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RACK1 Function in Cell Motility and Protein Synthesis

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Abstract

The receptor for activated C kinase 1 (RACK1) serves as an adaptor for a number of proteins along the MAPK, protein kinase C, and Src signaling pathways. The abundance and near ubiquitous expression of RACK1 reflect its role in coordinating signaling molecules for many critical biological processes, from mRNA translation to cell motility to cell survival and death. Complete deficiency of *Rack1* is embryonic lethal, but the recent development of genetic *Rack1* hypomorphic mice has highlighted the central role that RACK1 plays in cell movement and protein synthesis. This review focuses on the importance of RACK1 in these processes and places the recent work in the larger context of understanding RACK1 function.

Keywords: RACK1, translation, ribosomes, stress response, cell migration, cancer

Background

The 36-kDa receptor for activated C kinase 1 (RACK1) was first identified in a rat brain cDNA library screen designed to isolate anchor proteins that bound protein kinase C (PKC) in the presence of its activators diacylglycerol, calcium, and phosphatidylserine. Inhibition of the interaction was later shown to destabilize PKC and reduce the phosphorylation of its substrates.[1-3] However, because RACK1 contained no catalytic domains, it was suggested to function as a scaffold protein that shuttled activated PKC to the sites of its substrates.[4] Although the RACK1–PKC interaction was the first to be described, it is now known that RACK1 interacts with numerous proteins in distinct cellular compartments and plays a critical role in many fundamental physiological processes.

RACK1 belongs to the family of WD40 repeat proteins (short ~40-amino acid motifs often terminating in a Trp-Asp [W-D] dipeptide, also known as WD or β-transducin repeats). More than 100 WD repeat proteins are known, and although they play varying roles, they share an ability to function as protein scaffolds.[5] WD domains adopt β-propeller structures that are thought to serve as docking sites for interacting proteins.[6] RACK1 contains a 7-bladed β-propeller structure and shows high homology to Gβ, the best-characterized WD repeat protein. RACK1 is evolutionarily conserved in yeast to humans, and the crystal structures from 4 species, including humans, have been determined.[7-12]

Expression of RACK1, encoded by the GNB2L1 (guanine nucleotide binding protein [G protein], β polypeptide 2-like 1) gene, is ubiquitous and tightly regulated.[13] Indeed, aberrant expression is associated with numerous pathologies, including cancer and age-related diseases.[14-16] More than 100 proteins are known to interact with RACK1, either directly or as part of a complex. Among these 100 proteins, 72 have been experimentally validated as binding partners that are functionally modulated by RACK1 (Table 1). Considering the diverse functions of these proteins, it is not surprising that RACK1 has been implicated in such fundamental processes as cell growth, proliferation, morphology, movement, death, and survival. Table 1 describes the 72 RACK1-interacting proteins segregated into functional clusters.

Here, we focus on the role of RACK1 in the cellular control of kinase activity in the stress response and its implication for cell migration and mRNA translation. For a more comprehensive discussion of RACK1, the reader is referred to a recently published review.[5]

RACK1 as a Hub for Protein Kinases

The diverse functions of RACK1 are mediated by acting as a scaffold for its binding partners, which may be constitutively associated (e.g., Src[17]) or bound in a transient stimulus-dependent manner (e.g., PKCβII), often through interactions between RACK1 WD repeats and modular structural domains of the binding partners (i.e., SH2 of Src). The function of RACK1 within these complexes also varies. For example, RACK1 may shuttle proteins to their sites of action (PKC), facilitate cross-talk between distinct signaling pathways (PKC-MAPK), or recruit other signaling proteins into the complexes. Moreover, binding of RACK1 to kinases can result

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Table 1. Putative Functional Binding Partners of RACK1

