p70 S6 kinase and actin dynamics
A perspective

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Overview of p70S6K
p70S6K belongs to the AGC subfamily of serine/threonine kinases, which also includes other important signaling molecules like Akt, protein kinase A and protein kinase C. p70S6K is encoded by the ribosomal protein S6 kinase, 70 kDa, polypeptide 1 gene (RPS6KB1), which is located on chromosome 17q23.1 in humans. p70S6K, with an apparent electrophoretic mobility of 70 kDa, consists of 502 amino acids and has a molecular weight of 56,153 Da. The amino acid sequence of p70S6K has 100% similarity in all mammals so far examined. The gene has also been identified in several invertebrate species, including Drosophila melanogaster[11] and Caenorhabditis elegans.[12] A novel S6K was recently found in the yeast Schizosaccharomyces pombe.[13] All these indicate that S6K is evolutionarily conserved among eukaryotes and therefore may represent a significant functional component.

Structure of p70S6K. p70S6K can be divided into five functional domains/regions: (1) the amino (N)-terminal domain, (2) the AGC-kinase conserved catalytic domain, (3) the linker region, (4) the putative autoinhibitory domain, and (5) the carboxyl (C)-terminal domain.[14] At least eight phosphorylation sites have been mapped in endogenous kinase, including Ser411, Ser418, Thr421 and Ser424 in the autoinhibitory domain,15,16 Thr229 in the terminal autoinhibitory domain, which has sequence similarity to the substrate region of the S6 protein, may act as a pseudosubstrate and interacts with the N-terminus (Fig. 1).17,18 The kinase exists in two conformations, inactive and active state. In the inactive state of p70S6K, the carboxyl-terminal autoinhibitory domain, which has sequence similarity to the substrate region of the S6 protein, may act as a pseudosubstrate and interacts with the N-terminus (Fig. 1). According to the current model, p70S6K activation is initiated by the release of the autoinhibition exerted by the autoinhibitory domain.[19] This is then followed by a series of phosphorylation of eight or more serine or threonine residues at the autoinhibitory domain, the linker region, and then the catalytic domain, to obtain full kinase activation.[20-22]

Regulation of p70S6K. The activity of p70S6K is regulated through phosphorylation/dephosphorylation events. The phosphorylation events are stimulated by a variety of mitogenic factors.[23,24] Several upstream in vivo signaling pathways have been identified to regulate the phosphorylation and activation of p70S6K. One pathway that has been widely accepted is the phosphatidylinositol 3-kinase (PI3K)/Akt pathway.[25,26] Following stimulation, PI3K is recruited to plasma membrane and activated by G-protein coupled receptors or receptor tyrosine kinase.

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Introduction
Cell migration is an essential component of a variety of processes including wound repair,[1] angiogenesis,[2] immunity,[3] and metastasis.[4] Coordinated changes in actin cytoskeleton reorganization in response to microenvironmental signals result in migration. Thus, much effort has been made to understand the molecular machinery that drives the movement of the cell and has focused on the nature of cytoskeletal structures. Indeed, the actin cytoskeleton is essential and central to every step of the migration process. The 70 kDa ribosomal S6 kinase (p70S6K), a member of the AGC serine/threonine kinase family, was initially identified as a key player, together with its downstream effector S6, in the regulation of cellular growth and survival. The p70S6K protein has emerged in recent years as a multifunctional protein which also regulates the actin cytoskeleton and thus plays a role in cell migration. This new function is through two important activities of p70S6K, namely actin cross-linking and Rac1 and Cdc42 activation. The testis is critically dependent on an intricate balance of fundamental cellular processes such as adhesion, migration, and differentiation. It is increasingly evident that Rho GTPases and actin binding proteins play fundamental roles in regulating spermatogenesis within the testis. In this review, we will discuss current findings of p70S6K in the control of actin cytoskeleton dynamics. In addition, the potential role of p70S6K in spermatogenesis and testicular function will be highlighted.
Active PKB then phosphorylates the membrane lipid phosphatidylinositol 4,5-biphosphate PIP2 to produce phosphatidylinositol 3,4,5-biphosphate PIP3 which recruits and activates protein kinase A (PKA), Akt, and protein kinase C (PKC), respectively.

