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Viral activation of stress-regulated Rho-GTPase signaling pathway disrupts sites of mRNA degradation to influence cellular gene expression

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Viruses are useful tools that often reveal previously unrecognized levels of control within a cell. By studying the oncogenic Kaposi's sarcoma-associated herpesvirus (KSHV), we discovered a new signaling axis in endothelial cells (ECs) that links actin cytoskeleton dynamics to post-transcriptional control of gene expression. Translational repression and rapid decay of mRNAs containing AU-rich elements (AREs) occurs in cytoplasmic RNA granules known as processing bodies (PBs). Rho-GTPase activity influences PB dynamics but mechanistic details remain obscure. We have previously shown that the KSHV Kaposin B protein blocks the degradation of ARE-mRNAs that encode potent cytokines and angiogenic factors, at least in part by preventing PB formation. Moreover, Kaposin B is sufficient to cause marked alterations in endothelial cell physiology including the formation of long parallel actin stress fibers and accelerated migration and angiogenic phenotypes. All of these phenotypes depend on Kaposin B-mediated activation of a non-canonical signaling pathway comprising the stress-inducible kinase MK2, hsp27, p115RhoGEF and RhoA. Accelerated endothelial cell migration and angiogenesis depends on the subsequent activation of the RhoA-dependent kinase ROCK, but PB disruption is ROCK-independent. In this *Commentary*, we discuss implications of the activation of this signaling axis, and propose mechanistic links between RhoA activation and PB dynamics.

Keywords: cytoskeleton, Kaposi's sarcoma-associated herpesvirus, MK2, p-body, Rho-GTPase

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Introduction

Kaposi's sarcoma-associated herpesvirus (KSHV), also known as human herpesvirus-8, is the infectious cause of the AIDS-related malignancy Kaposi's sarcoma (KS).[1] KS lesions are predominantly comprised of KSHV-infected proliferating endothelial cells (ECs) that display a hallmark elongated or 'spindled' morphology (**Fig. 1A**). KS lesions have a strong inflammatory character, with elevated levels of pro-inflammatory cytokines and angiogenic factors, and marked lymphocyte infiltration.

KSHV establishes persistent, life-long infection of its human host, and displays 2 modes of infection; a relatively quiescent 'latent' phase, and a 'lytic' phase marked by viral replication and release of infectious progeny. KSHV research has been greatly aided by primary $_{EC}$ infection models that support both latent and lytic phases of viral replication, while faithfully recapitulating many of the features of KS tumors. In the majority of KS spindle cells, or *in vitro*-infected primary ECs, the virus remains latent and gene expression is limited to 6 consensus protein products (LANA, v-cyclin, v-FLIP, Kaposins A, B, and C) and 12 pre-miRNAs that are processed into as many as 25 mature miRNAs.[2-4] Several latent gene products have been shown to contribute to dramatic alterations in $_{EC}$ physiology.[5-8] Meanwhile, KSHV lytic replication is thought to contribute to KS by promoting viral dissemination and the secretion of pathogenetically-important cytokines and growth factors[9,10] (**Fig. 1A**).

Both latent and lytic KSHV gene products have been shown to modulate RhoA activity, cytoskeleton dynamics and cell morphology. RhoA is activated in the earliest stages of infection, and is required for viral entry and capsid trafficking to the nucleus.[11-14] Upon establishment of