Function	Protein	Score	Function	Protein	Score
Protein kinases	PRKCE	0.845	Cell motility/polarity/organization	PDE4D	0.845
	SRC	0.845		PTPRM	0.845
	PRKCA	0.619		STAT3	0.825
	PRKCB	0.619		INSR	0.824
	PRKCD	0.559		IGF1R	0.821
	PRKCQ	0.559		ITGB1	0.808
	PRKD1	0.559		TUBB2A	0.619
IFN/immune signaling	IFNAR2	0.911		DNM1	0.619
	STAT1	0.784		PLEC	0.619
	NSMAF	0.619		PLCG1	0.619
	CSF2RB	0.619		SERBP1	0.552
	SLC9A3R1	0.619		ITGB7	0.538
	IL2RB	0.569		ITGB2	0.530
	IL4R	0.569		ITGB5	0.530
	JAK1	0.569	Neuronal function/brain	FYN	0.845
	JAK3	0.569		GABRB3	0.619
	JAK2	0.569		SYT1	0.619
	TYK2	0.569		GRIN2B	0.619
	EPOR	0.569		SLC6A16	0.530
	IFNAR1	0.530		SLC6A3	0.530
Ribosome/translation	RPS13	0.837	Others	GNB1	0.619
	RPS5	0.813		AGTRAP	0.619
	HABP4	0.792		AR	0.619
	RPS20	0.673		RASA3	0.619
	EIF6	0.619		NFATC1	0.619
	LARP4B	0.619		RASA1	0.619
	PABPC1	0.619		SUMO4	0.619
	RPS3	0.554		SREK1	0.603
	RPS15	0.548		SAP25	0.591
Cell death/survival	TP63	0.809		LRP12	0.563
	TNFRSF1A	0.619		ST7	0.563
	TP73	0.555		OTUB1	0.562
	BCL2L11	0.538		GRAP2	0.543
	RB1	0.530		DLC1	0.538
Cell proliferation	ACHE	0.619		HIF1A	0.530
	CCNA1	0.562		SAT1	0.530

Note: Seventy-two binding partners with functional relevance were suggested using the String 9.0 database (http://string-db.org) (setting: threshold of 0.5; prediction mode: experiment; protein names and string score are listed). Proteins were manually sorted into putative functional clusters.

in increased (JNK, MAPKs) or decreased (Src[17,18]) catalytic activity. At any given time, multiple RACK1 complexes exist that are coordinated in a dynamic stimulus- and compartment-dependent manner. One example of the latter is the function of RACK1 in suppressing Src tyrosine kinase activity at the membrane. PKC activation enhances the Src–RACK1 interaction,[18] which can be disrupted upon activation of IGF-1R.[19,20] Another example of compartmentalized RACK1 function occurs during regulation of the circadian cycle. Here, PKCα and RACK1 form a nuclear complex with the transcription factor BMAL1. Interestingly, the PKCα–RACK1–BMAL1 complex is formed in a rhythmic manner during the negative feedback phase of the circadian cycle, and complex formation suppresses CLOCK-BMAL1 transcriptional activity. Consequently, disruption of the complex results in a shortened circadian period.[21]

As mentioned above, RACK1 was initially identified as a PKCβII-anchoring protein that stabilizes the active conformation of the kinase and shuttles it to its substrates. RACK1 also serves as an adaptor to link PKC activation to other signaling pathways, such as the MAPK pathway. We have previously demonstrated that the RACK1–PKC complex binds to JNK in response to several stress stimuli, including ultraviolet (UV) irradiation or treatment with a PKC-activating phorbol ester.[22] Once bound, JNK is phosphorylated by PKC at serine 129, and although this is insufficient to activate JNK, S129 phosphorylation augments JNK activation by the canonical upstream kinases MKK4 and MKK7 (Fig. 1).

RACK1 can also influence the fate of the cell following exposure to stressors such as UV, H_2O_2, or sorbitol through regulation of the upstream MAP3K, MTK1. RACK1 binding is essential for the activation of MTK1, which induces apoptosis via the downstream stress-activated p38 and JNK enzymes.[23] Interestingly, RACK1 is also able to prevent apoptotic responses to other stressors (e.g., arsenite) by associating with stress