Figure 1. A model to illustrate domains and phosphorylation sites of p70S6K. p70S6K can be divided into five functional domains/regions: (1) the amino (N)-terminal domain (blue), (2) the AGC-kinase conserved catalytic domain (yellow), (3) the linker region (green), (4) the putative autoinhibitory domain (red), and (5) the carboxyl (C)-terminal domain (purple). Eight phosphorylation sites have been mapped.

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Actin Filament Dynamics

A dynamic actin cytoskeleton is essential for many cellular functions, such as maintenance of cell shape, cell junction, and cell motility. Actin in cells exists in three different forms: monomeric (globular-actin; G-actin), oligomeric, and polymeric (filamentous actin; F-actin). F-actin is polarized with a fast-growing plus end, also known as barbed end, and a slow-grown minus end, also known as pointed end. Reorganization of the actin cytoskeleton, including polymerization, depolymerization, nucleation, bundling/cross-linking, capping, severing, and branching, is facilitated by the actin binding proteins. The Rho family GTPases, including Rac1–3, Cdc42, and RhoA-C, play a central role in coordinating the actin binding proteins for cytoskeleton reorganization. Rac1 and Cdc42 transduce signals to the actin binding proteins through two major types of interacting proteins: (1) Wiskott-Aldrich syndrome protein (WASP)/suppressor of cAMP receptor (Scar)/WASP family verprolin homology protein (WAVE) and (2) p21-activated kinase 1 (PAK1). WASP/Scar/WAVE promotes F-actin nucleation upon Rac1 and Cdc42 activation. While WASP family protein is activated by Cdc42, Scar/WAVE family protein is indirectly activated by Rac1 through the Nck-adaptor complex. Active WASP/WAVE then undergoes conformational change and binds with the ATP-G-actin binding protein, profilin, and the actin-related protein2/3 (Arp2/3) complex. These work synergistically to speed up actin branching and polymerization through actin nucleation of ATP-G-actin to the pre-existing actin filaments, thereby facilitating the building of the dendritic actin network. On the other hand, PAK1, a downstream effector of Rac1 and Cdc42, phosphorylates and activates LIM kinase (LIMK). LIMK phosphorylates cofilin, an actin filament serving protein, leading to its inactivation, which in turn inhibits depolymerization and severing of actin filaments. LIMK can also be phosphorylated by p160 Rho-associated coiled-coil-containing protein kinase (ROCK), a downstream effector of Rho. Apart from the LIMK, Rho can also regulate actin polymerization through another downstream effector diaphanosus-related-filamin, which promotes the polymerization of unbranched filaments. p70S6K in the control of actin cytoskeleton. The Rho GTPases and p70S6K were first shown to coexist in the same pathway in a study by Chou et al. Rac1 and Cdc42, but not RhoA, complex with and activate p70S6K, which can be blocked by the mTOR inhibitor, rapamycin and the PI3K inhibitor, wortmannin. A role of p70S6K in actin cytoskeleton reorganization was further hinted by Berven et al. and through to colocalize with the stress fibers and actin act at the leading edge of Swiss3T3 fibroblasts under growth factor stimulation. This colocalization of p70S6K and stress fibers was suggested to regulate actin polymerization as rapamycin treatment could inhibit the elongation and organization of actin-stress fibers via inhibition of p70S6K. However, the biological function of such an interaction is not known. Recently, our lab not only identified p70S6K as a critical regulator of the actin cytoskeleton but also showed that it is pivotal for the directional migration of cancer cells, which is a prerequisite of metastasis (Fig. 2). Our findings provide several insights into the regulation of p70S6K on the actin cytoskeleton. First, we have demonstrated for the first time that p70S6K can directly bind with and cross-link F-actin in vitro. Moreover, active p70S6K colocalizes with the actin filaments at the leading edge of motile cells in vivo and p70S6K/F-actin colocalization is cytochalasin D-sensitive. However, unlike some actin bundling/cross-linking proteins,
p70S6K does not change the rate of actin polymerization, but stabilizes actin filaments by decreasing the rate and extent of ADP/ATP-dependent actin depolymerization.

