in protein microcrystallography. Acta Crystallogr. D Struct. Biol. 75, 138-150.
Hook, P., Sriramoju, V., Larsson, L., 2001. Effects of aging on actin sliding speed on myosin from single skeletal muscle cells of mice, rats, and humans. Am. J. Physiol. Cell Physiol. 280(4), C782-C788.
Huang, S., Chen, C.S., Ingber, D.E., 1998. Control of cyclin D1, p27(Kip1), and cell cycle progression in human capillary endothelial cells by cell shape and cytoskeletal tension. Mol. Biol. Cell 9(11), 3179-3193.
Humphries, B.A., Buschhaus, J.M., Chen, Y.C., Haley, H.R., Qyli, T., Chiang, B., Shen, N., Rajendran, S., Cutter, A., Cheng, Y.H., Chen, Y.T., Cong, J., Spinosa, P.C., Yoon, E., Luker, K.E., Luker, G.D., 2019. Plasminogen activator inhibitor 1 (PAI1) promotes actin cytoskeleton reorganization and glycolytic metabolism

in triple-negative breast cancer. Mol. Cancer Res. 17(5), 1142-1154.
Hurst, V., Shimada, K., Gasser, S.M., 2019. Nuclear actin and actin-binding proteins in DNA repair. Trends Cell Biol. 29(6), 462-476.
Hutter-Schmid, B., Humpel, C., 2016. Alpha-smooth muscle actin mRNA and protein are increased in isolated brain vessel extracts of Alzheimer mice. Pharmacology 98(5-6), 251-260.
Iglesias-Figueroa, B.F., Siqueiros-Cendon, T.S., Gutierrez, D.A., Aguilera, R.J., Espinoza-Sanchez, E.A., Arevalo-Gallegos, S., Varela-Ramirez, A., Rascon-Cruz, Q., 2019. Recombinant human lactoferrin induces apoptosis, disruption of F-actin structure and cell cycle arrest with selective cytotoxicity on human triple negative breast cancer cells. Apoptosis 24(7-8), 562-577.
Itoh, S., Umemoto, S., Hiromoto, M., Toma, Y., Tomochika, Y., Aoyagi, S., Tanaka, M., Fujii, T., Matsuzaki, M., 2002. Importance of NAD(P)H oxidase-mediated oxidative stress and contractile type smooth muscle myosin heavy chain SM2 at the early stage of atherosclerosis. Circulation 105(19), 2288-2295.
Jemiolo, B., Trappe, S., 2004. Single muscle fiber gene expression in human skeletal muscle: validation of internal control with exercise. Biochem. Biophys. Res. Commun. 320(3), 1043-1050.
Johnson, M.A., Sharma, M., Mok, M.T.S., Henderson, B.R., 2013. Stimulation of in vivo nuclear transport dynamics of actin and its co-factors IQGAP1 and Rac1 in response to DNA replication stress. Biochim. Biophys. Acta 1833(10), 2334-2347.
Kachar, B., Behar, T., Dubois-Dalcq, M., 1986. Cell shape and motility of oligodendrocytes cultured without neurons. Cell Tissue Res. 244(1), 27-38.
Kaksonen, M., Sun, Y., Drubin, D.G., 2003. A pathway for association of receptors, adaptors, and actin during endocytic internalization. Cell 115(4), 475-487.
Kapoor, P., Shen, X., 2014. Mechanisms of nuclear actin in chromatin-remodeling complexes. Trends Cell Biol. 24(4), 238-246.
Kasper, G., Mao, L., Geissler, S., Draycheva, A., Trippens, J., Kuhnisch, J., Tschirschmann, M., Kaspar, K., Perka, C., Duda, G.N., Klose, J., 2009. Insights into mesenchymal stem cell aging: involvement of antioxidant defense and actin cytoskeleton. Stem Cells 27(6), 1288-1297.
Kezimana, P., Dmitriev, A.A., Rozhmina, T.A., Novakovskiy, R.O., Romanova, E.V., Kudryavtseva, A.V., Melnikova, N.V., 2018. Assessment of genetic variation for SAD and FAD genes in flax by high-throughput sequencing. FEBS Open Bio 8, 466-466.
Khurana, S., Chakraborty, S., Cheng, X., Su, Y.T., Kao, H.Y., 2011. The actin-binding protein, actinin alpha 4 (ACTN4), is a nuclear receptor coactivator that promotes proliferation of MCF-7 breast cancer cells. J. Biol. Chem. 286(3), 1850-1859.
Krause, M., Sechi, A.S., Konradt, M., Monner, D., Gertler, F.B., Wehland, J., 2000. Fyn-binding protein (Fyb)/SLP-76-associated protein (SLAP), Ena/vasodilator-stimulated phosphoprotein (VASP) proteins and the Arp2/3 complex link T cell receptor (TCR) signaling to the actin cytoskeleton. J. Cell Biol. 149(1), 181-194.
Kristo, I., Bajusz, C., Borsos, B.N., Pankotai, T., Dopie, J., Jankovics, F., Vartiainen, M.K., Erdelyi, M., Vilmos, P., 2017. The actin binding cytoskeletal protein Moesin is involved in nuclear mRNA export. Biochim. Biophys. Acta Mol. Cell Res. 1864(10), 1589-1604.
Lafuente, E.M., van Puijenbroek, A.A., Krause, M., Carman, C.V., Freeman, G.J., Berezovskaya, A., Constantine, E., Springer, T.A., Gertler, F.B., Boussiotis,