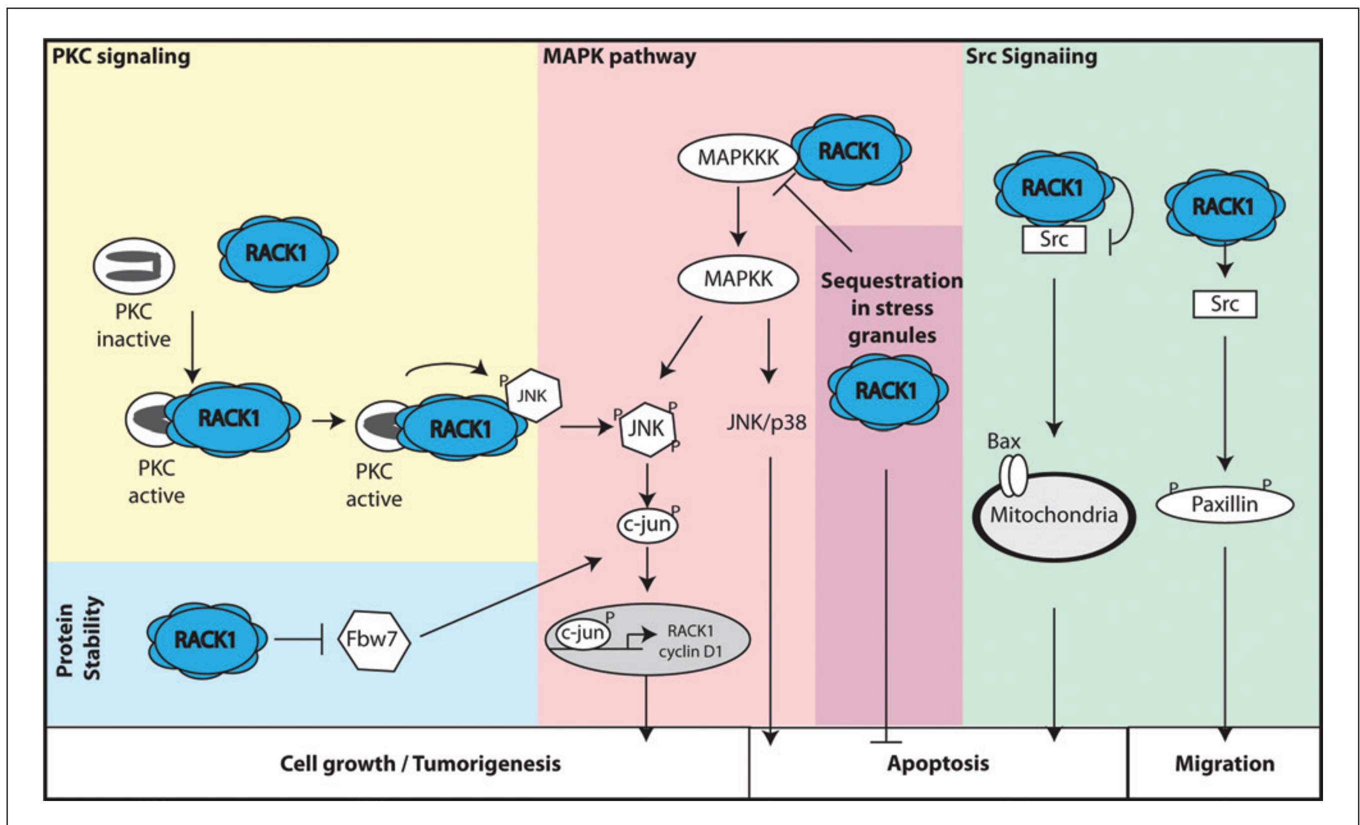

Figure 1. RACK1 signaling complexes. RACK1 links PKC signaling to the MAP kinase pathway: RACK1 binding to activated PKC leads to the recruitment of JNK into the complex. PKC-mediated phosphorylation of JNK augments JNK activation by the canonical JNK pathway. JNK activates c-Jun, which in turn regulates the transcription of cyclin D1 and RACK1. RACK1 further stabilizes c-Jun by inhibiting its proteasomal degradation through Fbw7. By enhancing JNK–c-Jun activity, RACK1 is implicated in tumorigenesis. RACK1 regulates apoptosis via MAPK and Src: RACK1 binds to MAP3K and activates stress-induced MAPK signaling, which results in apoptosis. In contrast, sequestration of RACK1 into stress granules attenuates MTK1 activation, which results in the inhibition of apoptosis. Binding of RACK1 to Src inhibits Src kinase activity. Upon apoptotic stimuli, inhibition of Src results in the oligomerization of Bax at the outer mitochondrial membrane, caspase activation, and cell death. RACK1 induces the oligomerization of Bax at the outer mitochondrial membrane, caspase activation, and cell death. RACK1 regulates Src activity during migration: Tight regulation of Src activity is necessary to mediate paxillin dynamics at focal adhesions during migration. Src phosphorylates paxillin, and RACK1 regulates paxillin phosphorylation dynamics by binding and releasing Src at its site of action, thereby enabling migration.