Second, our results suggest that the correlation of p70S6K with Rho GTPases and cell migration depends on the cell type or on the signaling context, leading to differential functions. In fibroblasts, p70S6K acts as a downstream effector of Rac1 and Cdc42. It is interesting to note that this activation of p70S6K by Rac1 and Cdc42 appears to be independent of the ability of these Rho GTPases to be activated during cell cycle progression. By contrast, in carcinomas and epithelial cells, we have shown that p70S6K functions upstream of both Rac1 and Cdc42 to regulate actin cytoskeleton reorganization and thus cell migration, in which Rac1 and Cdc42 are known to function. We also show an essential role for PAK1 in this process.

Third, the regulation of the actin cytoskeleton by p70S6K reveals that many oncogenic signals could mediate cancer cell invasion and metastasis by modulating p70S6K activity. For example, p70S6K is a downstream effector of the PI3K/Akt pathway, which is frequently activated in human cancers. Moreover, p70S6K also well known to be activated by hormones, cytokines, and growth factors. Our finding that p70S6K binding to the actin cytoskeleton is more effective in the presence than in the absence of p70S6K phosphorylation indicates that it is a dynamic regulation of the actin cytoskeleton, reinforcing the notion that cell migration is a finely tuned event. This also implies that the actin-binding domain in p70S6K in an inactive conformation may be important and suggests an additional regulation inside the cell.

Actin Cytoskeleton Reorganization and Spermatogenesis

Spermatogenesis is a process in which diploid spermatogonia (germ cells) go through a series of stages and differentiate into mature spermatozoa between Sertoli cells within the seminiferous tubule. Many cellular events are involved in this process, including cell division, differentiation, cell movement, reorganizing tissue and cell junctions,76 changes in cell shape and size such as differentiation of elongated spermatids from round spermatocytes, all of which require dynamic reorganization of the actin cytoskeleton. Actin cytoskeleton dynamics and some of the regulatory proteins in spermatogenesis have been comprehensively reviewed.77 We will focus on the activities of actin bundling/cross-linking and Rho GTPases.

Actin cytoskeletal network in Sertoli cell. Sertoli cells in the seminiferous tubule extend from the basal lamina to the lumen of the tubule and are able to alter their cell shape to accommodate morphological changes of germ cells, thereby providing both structural and nutritional support to the germ cells throughout their development.78 In Sertoli cells, F-actin are abundantly detected and are concentrated at the adherens junctions (AJs), the ectoplasmic specialization (ES) and the tubulobulbar complex (TBC).77 The arrangement of F-actin in the AJs, ES and TBC, is drastically different from that in other polarized epithelia which will be discussed in the following sections.

Ectoplasmic specialization (ES). ESs are localized at two sites in seminiferous epithelium: (1) junctions between adjacent Sertoli cells near the basal lamina of the seminiferous epithelium, namely basal ES; (2) and adhesion between Sertoli cells and elongating/elongated spermatids at the apical region of the seminiferous epithelium, namely apical ES. F-actin at the ES forms a hexagonal array between the plasma and endoplasmic reticulum membranes of Sertoli cells.79 Although myosin VIa, an actin motor protein, has been found to be enriched at the apical ES, the actin bundles at ES are thought to be non-muscle type. These actin bundles may structurally contribute to the stability of the inter-cellular adhesion at ES. The mechanisms underlying the above processes are largely unknown. However, based on the actin bundle structure at the ES, fornix that has been shown to be abundant in Sertoli cells has been proposed to be important in the regulation of actin polymerization at the ES.79,80 Ena/VASP family proteins that promote actin elongation at pointed end by stabilizing actin filaments by decreasing the rate and extent of ADP/cofilin-dependent actin depolymerization.