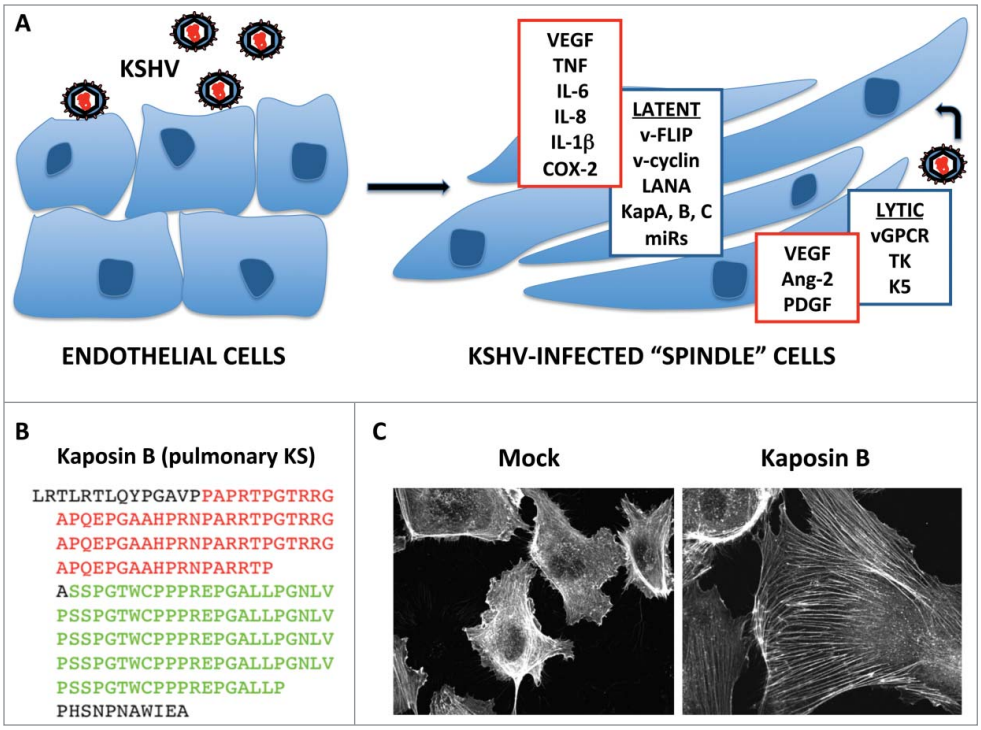

Figure 1. KSHV infection alters endothelial cell gene expression and physiology. (**A**) KSHV infection of endothelial cells (ECs) commonly results in the establishment of latency, wherein the viral genome is maintained as a circular episome in the nucleus, and gene expression is limited to products of the latency locus that include LANA, v-cyclin, v-FLIP, the Kaposins and 12 pre-miRNAs that can be processed into at least 25 mature miRNAs. In turn, these products modulate signal transduction pathways, altering the actin cytoskeleton and cell-cell contacts, which leads to the distinctive spindle shape. Reactivation from latency and expression of a wider range of viral gene products associated with lytic replication is commonly observed in KS tumors; lytic gene products include vGPCR, K5 and TK. Increased Kaposin mRNA transcription during lytic replication causes marked increases in production of Kaposin proteins. Together, KSHV latent and lytic gene products markedly alter the EC secretome, causing increased release of angiogenic factors and pro-inflammatory cytokines. (**B**) The Kaposin mRNA is largely comprised of 2 sets of GC-rich tandem repeats; the chief product of this transcript is Kaposin B, which comprises proline/arginine-rich repeats (red) fused to proline/leucine-rich repeats (green). (**C**) Kaposin B expression in primary ECs (HUVECs) is sufficient to cause the formation of actin stress fibers.

latency, the latent gene product viral FLICE inhibitory protein (v-FLIP) causes potent NF-κB activation and contributes to cytoskeletal remodeling and spindling of ECs.[6,15] Reactivation from latency causes expression of the full range of viral gene products, including a potent cell surface localized signaling protein, viral G protein-coupled receptor (vGPCR), and a viral tyrosine kinase (TK), that activate RhoA and remodel the actin cytoskeleton.[16,17] Meanwhile, EC morphology and adherens junction integrity is compromised during lytic replication at least in part through the action of K5, a homolog of the MARCH family of human E3 ubiquitin ligases, which disrupts adherens junctions by proteasomal destruction of vascular endothelial (VE) cadherin[18] (**Fig. 1A**). Thus, viral gene products elicit dramatic EC morphology changes in both latent and lytic phases of KSHV infection.

Kaposin B Activates the Stress-Responsive MK2-RhoA Signaling Axis

During latent KSHV infection, a complex translational program involving initiation at non-canonical start codons on the kaposin transcript, and decoding multiple GC-rich repeats, results in the generation of several kaposin protein products, including Kaposin B (KapB). KapB is a highly repetitive, proline-rich protein comprised largely of 2 sets of reiterated 23-amino acid direct repeats, known as DR1 and DR2[19,20] (**Fig. 1B**). A genetic screen revealed that KapB binds the host cell kinase mitogen-activated protein kinase (MAPK)-associated protein kinase 2 (MK2),[20] an important downstream effector kinase in the stress-activated p38 MAPK signaling pathway that responds to extracellular inflammatory signals or environmental stress. Activated MK2 phosphorylates a variety of nuclear and cytoplasmic target proteins, including the small heat shock protein hsp27. Phosphorylated hsp27 participates in actin remodeling by forming an active complex with p115RhoGEF and RhoA.[21] By binding and activating MK2, KapB achieves constitutive activation of this non-canonical MK2/hsp27/p115RhoGEF/RhoA signaling axis.[22] Many studies have linked either p38/MK2 or RhoA activation to a common set of EC phenotypes that include actin stress fibers, changes to cell migration, angiogenesis and permeability (**Table 1**). The emergence of this new non-canonical signaling pathway may reconcile some of these disparate observations into a unified model of stress-regulated cytoskeleton control, especially as it relates to EC physiology.