V.A., 2004. RIAM, an Ena/VASP and Profilin ligand, interacts with Rap1-GTP and mediates Rap1-induced adhesion. Dev. Cell 7(4), 585-595.
Lancioni, H., Lucentini, L., Palomba, A., Fulle, S., Micheli, M.R., Panara, F., 2007. Muscle actin isoforms are differentially expressed in human satellite cells isolated from donors of different ages. Cell Biol. Int. 31(2), 180-185.
Lang, L., Hou, Y., Chen, Y., Tu, G., Tao, J., Yang, D., Xi, L., Fu, L., Sun, K., Yin, J., Chen, R., Peng, M., Liu, S., Liu, M., 2018. ATM-mediated phosphorylation of cortactin involved in actin polymerization promotes breast cancer cells migration and invasion. Cell. Physiol. Biochem. 51(6), 2972-2988.
Larsson, L., Li, X., Frontera, W.R., 1997. Effects of aging on shortening velocity and myosin isoform composition in single human skeletal muscle cells. Am. J. Physiol. 272(2 Pt 1), C638-C649.
Lee, K.G., Song, K., 2007. Actin dysfunction activates ERK1/2 and delays entry into mitosis in mammalian cells. Cell Cycle 6(12), 1487-1495.
Lee, S.H., Dominguez, R., 2010. Regulation of actin cytoskeleton dynamics in cells. Mol. Cells 29(4), 311-325.
Lee, Y.J., Keng, P.C., 2005. Studying the effects of actin cytoskeletal destabilization on cell cycle by cofilin overexpression. Mol. Biotechnol. 31(1), 1-10.
Letort, G., Ennomani, H., Gressin, L., Thery, M., Blanchoin, L., 2015. Dynamic reorganization of the actin cytoskeleton. F1000Res. 4, 940.
Li, M.Y., Peng, W.H., Wu, C.H., Chang, Y.M., Lin, Y.L., Chang, G.D., Wu, H.C., Chen, G.C., 2019. PTPN3 suppresses lung cancer cell invasiveness by counteracting Src-mediated DAAM1 activation and actin polymerization. Oncogene 38(44), 7002-7016.
Li, X., Larsson, L., 1996. Maximum shortening velocity and myosin isoforms in single muscle fibers from young and old rats. Am. J. Physiol. 270(1 Pt 1), C352-C360.
Li, Z., Jiao, Y., Fan, E.K., Scott, M.J., Li, Y., Li, S., Billiar, T.R., Wilson, M.A., Shi, X., Fan, J., 2017. Aging-impaired filamentous actin polymerization signaling reduces alveolar macrophage phagocytosis of bacteria. J. Immunol. 199(9), 3176-3186.
Limatola, N., Vasilev, F., Chun, J.T., Santella, L., 2019. Altered actin cytoskeleton in ageing eggs of starfish affects fertilization process. Exp. Cell Res. 381(2), 179-190.
Liu, Y., Liu, N., Wu, D., Bi, Q., Meng, S., 2015. The longevity of tor1Δ, sch9Δ, and ras2Δ mutants depends on actin dynamics in Saccharomyces cerevisiae. Cell Biosci. 5, 18.
Mackenzie, A.C., Kyle, D.D., McGinnis, L.A., Lee, H.J., Aldana, N., Robinson, D.N., Evans, J.P., 2016. Cortical mechanics and myosin-II abnormalities associated with post-ovulatory aging: implications for functional defects in aged eggs. Mol. Hum. Reprod. 22(6), 397-409.
Maruta, H., Tikoo, A., Shakri, R., Shishido, T., 1999. The anti-RAS cancer drug MKT-077 is an F-actin cross-linker. Ann. N. Y. Acad. Sci. 886, 283-284.
Miralles, F., Posern, G., Zaromytidou, A.I., Treisman, R., 2003. Actin dynamics control SRF activity by regulation of its coactivator MAL. Cell 113(3), 329-342.
Mishra, M., Huang, J., Balasubramanian, M.K., 2014. The yeast actin cytoskeleton. FEMS Microbiol. Rev. 38(2), 213-227.
Misu, S., Takebayashi, M., Miyamoto, K., 2017. Nuclear actin in development and transcriptional reprogramming. Front. Genet. 8, 27.
Miyamoto, K., Gurdon, J.B., 2013. Transcriptional regulation and nuclear reprogramming: roles of nuclear actin and actin-binding proteins. Cell. Mol.

