Regulation of eukaryotic translation by the RACK1 protein: a platform for signalling molecules on the ribosome

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The receptor for activated C-kinase (RACK1) is a scaffold protein that is able to interact simultaneously with several signalling molecules. It binds to protein kinases and membrane-bound receptors in a regulated fashion. Interestingly, RACK1 is also a constituent of the eukaryotic ribosome, and a recent cryo-electron microscopy study localized it to the head region of the 40S subunit in the vicinity of the messenger RNA (mRNA) exit channel. RACK1 recruits activated protein kinase C to the ribosome, which leads to the stimulation of translation through the phosphorylation of initiation factor 6 and, potentially, of mRNA-associated proteins. RACK1 therefore links signal-transduction pathways directly to the ribosome, which allows translation to be regulated in response to cell stimuli. In addition, the fact that RACK1 associates with membrane-bound receptors indicates that it promotes the docking of ribosomes at sites where local translation is required, such as focal adhesions.

Keywords: focal adhesion; PKC; RACK1; ribosomes; translation

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Introduction

The ability of eukaryotic cells to respond to various stimuli through signal-transduction pathways is important for many cellular processes. Traditionally, signalling pathways have been thought to alter the proteome mainly through changes in transcription. However, a recent study showed that two important signalling pathways, the Ras and Akt pathways, primarily target the association of specific messenger RNAs (mRNAs) with ribosomes (Rajasekhar *et al*, 2003). This regulated change in the identity of the mRNAs that are being translated leads to a rapid alteration in the

proteome. Another important example of translational regulation is the ability of signalling pathways to mediate a local stimulation of translation at the postsynapse in response to stimuli, which is important for activity-dependent synaptic modification (Steward & Schuman, 2003). Other processes that require regulated local protein synthesis are growth-cone navigation (Steward & Schuman, 2003) and the establishment of focal adhesions (Chicurel *et al*, 1998; de Hoog *et al*, 2004).

Having recognized that the regulation of translation is an important aspect of signalling pathways, we need to address the questions of how and where translation is activated, and which mRNAs are translated. Several signal-transduction pathways target the phosphorylation of translation-initiation factors, and much attention has been paid to the phosphorylation of the cap-binding protein-initiation factor 4E (eIF4E) and the group of proteins that bind to it (the 4E-BPs). Recently, a new participant in translation regulation has been recognized: the already well-known receptor for activated C-kinase (RACK1). RACK1 has been reported to interact with several signalling molecules (McCahill *et al*, 2002). A mass-spectroscopy study showed RACK1 to be part of the small ribosomal subunit (Link *et al*, 1999) and a recent cryo-electron microscopy (cryo-EM) study (Sengupta *et al*, 2004) located it on the head of the small subunit, in the immediate vicinity of the mRNA exit site (Fig 1A). In this review, we focus on the role of RACK1 as a ribosomal protein and discuss the manner in which it might regulate eukaryotic translation.

RACK1 as a receptor of signalling molecules

The RACK1 protein (note that both Asc1p in *Saccharomyces cerevisiae* and Cpc2 in *Schizosaccharomyces pombe* are referred to here as RACK1) is highly conserved and has homology to the β -subunit of heterotrimeric G proteins. On the basis of this homology, the RACK1 protein is predicted to fold into a β -propeller structure comprising seven WD40 repeats, in agreement with the cryo-EM findings. Various studies have indicated that RACK1 has several independent protein-binding sites (Rodriguez *et al*, 1999). The individual WD40 repeats can simultaneously interact with different signalling molecules, which allows RACK1 to integrate inputs from distinct signalling pathways.

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The role of RACK1 as a scaffold protein in signalling processes has been widely investigated. Signalling molecules that bind to RACK1 can be classified into two main groups: soluble signalling proteins and the cytosolic domains of membrane-spanning receptors (Table 1; for an extensive list, see McCahill *et al.*, 2002). RACK1 serves as a receptor for activated protein kinase C β (PKC β ; Ron *et al.*, 1994) and other PKC isoforms, including PKC δ (Rosdahl *et al.*, 2002), and PKC μ (Hermanto *et al.*, 2002). The binding of RACK1 to PKC leads to an increase in kinase activity (Ron *et al.*, 1994), and RACK1 is thought to shuttle activated PKC to its correct cellular location (Ron *et al.*, 1999). RACK1 also interacts with the Src kinase, which is involved in regulating cell growth and adhesion. In contrast to its effect on PKC, RACK1 mainly inhibits the kinase activity of Src, although some uncharacterized Src substrates seem to be phosphorylated to a greater extent in the presence of RACK1 (Chang *et al.*, 1998).