Rho GTPases and cell migration depends on the cell type or on the signaling context, leading to differential functions. In fibroblasts, p70S6K acts as a downstream effector of Rac1 and Cdc42. It is interesting to note that this activation of p70S6K by Rac1 and Cdc42 appears to be independent of the ability of these Rho GTPases to be activated during cell cycle progression. By contrast, in carcinomas and epithelial cells, we have shown that p70S6K functions upstream of both Rac1 and Cdc42 to regulate actin cytoskeleton reorganization and thus cell migration, in which Rac1 and Cdc42 are known to function. We also show an essential role for PAK1 in this process.

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apical TBC,28 supporting the proposed mechanism of the actin network formation. Rac1 and Cdc42 that activate the Aps2/3 mechanism have been detected in the cytoplasm of Sertoli cells around the spermatid head29 and inactivation of Rho GTPases by toxin A causes disaggregation of actin cytoskeleton in Sertoli cells.30 In addition to the actin binding proteins mentioned above, coflin,26 and Ep38 have also been shown to localize to the TBC, suggesting that actin bundling and actin severing and/or depolymerization are required in the formation of actin network at the TBC.

Actin regulatory proteins in germ cells. During spermatogenesis, round germ cells undergo dramatic morphological changes and remodel into mature spermatozoa with head and tail. F-actin in spermatids is concentrated in the intercellular junctions, the subacrosomal space, the acroplaxome, and the manchette. Actin and its regulatory proteins therefore have important functions in regulating the development and morphogenesis of germ cells. The actin bundling protein fascin has been shown to express in the head of elongating spermatids. Another actin bundling protein Ep38 has also been detected in germ cells although its expression is less than that in Sertoli cells.31 In addition to the actin bundling proteins, the actin polymerization and branching promoters mDia1/281 and WAVE198 have also been shown to express in spermatocytes or spermatids, suggesting actin bundling, polymerization, and branching may be involved in spermatid development.

**p70**^{S6K} **in Spermatogenesis**

Several studies have suggested that **p70**^{S6K} may have a role in spermatogenesis by regulating the development of primary Sertoli cells under follicle stimulating hormone (FSH) and luteinizing hormone (LH) stimulation.9,32 Although there are no studies demonstrating that **p70**^{S6K} may play a role in actin cytoskeleton reorganization in Sertoli cells, a report by Riera et al., which focused on the interaction between p70S6K-stimulated lactate production in Sertoli cells,105 may provide hints on this role. The results showed that IL-1β increases phosphorylation of **p70**^{S6K}, but the activation is not related to lactate production. Recent studies have also shown that IL-1 can regulate the dynamics of actin cytoskeleton and cell junctions in addition to its well-known role in innate immunity109 and tissue homeostasis,15 suggesting that **p70**^{S6K} may be a regulator of IL-1 on actin cytoskeleton reorganization. Some other cytokines and growth factors which are potent activator of **p70**^{S6K} in other cell types, such as TGFβ, and hepatocyte growth factor (HGF), also have important functions in testicular development and spermatogenesis (Table 1).

**Cytokines involved in spermatogenesis** have been reviewed by Xia et al.104 These cytokines mostly activate **p70**^{S6K} through PI3K/Akt and MEK/ERK pathways, which have been shown to regulate AJ dynamics and spermatogenesis. The expression or activities of the key components in PI3K/Akt and MAPK pathways, including the 85α and p110α subunits of PI3K, Akt, and ERK1/2, have been shown to increase during the AJ assembly of Sertoli cells and germ cells (i.e., apical ES). Both PI3K and active Akt are abundant at the site of apical ES from stages IV to VII and are detected at the basal ES. Inhibition of PI3K using inhibitors is able to disrupt the AJ.104 All these suggest that the PI3K/Akt and MAPK pathways may be required for AJ assembly (for ERK pathway review, ref. 106). Siu et al. has also shown the expression of PAK2 during AJ assembly and suggested a role of PAK in AJ formation. Although the expression of PAK2 but not PAK1 increases during AJ assembly, the activity of PAK1 was not detected in the study.108 Recently, Wong et al. has revealed that Cdc42 mediates TGFβ3-induced BTB disruption by enhancing endocytosis of integral membrane proteins at BTB.107 This suggests a possible mechanism by which **p70**^{S6K} may regulate the BTB restructuring at stage VIII through mediating the activation of PI3K/Akt and MAPK pathways.