We are actively investigating the role of the MK2-RhoA signaling axis in KSHV infection. We have shown that stimulation of this pathway by KapB has several significant outcomes. MK2 and RhoA are both major regulatory proteins of the actin cytoskeletal network; their activation by KapB has several predictable outcomes, including changes in cell shape, polymerization of actin and rearrangement of actin filaments (**Fig. 1C**), cell migration and angiogenesis. All of these processes have been previously linked to RhoA activity. However, by hijacking this key regulatory signaling axis, KapB also disperses cellular PBs, which correlates with stabilization of labile AU-rich element (ARE)-containing

Table 1. Functional overlap between the phenotypic consequences of p38/MK2/hsp27 and RhoA/ROCK pathway activation in the literature. Several studies over the last 2 decades pinpoint the important role of these 2 pathways in the control of actin stress fiber formation, cell morphology, migration and endothelial barrier integrity. These pathways have also been shown to control gene expression via the modulation of mRNA stability and PB dispersion. However, very few studies have linked MK2 to the downstream activation of RhoA. Our recent work highlights the important connection between these 2 regulatory pathways.[22] Please note that the references within this table are a mere subset of the many excellent studies performed in this field (with a focus on work performed in endothelial cells) and the table is meant to illustrate the connection between phenotypes that now link these 2 fields. We apologize to the authors whose work was not cited here due to space limitations

Phenotype	p38/MK2/hsp27	RhoA/ROCK
Cell Morphology and Actin Stress Fibers	22,64,65,66,67,68,69,70,71,72,73,74,75,92,99	17,22,65,66,69,76,77,78,79,80,81,82,83,84,85,86,87,88,108
Cell Migration and Invasion	22,65,70,71,72,74,75,89,90,91,92,99	22,41,42,65,79,86,93,94,95,96
Endothelial Barrier Dysfunction	64,69,73,97,98,99,100,101	69,77,80,81,82,84,85,101,102,103,104,105,106,107,108,109,110
Processing Body Dynamics	22,28	22,27,28
Gene Expression (mRNA decay)	22,28,71,72,111,112,113,114,115,116,117,118,119,120,121,122	22,27,28,117,121,123,124

mRNAs. Previous studies linked activation of the p38/MK2 pathway with enhanced stability of ARE-mRNAs and increased expression of ARE-mRNA products including potent pro-inflammatory cytokines, angiogenic molecules, and EC barrier regulators.[23,24] MK2 phosphorylates several ARE-binding proteins (ARE-BPs), thereby enhancing ARE-mRNA stability.[20,25] PBs are a major site of ARE-mRNA decay;[26] our work shows that KapB mediates PB dispersion in a RhoA-dependent manner that correlates with the increased stability of ARE-mRNAs.[22,27,28] Notably, KapB is not alone in activating MK2 and RhoA; we and others have shown that the lytic gene product vGPCR, a constitutively active homolog of the human CXCR2 chemokine receptor, activates MK2 via Rac1-dependent MAPK activation, and independently activates RhoA by assembly of canonical cell surface G-protein-containing signaling complexes.[28] Thus, vGPCR also affects PB dynamics, ARE-mRNA stability and actin polymerization, but by distinct means. The functional relevance of the convergence of KapB and vGPCR on these common phenotypes remains unclear, but suggests that manipulation of these central nodes of stress signaling may support efficient viral replication.