A well-established example of a membrane-spanning receptor that binds to RACK1 is the cytoplasmic domain of the β -subunit of the integrin receptor (β 1, β 2, β 3 and β 5 subtypes; Liliental & Chang, 1998; Buensuceso *et al.*, 2001). The integrin receptor makes contact with the extracellular matrix and is important in establishing focal adhesions. It interacts with RACK1 only after the activation of PKC (Liliental & Chang, 1998). Moreover, as an integrin- β -RACK1-PKC complex has been observed (Besson *et al.*, 2002), it seems that the interaction between RACK1 and the receptor results in the recruitment of other RACK1-bound signalling molecules.

RACK1 is a ribosomal protein

Although RACK1 is a well-established receptor for signalling molecules, its role as a genuine ribosomal protein is only beginning to be appreciated.

A mass-spectrometry study of yeast and human ribosomes showed that RACK1 is a component of the small subunit and seems to be present at a 1:1 ratio with other ribosomal proteins (Link *et al.*, 1999; Gerbasi *et al.*, 2004). In a recent study, we used cryo-EM to localize RACK1 on the eukaryotic ribosome by comparing ribosomes that were depleted of RACK1 with wild-type ribosomes (Fig 1A). Our results showed that RACK1 is located at the back of the 40S head region and makes direct contact with the ribosomal RNA (Sengupta *et al.*, 2004). Inspection of different cryo-EM maps of various eukaryotic ribosomes showed that the location of RACK1 is conserved. However, an interesting

◀ **Fig 1** | Position of receptor for activated C-kinase (RACK1) on the ribosome and its putative interactions with signalling molecules. (A) Cryo-electron microscopy map of 80S ribosomes from *Saccharomyces cerevisiae* showing the localization of RACK1 (red) on the small subunit (yellow). The mRNA exit channel is indicated by an arrow. (B–D) Schematic illustrations of RACK1 (red) bound to regulatory molecules on the ribosome in the vicinity of the mRNA (pink). (B) Protein kinase C (PKC; light blue) bound to ribosomes in the proximity of mRNA-associated proteins, such as initiation factor eIF4E (grey). (C) RACK1 bound to an mRNA-specific binding protein, such as Scp160p (grey) associated with mRNA. (D) Ribosomes recruited to sites of attachment through an interaction between integrin- β (dark brown) and RACK1. The illustrations of bound mRNA (pink), tRNA (green) and elongation factor 2 (eEF2; orange) in the intersubunit cleft show that translation could proceed while RACK1 interacts with the receptor.

corollary is that RACK1 is absent in mitochondrial (Sharma *et al*, 2003) and protozoan ribosomes (H. Gao, M.J. Ayub, M.J. Levin & J.F., unpublished data), which points to a probable prokaryotic origin of these ribosomes.

Most ribosomal proteins are constitutively bound to the ribosome; however, during the stationary growth phase of *S. cerevisiae*, RACK1 is present in both a ribosome- and a non-ribosome-bound form (Baum *et al*, 2004). This seems to be the result of an upregulation of RACK1 levels, rather than a dissociation of RACK1 from the ribosome. In humans and fission yeast, a non-ribosome-bound form of RACK1 has also been observed (Ceci *et al*, 2003; Shor *et al*, 2003), although a recent study showed that RACK1 is not present in a soluble form (Gerbasí *et al*, 2004). It is not known whether all ribosomes harbour RACK1 or whether the soluble RACK1 fraction that is observed in some studies is the result of higher levels of the protein compared with ribosomes. However, the persistence of the RACK1 interaction with ribosomes under high-salt conditions (Inada *et al*, 2002), the presence of RACK1 at a 1:1 ratio with other ribosomal proteins (Link *et al*, 1999) and its confirmed high-occupancy presence in cryo-EM maps of eukaryotic ribosomes (Sengupta *et al*, 2004) indicate that most ribosomes in the cell contain RACK1. The ribosomal position of RACK1 shows that the repeats that are responsible for receptor/kinase binding are exposed to the solvent, which implies that RACK1 might assemble signalling complexes on the ribosome, although this has yet to be experimentally verified (Fig 1).