Life Sci. 70(18), 3289-3302.
Morikawa, Y., Zhang, M., Heallen, T., Leach, J., Tao, G., Xiao, Y., Bai, Y., Li, W., Willerson, J.T., Martin, J.F., 2015. Actin cytoskeletal remodeling with protrusion formation is essential for heart regeneration in Hippo-deficient mice. Sci. Signal. 8(375), ra41.
Moshier, J.A., Cornell, T., Majumdar, A.P., 1993. Expression of protease genes in the gastric mucosa during aging. Exp. Gerontol. 28(3), 249-258.
Moulding, D.A., Blundell, M.P., Spiller, D.G., White, M.R., Cory, G.O., Calle, Y., Kempski, H., Sinclair, J., Ancliff, P.J., Kinnon, C., Jones, G.E., Thrasher, A.J., 2007. Unregulated actin polymerization by WASp causes defects of mitosis and cytokinesis in X-linked neutropenia. J. Exp. Med. 204(9), 2213-2224.
Murray, P.J., Wynn, T.A., 2011. Protective and pathogenic functions of macrophage subsets. Nat. Rev. Immunol. 11(11), 723-737.
Nakamura, M., Sunagawa, M., Kosugi, T., Sperelakis, N., 2000. Actin filament disruption inhibits L-type Ca^{2+} channel current in cultured vascular smooth muscle cells. Am. J. Physiol. Cell Physiol. 279(2), C480-C487.
Nersesian, S., Williams, R., Newsted, D., Shah, K., Young, S., Evans, P.A., Allingham, J.S., Craig, A.W., 2018. Effects of modulating actin dynamics on HER2 cancer cell motility and metastasis. Sci. Rep. 8(1), 17243.
Nithianandam, V., Chien, C.T., 2018. Actin blobs prefigure dendrite branching sites. J. Cell Biol. 217(10), 3731-3746.
Noble, J.M., Ford, G.A., Thomas, T.H., 1999. Effect of aging on CD11b and CD69 surface expression by vesicular insertion in human polymorphonuclear leucocytes. Clin. Sci. (Lond.) 97(3), 323-329.
Nolz, J.C., Gomez, T.S., Zhu, P., Li, S., Medeiros, R.B., Shimizu, Y., Burkhardt, J.K., Freedman, B.D., Billadeau, D.D., 2006. The WAVE2 complex regulates actin cytoskeletal reorganization and CRAC-mediated calcium entry during T cell activation. Curr. Biol. 16(1), 24-34.
Okreglak, V., Drubin, D.G., 2007. Cofilin recruitment and function during actin-mediated endocytosis dictated by actin nucleotide state. J. Cell Biol. 178(7), 1251-1264.
Orlandi, A., Hao, H., Ferlosio, A., Clement, S., Hirota, S., Spagnoli, L.G., Gabbiani, G., Chaponnier, C., 2009. Alpha actin isoforms expression in human and rat adult cardiac conduction system. Differentiation 77(4), 360-368.
Paavilainen, V.O., Bertling, E., Falck, S., Lappalainen, P., 2004. Regulation of cytoskeletal dynamics by actin-monomer-binding proteins. Trends Cell Biol. 14(7), 386-394.
Paavilainen, V.O., Hellman, M., Helfer, E., Bovellan, M., Annila, A., Carlier, M.F., Permi, P., Lappalainen, P., 2007. Structural basis and evolutionary origin of actin filament capping by twinfilin. Proc. Natl. Acad. Sci. U. S. A. 104(9), 3113-3118.
Pan, Y., Shadel, G.S., 2009. Extension of chronological life span by reduced TOR signaling requires down-regulation of Sch9p and involves increased mitochondrial OXPHOS complex density. Aging 1(1), 131-145.
Park, B., Oh, S., Jo, S., Kang, D., Lim, J., Jung, Y., Lee, H., Jun, S.C., 2018. Determination of the molecular assembly of actin and actin-binding proteins using photoluminescence. Colloids Surf. B Biointerfaces 169, 462-469.
Paunola, E., Mattila, P.K., Lappalainen, P., 2002. WH2 domain: a small, versatile adapter for actin monomers. FEBS Lett. 513(1), 92-97.
Percipalle, P., 2009. The long journey of actin and actin-associated proteins from genes