Processing Bodies Control Inflammatory Mediator Release by ECs

The precise coordination of mRNA (mRNA) turnover and translation is a central feature of eukaryotic gene expression. Processing bodies (PBs) are small ribonucleoprotein (RNP)-containing cytoplasmic granules that promote the decay or translational arrest of cytoplasmic mRNA molecules. PBs regulate the constitutive decay of ARE-mRNAs,[26,29-32] a class of constitutively labile mRNAs that encode potent regulatory molecules such as growth factors, pro-inflammatory cytokines, and angiogenic factors. ARE-mRNA turnover can be prevented by specific signaling events, thereby providing a mechanism for the cell to rapidly increase pools of a specific class of 'early response' mRNAs and their protein products. Thus, precise control of PB assembly and disassembly can significantly impact the expression of potent regulatory molecules.

PBs form visible cytoplasmic foci that are constitutively present in most cells and contain the requisite enzymes for rapid mRNA deadenylation, decapping and 5′-3′ exonucleolytic degradation.[29,30,32-35] PBs are extremely dynamic, changing in size and number in response to cell cycle stage, nutrient availability, and stresses such as ultraviolet light (UV), osmotic shock and other inhibitors of global translation.[27,33,35,36] PBs can also transiently associate and exchange cargo with stress granules (SGs), cytoplasmic foci that triage stalled translationally-competent mRNPs.[34] PB assembly and disassembly is influenced by changes in the degradative capacity of the cell; for example, when 5′-3′ exonucleolytic decay is prevented, the resulting accumulation of cytoplasmic mRNA awaiting destruction causes PB size and number to increase, whereas inhibiting *de novo* transcription or halting translation by trapping mRNA in polysomes has the opposite effect.[37,38] PBs also maintain a dynamic relationship with the cytoskeleton; stationary PBs associate with actin bundles whereas mobile PBs connect to the microtubule network.[36,39,40] Though PB formation was recently shown to be modified by the cytoskeletal regulator RhoA,[22,27,28] the precise mechanism of action remains to be elucidated.

RhoA as a Regulator of Gene Expression

The Rho family of small GTPases are molecular switches that cycle between inactive GDP- and active GTP-bound forms and thereby control several fundamental cellular processes. RhoA regulates actin cytoskeleton dynamics to facilitate normal cell attachment, the formation of actin stress fibers, cell migration and angiogenesis (summarized in[41-46] and **Table 1** and references therein). RhoA activation also couples changes to the actin cytoskeleton with increased transcription and translation under certain circumstances (described below). Additional mechanisms for RhoA-mediated control of gene expression have recently emerged in the literature, including intriguing new cytoskeleton-independent modes of control. Considering the wealth of literature on RhoA and cytoskeletal dynamics, we are actively exploring several potential models for MK2/RhoA-dependent PB dissolution.

RhoA Regulates Transcription by Modifying the Status of the Actin Cytoskeleton

RhoA controls the transcription of genes containing serum-response elements (SREs) because it modifies the balance of monomeric globular actin (G-actin) and filamentous actin (F-actin) within the cell. As a general rule, in cultured cells the ratio of G-actin to F-actin is approximately 1:1.[47] RhoA activation causes increased actin polymerization and formation of stress fibers. The subsequent loss of free G-actin leads to the dissociation of the transcriptional co-activator megakaryoblastic leukemia 1 (MKL1) that normally binds G-actin monomers in the cytoplasm. Free MKL1 translocates to the nucleus and collaborates with serum response factor (SRF) to induce transcription of SRE-regulated genes, including many cytoskeletal genes. In this way, RhoA couples changes in the actin cytoskeleton to transcription control.[48-50]

RhoA has also been linked to transcriptional regulation by the growth-regulating Hippo pathway. In the canonical Hippo tumor suppressor pathway the Mst1/2 and Lats1/2 kinases phosphorylate pro-growth YAP/TAZ transcription factors causing their nuclear exclusion and degradation. This pathway is exquisitely sensitive to changes in RhoA and the cytoskeleton. RhoA inhibition or F-actin disruption inhibits YAP/TAZ transcription.[51-53] Conversely, stabilization of the actin cytoskeleton with jasplakinolide causes YAP/TAZ activation.[54] Unlike the RhoA/actin/MKL1 pathway described above, the Hippo pathway is insensitive to changes in G-actin:F-actin ratio.[51] Rather, emerging evidence indicates that F-actin structure and cell morphology regulate YAP/TAZ localization and activity.[51-53,55]

G-actin Regulates Translation Initiation in Times of Stress

Eukaryotic cells have mechanisms to arrest protein synthesis and promote cell survival in times of stress through the action of kinases that phosphorylate eukaryotic initiation factor-2-α (eIF2α). - This is known as the integrated stress response (ISR).[56] When stress is resolved, the resumption of protein synthesis requires eIF2α dephosphorylation by a phosphatase complex comprised of a catalytic domain (protein phosphatase 1 [PP1]) and a regulatory domain (PPP1R15).[57] Two recent papers together indicate that G-actin associates with this complex and is required for efficient dephosphorylation of eIF2α.[57,58] Depletion of the G-actin pool with jasplakinolide causes PPP1R15A-PP1 complex destabilization, thereby extending the period of translation arrest. Thus, proper orchestration of the ISR requires integration of signals from the actin cytoskeleton.