granules.[24] Recruitment of RACK1 to stress granules significantly reduces its ability to associate with MTK1 and therefore inhibits the MTK1-dependent apoptotic stress response in a seemingly passive manner. On the other hand, sequestration of RACK1 in stress granules might be an active mechanism to inhibit translation, although this remains to be clarified. The function of RACK1 in the stress response is not confined to mammalian cells. In yeast, RACK1 appears to control the stress response by regulating translation of the tyrosine phosphatases that negatively regulate the MAPK pathway.[25]

Genetic Mouse Models of RACK1 Deficiency

The first mouse models of RACK1 deficiency have been developed only recently.[26] Although complete knockout of the gene fails to produce viable embryonic stem cells, a *Rack1* hypomorphic allele was successfully constructed by introducing a deletion into intron 2. Crossing of heterozygous (ΔF/+) mice produced wild-type and ΔF/+ animals at the expected Mendelian frequency, but homozygosity at the defective allele (ΔF/ΔF) was lethal at the gastrulation stage. The most obvious phenotype of the ΔF/+ animals was a pigmentation deficit, evident as a white belly spot and hypopigmented tail and paws. Other developmental abnormalities of varying severity were found in young ΔF/+ females but not in male littermates. Notably, these mice also showed defects in protein synthesis. Given the relatively mild downregulation of RACK1 expression in ΔF/+ animals, the observed pigmentation and protein expression phenotypes are consistent with a critical role for RACK1 in controlling cell (melanocyte/melanoblast) migration and mRNA translation.

We have previously described a role for RACK1 in melanoma development

and resistance to therapy, but a link between this protein and normal melanocyte biology has not been established. During development, melanocytes are specified from pluripotent neural crest cells of the neural tube, which undergo epithelial-to-mesenchymal transition and migrate as melanocyte precursors (melanoblasts) over large distances to invade and populate the epidermis and hair follicles.[27] Melanoma cells retain several key features of melanocytes, including the ability to dissociate from an epithelial microenvironment, invade surrounding tissues, and migrate to distant organs. Lineage-specific factors that regulate melanocyte development, such as the tyrosine kinase receptor KIT and microphthalmia-associated transcription factor (MITF), are reactivated or mutated during melanomagenesis and are important for melanoma progression and metastasis. The pigmentation phenotype observed in the ΔF/+ *Rack1* mice might thus result from impaired migration of melanoblasts or reduced numbers of mature melanocytes at the affected sites. Several key questions that remain to be addressed include whether RACK1 affects MITF, the master regulator of melanocytes, or directly affects the migration of melanocytes. The results of such studies will undoubtedly provide insights not only into melanocyte biology but also into the development and progression of melanoma.

RACK1 in the Control of Cell Migration

Cell migration is a dynamic process involving multiple steps: cytoskeletal reorganization to form leading edge protrusions, turnover of focal adhesions, generation of mechanic forces, retraction of the cell tail, and detachment from the surrounding extracellular matrix. There is mounting evidence that RACK1 is involved at several stages of this process.

RACK1 interacts with the cytoplasmic domain of the integrin β1/2 subunit in 293 and JY lymphoblastoid cells, respectively.[28] RACK1 has been proposed to integrate IGF-1R and integrin signaling, and its scaffolding functions are necessary to regulate focal adhesion turnover and cell migration in v-Src- or IGF-1R-transformed fibroblasts or epithelial cells.[29] RACK1 enhances IGF-1R-mediated migration in breast and prostate cancer cells (MCF7 and DU145) by a mutually exclusive association with phosphatase 2A or β1 integrin.[30,31] Tight regulation of focal adhesion turnover, a process associated with cell migration, has also been shown to be regulated by RACK1, in part through its effect on Src activity with a concomitant effect on paxillin phosphorylation at focal adhesion complexes (Fig. 1).[32]