to polysomes. Cell. Mol. Life Sci. 66(13), 2151-2165.
Pfisterer, K., Jayo, A., Parsons, M., 2017. Control of nuclear organization by F-actin binding proteins. Nucleus 8(2), 126-133.
Philp, D., Badamchian, M., Scheremeta, B., Nguyen, M., Goldstein, A.L., Kleinman, H.K., 2003. Thymosin β4 and a synthetic peptide containing its actin-binding domain promote dermal wound repair in db/db diabetic mice and in aged mice. Wound Repair Regen. 11(1), 19-24.
Piazzolla, G., Tortorella, C., Serrone, M., Jirillo, E., Antonaci, S., 1998. Modulation of cytoskeleton assembly capacity and oxidative response in aged neutrophils. Immunopharmacol. Immunotoxicol. 20(2), 251-266.
Plackett, T.P., Boehmer, E.D., Faunce, D.E., Kovacs, E.J., 2004. Aging and innate immune cells. J. Leukoc. Biol. 76(2), 291-299.
Pollard, T.D., 2016. Actin and actin-binding proteins. Cold Spring Harb. Perspect. Biol. 8(8), a018226.
Pruyne, D., Legesse-Miller, A., Gao, L., Dong, Y., Bretscher, A., 2004. Mechanisms of polarized growth and organelle segregation in yeast. Annu. Rev. Cell Dev. Biol. 20, 559-591.
Rames, M., Yu, Y.D., Ren, G., 2014. Optimized negative staining: a high-throughput protocol for examining small and asymmetric protein structure by electron microscopy. J. Vis. Exp. 90, e51087.
Ramesh, N., Anton, I.M., Hartwig, J.H., Geha, R.S., 1997. WIP, a protein associated with wiskott-aldrich syndrome protein, induces actin polymerization and redistribution in lymphoid cells. Proc. Natl. Acad. Sci. U. S. A. 94(26), 14671-14676.
Randrianarison-Huetz, V., Papaefthymiou, A., Herledan, G., Noviello, C., Faradova, U., Collard, L., Pincini, A., Schol, E., Decaux, J.F., Maire, P., Vassilopoulos, S., Sotiropoulos, A., 2018. Srf controls satellite cell fusion through the maintenance of actin architecture. J. Cell Biol. 217(2), 685-700.
Rao, K.M., 1986. Age-related decline in ligand-induced actin polymerization in human leukocytes and platelets. J. Gerontol. 41(5), 561-566.
Rao, K.M., Currie, M.S., Padmanabhan, J., Cohen, H.J., 1992. Age-related alterations in actin cytoskeleton and receptor expression in human leukocytes. J. Gerontol. 47(2), B37-B44.
Ravichandran, A., Geng, M., Hull, K.G., Li, J., Romo, D., Lu, S.E., Albee, A., Nutter, C., Gordon, D.M., Ghannoum, M.A., Lockless, S.W., Smith, L., 2019. A novel actin binding drug with in vivo efficacy. Antimicrob. Agents Chemother. 63(1), e01585-18.
Reshetnikova, G., Barkan, R., Popov, B., Nikolsky, N., Chang, L.S., 2000. Disruption of the actin cytoskeleton leads to inhibition of mitogen-induced cyclin E expression, cdk2 phosphorylation, and nuclear accumulation of the retinoblastoma protein-related p107 protein. Exp. Cell Res. 259(1), 35-53.
Rodriguez-Fernandez, J.L., Gomez, M., Luque, A., Hogg, N., Sanchez-Madrid, F., Cabanas, C., 1999. The interaction of activated integrin lymphocyte function-associated antigen 1 with ligand intercellular adhesion molecule 1 induces activation and redistribution of focal adhesion kinase and proline-rich tyrosine kinase 2 in T lymphocytes. Mol. Biol. Cell 10(6), 1891-1907.
Rosenblatt, J., Cramer, L.P., Baum, B., McGee, K.M., 2004. Myosin II-dependent cortical movement is required for centrosome separation and positioning during mitotic spindle assembly. Cell 117(3), 361-372.
Rougerie, P., Miskolci, V., Cox, D., 2013. Generation of membrane structures during