A Novel Mechanism of Post-transcriptional Control of Gene Expression: RhoA–Mediated Dispersion of Cytoplasmic Processing Bodies

Through our studies of a PB-regulating virus, we discovered new links between the non-canonical stress-responsive MK2/hsp27/p115RhoGEF/RhoA signaling pathway and the regulation of PB dynamics. Our detailed investigation of the mechanism of KSHV KapB-mediated control of this pathway revealed signal bifurcation downstream of RhoA activation, leading to 2 mechanistically distinct outcomes; (i) ROCK1/2-dependent alterations in cell shape, actin polymerization and stress fiber formation, and enhanced migratory and angiogenic capacity of primary ECs, (ii) ROCK1/2-independent dissolution of PBs that correlated with increased stability and translation of normally labile ARE-mRNAs. With so little currently known about the dynamic regulation of PBs, this represents an excellent opportunity for further mechanistic studies. Here, we consider 3 possible models for RhoA-mediated PB dissolution (**Table 2**).

Model 1: PB disruption due to actin-mediated translation control. Similar to RhoA-mediated control of SRE transcription and the ISR, PB disruption may depend upon RhoA-induced stress fiber formation and reduced G-actin:F-actin ratio. If so, we predict that alteration of actin dynamics in a RhoA-independent manner will also affect PB size and number. These investigations are underway and employ 2 toxins: jasplakinolide, that causes aberrant F-actin bundles to form and thus depletes cytoplasmic G-actin, and latrunculin B, which depolymerizes actin to increase G-actin levels.[59] In this model, PBs could be inhibited by ISR potentiation and extended periods of translation arrest that may disrupt the bulk flow of mRNAs to nascent PBs. Alternatively, PB formation could be affected by modulation of MKL1 or Hippo pathway signal transduction

Table 2. Models describing potential interactions between Rho-GTPases, the actin cytoskeleton and p-bodies

Model 1	Model 2	Model 3
PB disruption due to alterations in G-actin:F-actin ratios	PB disruption by RhoA effector proteins	PB disruption due to interference with linkage to cytoskeleton
RhoA activation decreases ratio of G-actin:F-actin	RhoA activation stimulates specific downstream effector proteins.	RhoA activation stimulates specific downstream effector proteins and/or cytoskeleton alterations.
Decreased G-actin availability affects signal transduction and/or the ISR.	Disrupts PB Formation by causing post-translational modification or depletion of key PB scaffolding proteins	Mechanical disruption interfering with PB linkages to cytoskeleton, decreasing PB formation
actin dependent	actin independent	actin dependent or independent

(described above) in a previously unappreciated fashion.

Model 2: PB disruption by RhoA effector proteins. PB disruption could depend on downstream actions of known RhoA effector proteins, including Rho-associated kinases and Dia proteins. Recent studies have pinpointed phosphorylation of PB resident proteins as key to the control of their assembly.[60-62] For example, the direct phosphorylation of PB scaffolding protein Pat1 by cAMP-dependent protein kinase PKA causes PB dissolution and reduces cell survival in times of stress.[60] Similarly, several viruses have been shown to accelerate the decay of PB resident proteins, or recruit PB resident proteins to viral replication compartments to enhance replication.[63] We are actively investigating whether individual PB resident proteins are degraded or modified to alter the structural scaffolds required for PB assembly.

Model 3: PB disruption due to interference with linkage to cytoskeleton. Stationary PBs associate with actin bundles whereas mobile PBs connect to the microtubule network,[36,39,40] and these contact sites may be disrupted by active RhoA signaling and activation of specific downstream effector proteins. Alternatively, the formation of particular F-actin structures such as stress fibers may place a mechanical strain on the linkage between PB and cytoskeletal structures, mediating their dissociation. Time-lapse live confocal microscopy will permit precise measurements of PB dynamics in live cells, tracking the changes that occur to PBs, the actin cytoskeleton, and microtubules immediately after RhoA activation.