RACK1 also functions in direction sensing of migrating cells. A complex of RACK1, focal adhesion kinase (FAK), and the cAMP-degrading phosphodiesterase PDE4D5 is recruited to nascent adhesions, where it modulates cell polarity.[33] The RACK1–FAK–PDE4D5 complex acts by signaling to its small GTPase target Rap1 via the cAMP downstream target exchange protein activated by cAMP (EPAC, also known as RapGEF3). Disruption of this complex inhibits directional responses such as wound-induced polarization and chemotactic invasion.[33,34]

RACK1 seems to have a different function in nonadherent cells. For example, binding of chemoattractants to G protein-coupled receptors on Jurkat cells induces the association of RACK1 with Gβγ subunits and recruitment of the complex to the leading edge, where it inhibits chemotaxis. RACK1 is thought to negatively regulate migration by preventing Gβγ stimulation of phosphoinositide 3-kinases and phospholipase C.[35,36] Thus, although RACK1 clearly plays a role in fine-tuning the events that control cell adhesion and motility, whether RACK1 enhances or inhibits these processes seems to be cell, context, or stimulus dependent.

RACK1 in Disease

At least some of the importance of RACK1 in disease pathology results from its ability to modulate the innate immune response and activation of interferon (IFN) signaling. Many pathogens, especially viruses, evade the host immune response by interfering with IFN signaling. RACK1 interacts with the IFNα/β receptor and recruits STAT1 into this complex, which is required for IFN signaling.[37] The mumps virus protein V and the measles virus accessory proteins C and V bind to RACK1, which induces dissociation of the IFNAR–RACK1–STAT1 complex and inhibits the IFN response.[38,39] In addition to its role in innate immunity, RACK1 has been implicated in several psychological disorders and neuronal diseases. These aspects of RACK1 function are discussed in more detail in a recent review.[5]

Considering the pivotal role of RACK1 in cell growth, migration, and cell death, it is not surprising that it has been implicated not only in the development of cancer but also in the response to therapy. RACK1 has been suggested to be a prognostic marker in breast cancer, and elevated expression of this protein is associated with poor clinical outcome.[40,41] Furthermore, RACK1 promotes proliferation, migration, and metastasis of breast cancer cells *in vitro* and *in vivo* through activation of the RhoA/Rho kinase pathway.[42,43] RACK1 is thought to confer chemoresistance in breast cancer cells by promoting proteasomal degradation of the proapoptotic protein BIM_{EL}.[44] RACK1 has also been implicated in hepatocellular carcinoma (HCC) in which its expression is elevated compared to normal liver cells. In HCC, ribosomal RACK1 was shown to confer resistance to chemotherapeutic drugs and tumor growth *in vivo* and *in vitro*. Mechanistically, these tumor-promoting effects of RACK1 are likely mediated by its ribosomal localization and the preferential translation of tumor-promoting genes such as cyclin D1, MYC, and Bcl-2.[45] In addition to this