phagocytosis and chemotaxis of macrophages: role and regulation of the actin cytoskeleton. Immunol. Rev. 256(1), 222-239.

Ruggeri, E., DeLuca, K.F., Galli, C., Lazzari, G., DeLuca, J.G., Carnevale, E.M., 2015. Cytoskeletal alterations associated with donor age and culture interval for equine oocytes and potential zygotes that failed to cleave after intracytoplasmic sperm injection. Reprod. Fertil. Dev. 27(6), 944-956.

Salker, M.S., Schierbaum, N., Alowayed, N., Singh, Y., Mack, A.F., Stournaras, C., Schaffer, T.E., Lang, F., 2016. LeftyA decreases actin polymerization and stiffness in human endometrial cancer cells. Sci. Rep. 6, 29370.

Sasahara, Y., Rachid, R., Byrne, M.J., de la Fuente, M.A., Abraham, R.T., Ramesh, N., Geha, R.S., 2002. Mechanism of recruitment of WASP to the immunological synapse and of its activation following TCR ligation. Mol. Cell 10(6), 1269-1281.

Seixas, A.I., Azevedo, M.M., Paes de Faria, J., Fernandes, D., Mendes Pinto, I., Relvas, J.B., 2019. Evolvability of the actin cytoskeleton in oligodendrocytes during central nervous system development and aging. Cell. Mol. Life Sci. 76(1), 1-11.

Sellars, M.J., Vuocolo, T., Leeton, L.A., Coman, G.J., Degnan, B.M., Preston, N.P., 2007. Real-time RT-PCR quantification of Kuruma shrimp transcripts: a comparison of relative and absolute quantification procedures. J. Biotechnol. 129(3), 391-399.

Shah, A.A., Folino, G., Krasnogor, N., 2010. Toward high-throughput, multicriteria protein-structure comparison and analysis. IEEE Trans. Nanobioscience 9(2), 144-155.