**Table 1.** Potent activators of **p70**^{S6K} in testis

| Function of cytokines in testis | Activation of **p70**^{S6K} in testis | References |
|--------------------------------|--------------------------------------|------------|
| **Hormones** | | |
| FSH | Regulate the development of Sertoli cells | Yes | 100 |
| **Cytokines** | | |
| IL-1α | Regulate Sertoli-germ cell adhesion | n.d. | 99,100 |
| IL-1β | Regulate lactate production in Sertoli cells | Yes | 101 |
| BMP-4 | Maintain spermatogenesis, promote differentiation of spermatagonia | n.d. | 110-112 |
| **Growth factors** | | |
| EGF | Enhance spermatogenesis proliferation and differentiation | n.d. | 113-114 |
| FGF2 | Induce testosterone production in Leydig cells | Yes | 115 |
| HGF | Modulate Sertoli-Sertoli tight junction dynamics; increase steroidogenetic activity of Leydig cell | n.d. | 116-118 |
| PDGF | Regulate the development of the Leydig cell lineage and spermatogenesis | n.d. | 110,111 |
| TGFβ1 | Inhibit steroidogenesis in Leydig cells | n.d. | 119,120 |

**Abbreviations:** BMP-4, bone morphogenetic protein-4; EGF, epidermal growth factor; FGF2, fibroblast growth factor 2; FSH, follicle stimulating hormone; HGF, hepatocyte growth factor; IL-1α, interleukin-1α; IL-1β, interleukin-1β; n.d., not determined; PDGF, platelet-derived growth factor; SCF, stem cell factor; TGFβ1, transforming growth factor-β1.
of Cdc42. Thus, extracellular stimuli may activate p70S6K via PI3K/Akt and MAPK pathways, which in turn may lead to actin cytoskeleton reorganization at AJs and BTB restructuring through Rac1/Cdc42 activation. A possible perspective of p70S6K in regulating the actin cytoskeleton dynamics of spermatogenesis in Sertoli cells is shown in Figure 3.

In germ cells, the expression of p70S6K is relatively constant during its maturation; however, the kinase activity of p70S6K is increased. Immunohistochemistry detection of p70S6K also showed that there is a nucleus-to-cytoplasm translocation of p70S6K during spermatogenesis. Moreover, p70S6K has been shown to mediate cytokine-induced signaling to stimulate proliferation of type A spermatogonia, which may play a role in the biosynthesis and preparation of germ cells for fertilization.

Concluding Remarks and Perspectives

The regulation of ES recently has received a great deal of attention because they may shed light on male contraceptive development. However, the signaling pathways that regulate actin polymerization and depolymerization at the ES have not been studied in detail. It is suspected that different cytokines and hormones may be involved in changes in the dynamics of actin filaments in the testis. Our new findings have linked p70S6K to the actin cytoskeleton and have led to the suggestion that this widely studied kinase may play a key role in epithelial cell motility. Altered expression of p70S6K and several actin bundling/cross-linking proteins are being reported in the testis. Rho GTPases activities are important for the maintenance and formation of the actin cytoskeleton in Sertoli cells. Further demonstration of this intriguing phenomenon of a new role for p70S6K in regulating the actin dynamics in the testis would have interesting and important consequences. In addition, a better understanding of how the different networks of p70S6K functional interactions are orchestrated in a stimulus or context-specific way, as well as the functional roles on actin reorganization in specific cellular and animal experimental models are essential. This knowledge likely will contribute to a new and important piece in the complex jigsaw of spermatogenesis and male infertility.

Figure 3. Schematic perspective of p70S6K on spermatogenesis regulation in Sertoli cells. p70S6K activation through the PI3K/Akt or MAPK pathways may have a possible role in regulating the actin cytoskeleton at AJs and BTB restructuring through Rac1/Cdc42 activating activities.
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