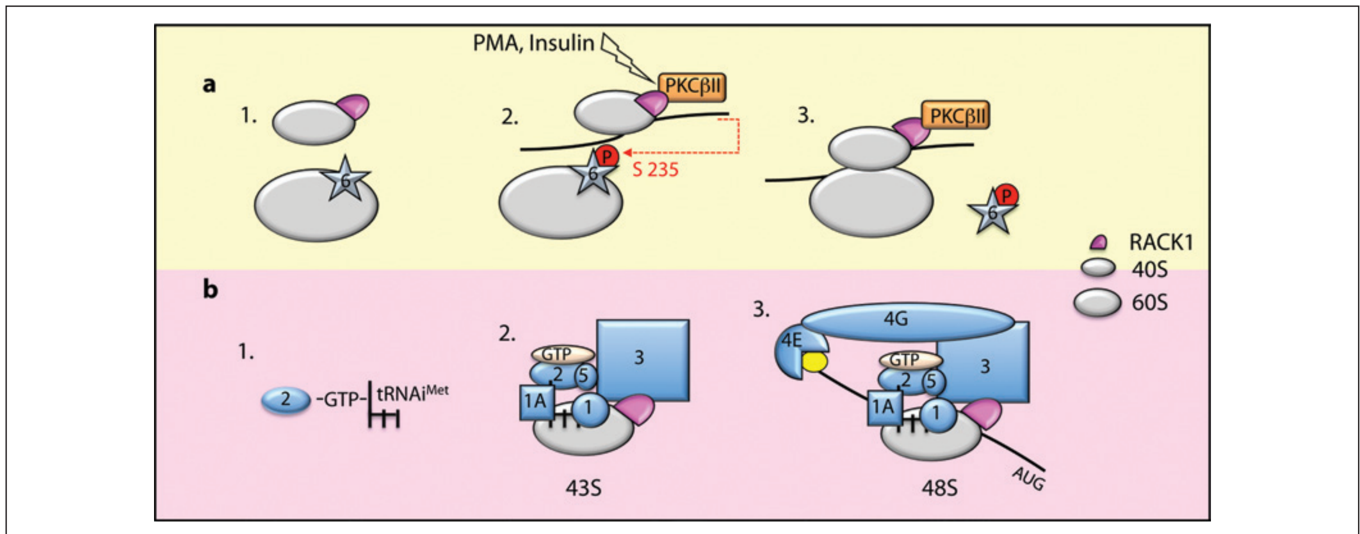

Figure 2. Schematic representation of RACK1's putative role in translation initiation. (**A**) RACK1 and the antiassociation factor eIF6 bind 40S and 60S, respectively (**1**). RACK1 recruits PKCβII to the ribosome, and PKCβII phosphorylates eIF6 on serine 235 (**2**). Release of phosphorylated eIF6 allows 80S formation on the mRNA (**3**). (**B**) The ternary complex (eIF2-GTP-tRNAi^{Met}) (**1**) is recruited to 40S with a multimeric complex composed of eIF1A, eIF1, eIF5, and eIF3. eIF3 binding to RACK1 stabilizes the ternary complex on the ribosome (**2**). The 43S complex is then recruited to the mRNA and stabilized through an eIF3-eIF4G interaction (**3**). The 48S complex scans the mRNA to reach the initiation codon (AUG).

translational function, RACK1 stimulates MKK7 in HCC, which augments JNK activity, confers resistance to TRAIL- or Fas-induced apoptosis, and promotes tumor growth *in vivo*.[46] In agreement with this study, we have previously demonstrated that RACK1 augments JNK activation in melanoma and renders melanoma cells resistant to stress-induced apoptosis.[22,47,48] We also identified a feed-forward mechanism between JNK activation and constitutively active ERK signaling, which is present in the vast majority of melanomas. Constitutive ERK activation increases both the transcription and stability of c-Jun, which targets cyclin D1 and RACK1. In turn, because RACK1 bolsters phosphorylation of JNK and augments its activity, c-Jun activity is further amplified.[22,47,48] RACK1 can also promote this feed-forward signaling loop by inhibiting the proteasomal degradation of c-Jun.[49]

The involvement of RACK1 in the initiation and progression of tumors and in their resistance to therapy has raised the possibility that it could be an appropriate target for the development of therapeutic drugs. However, optimism for this idea is tempered by the findings that RACK1 has several properties consistent with a tumor suppressor function. For example, RACK1 is known to suppress Src activation and has also been reported to have a proapoptotic role in colon cancer cells.[50] In addition, RACK1 has been implicated in the downregulation of HIF1α by competing with HSP90-HIF1α binding.[51] Given the near ubiquitous expression of RACK1 and its large number of client proteins, these tumor promoter and suppressor roles are likely to vary in different cells and tissues. Understanding the function of RACK1 in activating and inactivating cancer-related pathways could thus lead to novel therapeutic strategies that specifically target RACK1 tumor-promoting activities while sparing its tumor suppressor functions.

RACK1 in the Control of Protein Synthesis

RACK1 associates with the 40S small ribosomal subunit of numerous species, and it is localized on the head of the 40S subunit near the mRNA exit channel (Fig. 2).[52] RACK1 is anchored to ribosomal RNA by the universally conserved residues Arg38 and Lys40.[8] Importantly, WD repeats 1, 2, and 5 of ribosome-associated RACK1 are obscured by rRNA, which is likely to modify its signaling functions.[10]