Sharpless, N.E., Depinho, R.A., 2007. How stem cells age and why this makes us grow old. Nat. Rev. Mol. Cell Biol. 8, 703–713.

Simpson, P.B., Armstrong, R.C., 1999. Intracellular signals and cytoskeletal elements involved in oligodendrocyte progenitor migration. Glia 26(1), 22-35.

Sokolova, M., M. Moore, H., Prajapati, B., Dopie, J., Meriläinen, L., Honkanen, M., Matos, R.C., Poukkula, M., Hietakangas, V., Vartiainen, M.K., 2018. Nuclear actin is required for transcription during drosophila oogenesis. iScience 9, 63-70.

Song, J., Goetz, B.D., Baas, P.W., Duncan, I.D., 2001. Cytoskeletal reorganization during the formation of oligodendrocyte processes and branches. Mol. Cell. Neurosci. 17(4), 624-636.

Sousa-Squiavinato, A.C.M., Rocha, M.R., Barcellos-de-Souza, P., de Souza, W.F., Morgado-Diaz, J.A., 2019. Cofilin-1 signaling mediates epithelial-mesenchymal transition by promoting actin cytoskeleton reorganization and cell-cell adhesion regulation in colorectal cancer cells. Biochim. Biophys. Acta Mol. Cell Res. 1866(3), 418-429.

Spears, W., Furgerson, M., Sweetnam, J.M., Evans, P., Gearing, M., Fechheimer, M., Furukawa, R., 2014. Hirano bodies differentially modulate cell death induced by tau and the amyloid precursor protein intracellular domain. BMC Neurosci. 15, 74.

Staiculescu, M.C., Galinanes, E.L., Zhao, G.L., Ulloa, U., Jin, M.S., Beig, M.I., Meininger, G.A., Martinez-Lemus, L.A. (2013) Prolonged vasoconstriction of resistance arteries involves vascular smooth muscle actin polymerization leading to inward remodelling. Cardiovasc. Res. 98(3), 428-436.

Sumi, T., Hashigasako, A., Matsumoto, K., Nakamura, T., 2006. Different activity regulation and subcellular localization of LIMK1 and LIMK2 during cell cycle transition. Exp. Cell Res. 312(7), 1021-1030.

Sun, J., Luo, Q., Liu, L., Yang, X., Zhu, S., Song, G., 2017. Salinomycin attenuates liver cancer stem cell motility by enhancing cell stiffness and increasing F-actin formation via the FAK-ERK1/2 signalling pathway. Toxicology 384, 1-10.

Taniuchi, I., Kitamura, D., Maekawa, Y., Fukuda, T., Kishi, H., Watanabe, T., 1995. Antigen-receptor induced clonal expansion and deletion of lymphocytes are impaired in mice lacking HS1 protein, a substrate of the antigen-receptor-coupled tyrosine kinases. EMBO J. 14(15), 3664-3678.

Terman, J.R., Kashina, A., 2013. Post-translational modification and regulation of actin. Curr. Opin. Cell Biol. 25(1), 30-38.

Tikoo, A., Shakri, R., Connolly, L., Hirokawa, Y., Shishido, T., Bowers, B., Ye, L.H., Kohama, K., Simpson, R.J., Maruta, H., 2000. Treatment of ras-induced cancers by the F-actin-bundling drug MKT-077. Cancer J. 6(3), 162-168.

Ushijima, T., Fujimoto, N., Matsuyama, S., Kan, O.M., Kiyonari, H., Shioi, G., Kage, Y., Yamasaki, S., Takeya, R., Sumimoto, H., 2018. The actin-organizing formin protein Fhod3 is required for postnatal development and functional maintenance of the adult heart in mice. J. Biol. Chem. 293(1), 148-162.

Uzbekov, R., Kireyev, I., Prigent, C., 2002. Centrosome separation: respective role of microtubules and actin filaments. Biol. Cell 94(4-5), 275-288.

van de Willige, D., Hummel, J.J., Alkemade, C., Kahn, O.I., Au, F.K., Qi, R.Z., Dogterom, M., Koenderink, G.H., Hoogenraad, C.C., Akhmanova, A., 2019. Cytolinker Gas2L1 regulates axon morphology through microtubule-modulated actin stabilization. EMBO Rep. 20(11), e47732.