Viruses are excellent teachers, and the study of KSHV has shed new light on a poorly characterized MK2/hsp27/p115RhoGEF/RhoA signaling pathway, providing links to important aspects of EC physiology. The most important questions now facing us relate to links between this stress-regulated signaling pathway and control of PB formation. Elucidating these mechanistic details will expand our understanding of RhoA-mediated control of gene expression.

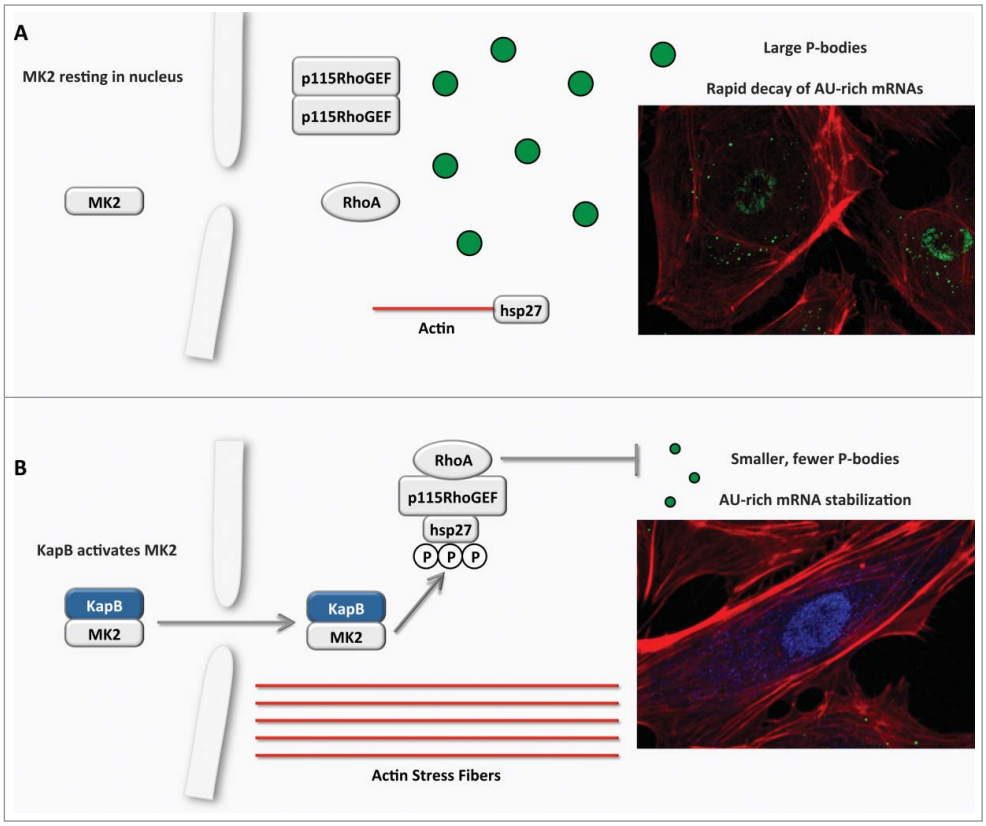

Figure 2. Model describing the effects of KapB in altering endothelial cell cytoskeleton and reprogramming gene expression by disrupting P-bodies and stabilizing ARE-mRNAs. (**A**) In the absence of environmental stress or infection, MK2 remains in the nucleus, hsp27 participates in capping actin filaments, p115RhoGEF is found in a cytosolic oligomer-induced inhibitory state, and RhoA is not active. In this resting state, p-bodies are clearly evident in the cytoplasm and participate in the decapping and degradation of labile AU-rich element (ARE) containing mRNAs. (**B**) KapB mimics the stress-induced MK2 activation by binding to MK2 and stimulating its kinase activity, resulting in hsp27 phosphorylation and the stimulation of p115RhoGEF activity, leading to RhoA activation. The consequences of the dual stimulation of RhoA and MK2 by KapB are as follows: 1. RhoA and ROCK-dependent formation of actin stress fibers, and migratory and angiogenic phenotype and 2. RhoA-dependent but ROCK-independent dispersal of PBs that correlates with the increased stability of ARE-containing mRNAs and the translation of their encoded proinflammatory and angiogenic protein products.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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