Consistent with its initial identification as a primary RACK1-binding partner,[1,53] PKCβII has been identified as an important factor linking ribosomal RACK1 and translational control in mammals. PKCβII binds 40S-associated RACK1 in 2 regions close to WD blades 3 and 4.[1,54,55] RACK1 recruits active PKCβII on ribosomes, where it phosphorylates eukaryotic initiation factor 6 (eIF6) on serine 235.[55] eIF6 binds to the 60S subunit at the interface with 40S, impeding the association of the 2 subunits.[56] Upon phosphorylation, eIF6 is released from the 60S subunit, and the 80S ribosome can be assembled on the mRNA. Indeed, eIF6$^{+/-}$ heterozygous mouse embryonic fibroblasts (MEFs) accumulate monosomes and have defects in PMA- and insulin-stimulated mRNA translation. The defects cannot be rescued by expression of the nonphosphorylatable mutant of eIF6^{Ser235Ala},[56] thus corroborating the importance of the

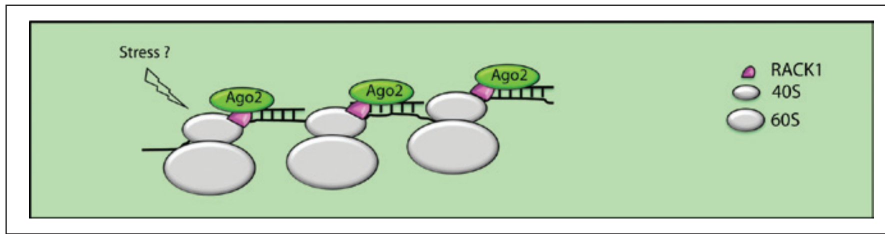

Figure 3. Schematic representation of RACK1 in miRNA-mediated repression. RACK1 binds translating ribosomes, where it recruits the Ago2–let-7 complex to silence the mRNA translation of let-7 targets.

RACK–PKCβII–eIF6 complex in translational control (Fig. 2).

In agreement with a role for RACK1 in the control of protein synthesis, mice heterozygous for RACK1 (ΔF/+) show moderate accumulation of monosomes and impaired protein synthesis, which phenocopies the defects observed in livers and MEFs from eIF6 heterozygous mice. Interestingly, the defects in neural crest–derived melanocyte development observed in RACK1 ΔF/+ mice are also seen in mice heterozygous for the ribosomal protein rpL24, a protein localized on the large ribosomal subunit close to the eIF6 binding site.

The role of ribosomal RACK1 in the control of gene expression at the posttranscriptional level has been extensively studied in yeast, revealing properties of ribosomal RACK1 that would merit further investigation in higher eukaryotes. In yeast, the RACK1 homolog Asc1 associates with the 40S subunit in growing cells but is found predominantly in the ribosome-free fraction of cells entering the stationary phase,[57] suggesting that RACK1 may be necessary only on actively translating ribosomes. RACK1 interacts with the C-terminal domain of eIF3c/NIP1 at WD blades 1 to 3, stabilizing the binding between eIF3c and the 40S subunit.[58] eIF3c is a component of the multimeric translation initiation factor eIF3, which, together with eIF1 and eIF1A, binds to the free 40S subunit and acts as an acceptor for the ternary complex (eIF2–GTP–tRNAi^{Met}).[59] Thus, eIF3c binding to RACK1 may anchor the ternary complex to the 40S subunit. Indeed, loss of RACK1 impairs the recruitment of the ternary complex, suggesting that RACK1 could regulate the initiation phase of translation.[58] Intriguingly, eIF3 is released upon 80S assembly, while RACK1 remains associated to translating ribosomes, namely polysomes. This observation suggests that RACK1 could modulate not only translation initiation but also subsequent steps of protein synthesis (e.g., elongation). A previously identified RACK1 interactor on polysomes is the Scp160 protein. Scp160 cosediments with polysomes[60] and associates with specific polyadenylated mRNAs.[61] Mutation of the conserved amino acid residues on RACK1 necessary for its binding to the 40S subunit impaired the recruitment of Scp160 on the polysomes.[62] The fact that Scp160 associates with specific mRNAs suggests that RACK1 may regulate the translation of a subset of specific mRNAs rather than global translation. In agreement with this hypothesis, RACK1 is not an essential gene in yeast. RACK1 yeast mutants are viable[63] and show a slight impairment in the translation of a specific subset of mRNAs[64] unless challenged with stress.[25,63]