Vasicova, P., Lejskova, R., Malcova, I., Hasek, J., 2015. The stationary-phase cells of Saccharomyces cerevisiae display dynamic actin filaments required for processes extending chronological life span. Mol. Cell Biol. 35(22), 3892-3908.

Verma, A.S., Shapiro, B.H., 2006. Sex-dependent expression of seven housekeeping genes in rat liver. J. Gastroenterol. Hepatol. 21(6), 1004-1008.

Wang, M., Han, X., Sun, W., Li, X., Jing, G., Zhang, X., 2018. Actin filament-associated protein 1-like 1 mediates proliferation and survival in non-small cell lung cancer cells. Med. Sci. Monit. 24, 215-224.

Wang, W.Q., Chen, L.Y., Ding, Y.B., Jin, J., Liao, K., 2008. Centrosome separation driven by actin-microfilaments during mitosis is mediated by centrosome-associated tyrosine-phosphorylated cortactin. J. Cell Sci. 121(8), 1334-1343.

Wei, M., Fabrizio, P., Madia, F., Hu, J., Ge, H.Y., Li, L.M., Longo, V.D., 2009. Tor1/Sch9-regulated carbon source substitution is as effective as calorie restriction in life span extension. PLoS Genet. 5(5), e1000467.

Wilson, R., Brophy, P.J., 1989. Role for the oligodendrocyte cytoskeleton in myelination. J. Neurosci. Res. 22(4), 439-448.

Wu, T., Mu, Y., Bogomolovas, J., Fang, X., Veevers, J., Nowak, R.B., Pappas, C.T., Gregorio, C.C., Evans, S.M., Fowler, V.M., Chen, J., 2017. HSPB7 is indispensable for heart development by modulating actin filament assembly. Proc. Natl. Acad. Sci. U. S. A. 114(45), 11956-11961.

Wu, W., Zhou, Q., Zhao, W., Gong, Y., Su, A., Liu, F., Liu, Y., Li, Z., Zhu, J., 2018. Ginsenoside Rg3 inhibition of thyroid cancer metastasis is associated with alternation of actin skeleton. J. Med. Food 21(9), 849-857.

Xiao, H.L., Han, B., Lodyga, M., Bai, X.H., Wang, Y.C., Liu, M.Y., 2012. The actin-binding domain of actin filament-associated protein (AFAP) is involved in the regulation of cytoskeletal structure. Cell. Mol. Life Sci. 69(7), 1137-1151.

Yamada, H., Chen, D., Monstein, H.J., Hakanson, R., 1997. Effects of fasting on the expression of gastrin, cholecystokinin, and somatostatin genes and of various

housekeeping genes in the pancreas and upper digestive tract of rats. Biochem. Biophys. Res. Commun. 231(3), 835-838.

Yamamoto, M., Marui, N., Sakai, T., Morii, N., Kozaki, S., Ikai, K., Imamura, S., Narumiya, S., 1993. ADP-ribosylation of the rhoA gene product by botulinum C3 exoenzyme causes Swiss 3T3 cells to accumulate in the G1 phase of the cell cycle. Oncogene 8(6), 1449-1455.

Ye, Y.P., Jiao, H.L., Wang, S.Y., Xiao, Z.Y., Zhang, D., Qiu, J.F., Zhang, L.J., Zhao, Y.L., Li, T.T., Li, L., Liao, W.T., Ding, Y.Q., 2018. Hypermethylation of DMTN promotes the metastasis of colorectal cancer cells by regulating the actin cytoskeleton through Rac1 signaling activation. J. Exp. Clin. Cancer Res. 37(1), 299.