RACK1 as a Repressor of Protein Synthesis

The role of RACK1 in translational regulation may be even more complex than the preceding section suggests. In addition to a positive role for ribosomal RACK1 in mRNA translation, a negative role for RACK1 in gene expression at the posttranscriptional level has been reported in yeast. Depletion of RACK1 results in increased ribosomal activity in a cell-free *in vitro* translation assay and a concomitant increase in protein levels *in vivo*.[65] A more recent finding has linked ribosomal RACK1 with miRNA-dependent repression of translation in *Caenorhabditis elegans* and humans.[66] RACK1 interacts with Ago2 and *let-7* miRNA. Analysis on sucrose gradients revealed that let-7 and RACK1 co-sediment on the polysomes, while RACK1 depletion significantly affects the amount of *let-7* miRNAs on translating ribosomes (Fig. 3).[66]

RACK1 as a Regulator of the Quality Control of Newly Synthesized Polypeptides

Mistakes are commonly made during mRNA transcription that generate aberrant transcripts, including mRNAs with a premature stop codon and mRNAs lacking a poly(A) tail or an in-frame stop codon. In the absence of a stop codon, the ribosomes would reach the poly(A) tail in the translating mRNAs and stall on the lysine-rich sequence, leading to elongation arrest.[67,68] This phenomenon is probably a result of the high affinity between the positive charges in the lysine-rich region in the nascent polypeptides and the negative charges of the exit tunnel of the ribosome.[69] These aberrant nascent polypeptides must be co-translationally degraded by the proteasome[70] to avoid the accumulation of misfolded proteins that may have deleterious effects on cell physiology. In yeast, ribosomes lacking RACK1 are unable to impede the translation of aberrant polypeptides, and their cellular levels increase.[71] Thus, ribosomal RACK1 could also participate in the quality control of nascent polypeptides, although it is not yet clear how this might occur. RACK1 binding to the 40S subunit can remodel the 80S ribosome,[52] perhaps stabilizing factors that monitor the properties of the nascent polypeptides.

Our recent studies identified RACK1 recruitment of JNK as part of the mechanism underlying the quality control of newly synthesized proteins under stress conditions.[72] In response to phorbol ester treatment or UV irradiation, RACK1 acts as a scaffold protein to recruit activated JNK on 40S and on translating ribosomes. Strikingly, disruption of RACK1 binding to 40S impairs ubiquitination and degradation of newly synthesized polypeptides (NSPs), pointing to its pivotal role in the control of NSP stability. Inhibition of JNK upon stress recapitulates this phenomenon, thus revealing a role for the RACK–JNK complex in the degradation of NSPs. Notably, our studies identified that RACK1 recruits JNK to polysomes, resulting in the phosphorylation of the elongation factor eEF1A2 at serine 205 and 358, which in turn promotes its binding to NSPs, with concomitant effects on their ubiquitination and degradation. These findings are consistent with the reported binding of eEF1A2 to damaged NSPs,[73,74] which was reported to promote their degradation by the proteasome.[75-77]

Summary and Perspectives

RACK1 is an abundant adaptor protein, and as such, it is not surprising that it participates in numerous cellular functions. Yet, recent data obtained from genetic RACK1 hypomorphic animals revealed distinct phenotypes associated with only 2 RACK1 functions: namely, its role in melanocyte biogenesis, which may be associated with cellular migration and movement of components of the neural crest lineage, and its clear role in mRNA translation. While this review has focused primarily on these aspects of RACK1 biology, it is apparent that many questions must be answered before we have a complete understanding of the function of RACK1 in mRNA translation, cellular movement, and melanocyte biology. In addition, as a component of signaling complexes that respond to extracellular stimulation, RACK1 regulation and function are expected to be both temporal and spatial. The mechanisms underlying the dynamics of RACK1 complex assembly and localization at subcellular domains will need to be deciphered as our ability to monitor such events at high resolution improves. Tracking the movement of RACK1 along cytoskeletal filaments in response to varying external stimuli may allow us to understand the roadmap used for the diverse functions of RACK1. Whether select RACK1 complexes could be targeted as novel therapeutic modalities remains an important area of research with implications for translation to the clinic.

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Declaration of Conflicting Interests

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