Yoo, J.Y., Jung, N.C., Lee, J.H., Choi, S.Y., Choi, H.J., Park, S.Y., Jang, J.S., Byun, S.H., Hwang, S.U., Noh, K.E., Park, Y., Lee, J., Song, J.Y., Seo, H.G., Lee, H.S., Lim, D.S., 2019. Pdlim4 is essential for CCR7-JNK-mediated dendritic cell migration and F-actin-related dendrite formation. FASEB J. 33(10), 11035-11044.

Yu, F., Degens, H., Li, X., Larsson, L., 1998. Gender- and age-related differences in the regulatory influence of thyroid hormone on the contractility and myosin composition of single rat soleus muscle fibres. Pflugers Arch. 437(1), 21-30.

Zacharopoulou, N., Tsapara, A., Kallergi, G., Schmid, E., Tsichlis, P.N., Kampranis, S.C., Stournaras, C., 2018. The epigenetic factor KDM2B regulates cell adhesion, small rho GTPases, actin cytoskeleton and migration in prostate cancer cells. Biochim. Biophys. Acta Mol. Cell Res. 1865(4), 587-597.

Zhang, J., Shehabeldin, A., da Cruz, L.A., Butler, J., Somani, A.K., McGavin, M., Kozieradzki, I., dos Santos, A.O., Nagy, A., Grinstein, S., Penninger, J.M., Siminovitch, K.A., 1999. Antigen receptor-induced activation and cytoskeletal rearrangement are impaired in Wiskott-Aldrich syndrome protein-deficient lymphocytes. J. Exp. Med. 190(9), 1329-1342.

Zhang, S.X., Duan, L.H., He, S.J., Zhuang, G.F., Yu, X., 2017. Phosphatidylinositol 3,4-bisphosphate regulates neurite initiation and dendrite morphogenesis via actin aggregation. Cell Res. 27(2), 253-273.

Zhao, X., Jiang, M., Wang, Z., 2019. TPM4 promotes cell migration by modulating F-actin formation in lung cancer. Onco Targets Ther. 12, 4055-4063.

Zhao, Z.S., Lim, J.P., Ng, Y.W., Lim, L., Manser, E., 2005. The GIT-associated kinase PAK targets to the centrosome and regulates Aurora-A. Mol. Cell 20(2), 237-249.

Zhaojie, L., Yuchen, L., Miao, C., Yacun, C., Shayi, W., Anbang, H., Xinhui, L., Meng, Z., Peipei, W., Hongbing, M., Feng, W., Zhiming, C., Xinyuan, G., 2019. Gelsolin-like actin-capping protein has prognostic value and promotes tumorigenesis and epithelial-mesenchymal transition via the Hippo signaling pathway in human bladder cancer. Ther. Adv. Med. Oncol. 11, 1758835919841235.

Zipfel, P.A., Bunnell, S.C., Witherow, D.S., Gu, J.J., Chislock, E.M., Ring, C., Pendergast, A.M., 2006. Role for the Abi/wave protein complex in T cell receptor-mediated proliferation and cytoskeletal remodeling. Curr. Biol. 16(1), 35-46.

Figure Legends

Table 1 Relevance of the actin cytoskeleton to different processes in cancer development and progression.

Table 2 Examples of agents that enable manipulation of the functioning and organization of the actin cytoskeleton.

Fig. 1 (a) SEM and (b) TEM images of F-actin, α-actinin, and bundled actin. (c) Fluorescent images of the actin network formed by 5 μM G-actin and (d) 5 μM G-actin with 2 μM α-actinin. The G-actin has been stained with Alexa-488-labelled phalloidin. Reproduced from Park et al., 2018 with permission from Elsevier B.V.

Fig. 2 Major factors contributing to age-associated changes in actin expression.

Fig. 3 Overview of the relevance of actin dynamics to the functional decline and age-associated disorders.

Fig. 4 (A) Confocal microscopic images of nurse cell nuclei of ovarian egg chambers, stained with actin antibodies and DAPI, from (a) the wild-type fly and (b) the mutant. Scale bar = 10 μm. (B) Scanning electron micrographs of the eggs laid by (a) the wild-type fly and (b) the mutant. Magnification = 450×. Scale bar = 200 μm. Reproduced from Sokolova et al., 2018 with permission from Elsevier B.V.