Cellular processes that are regulated by RACK1

In mammals, RACK1 regulates several processes that involve contact with the extracellular matrix, such as cell spreading, the establishment of focal adhesions and cell–cell contacts.

Depletion of RACK1 by antisense RNA in mouse fibroblast cells (Hermanto *et al*, 2002) prevented cell spreading and reduced the number of focal adhesions, which indicates that RACK1 is a positive regulator of these processes. The ability of RACK1 to regulate attachment depends on its ability to recruit PKC to the integrin receptor in the system that is being studied. The RACK1–Src interaction has also been implicated in regulating attachment, as the presence of a RACK1 mutant that is unable to bind the Src kinase leads to a loss of central focal adhesions (Cox *et al*, 2003). In summary, RACK1 has an important role in coordinating the signalling events that control contact with the extracellular matrix through recruiting PKC and Src to the integrin receptor.

A recent study reported that the association between RACK1 and two important focal-adhesion components, talin and vinculin, is regulated by the adherence state of the cell. In suspended cells, RACK1 interacts more strongly with talin, whereas on attachment, RACK1 binds robustly to vinculin (de Hoog *et al*, 2004). Immunofluorescence studies at the early stages of spreading showed colocalization of RACK1 and vinculin in structures that are known as spreading initiation centres (SICs); however, RACK1 was not detected in mature focal adhesions. Interestingly, SICs contain several RNA-binding proteins, RNA and ribosomal RNA, which is consistent with previous studies that showed the recruitment of ribosomes and poly(A) mRNA to attachment sites (Chicurel *et al*, 1998). This indicates that translation might be required early in the establishment of focal adhesions, although the mechanism of localizing translational components remains uncharacterized.

Table 1 | RACK1 interactions on the ribosome

Protein bound to RACK1	Potential role in translation
PKC	Phosphorylates eIF6 and mRNA-associated proteins
eIF6	Leads to PKC phosphorylation of eIF6
Src	Controls the Src phosphorylation of mRNA-bound proteins, such as hnRNPK and Sam68
Scp160p	Recruits specific mRNAs to the small subunit
Integrin- β	Recruits ribosomes to sites of attachment
eIF6, initiation factor 6; hnRNPK, heterogeneous ribonucleoprotein K; mRNA, messenger RNA; PKC, protein kinase C; RACK1, receptor for activated C-kinase; Sam68, Src-associated in mitosis; Scp160p, KH-domain-containing protein.	

Regulation of translation by RACK1

In mammals, the only known signalling molecule with which RACK1 interacts on the ribosome is activated PKC (Table 1). The subsequent stimulation of translation is the result of the PKC-mediated phosphorylation of eIF6. In its non-phosphorylated form, this initiation factor binds to the large subunit of the ribosome and prevents its association with the smaller subunit; however, on PKC phosphorylation, eIF6 dissociates and a functional ribosome assembles (Ceci *et al*, 2003). It should be noted that PKC-induced subunit assembly was only observed in eIF6-overexpressing cells, which raises the question of whether there is sufficient eIF6 to block most 60S subunits in the cell. The ribosome–RACK1–PKC complex therefore regulates a late step in translation initiation in response to cell stimuli. Whether other translation factors are targeted by the recruited PKC is not known, but the kinase has been reported to phosphorylate the cap-binding protein eIF4E *in vitro* on the same serine that is known to be phosphorylated *in vivo* (Whalen *et al*, 1996). It is uncertain whether PKC does indeed phosphorylate eIF4E *in vivo* (Pyronnet *et al*, 1999), but from a structural point of view, the recruitment of PKC to ribosomes by RACK1 would place it close to mRNA-associated proteins (Fig 1B). Experiments with oligo-dT-purified messenger ribonucleoprotein (mRNP) complexes and subsequent PKC phosphorylation showed that some of the mRNP-associated proteins were phosphorylated, although the precise nature of the targeted proteins was not identified (Angenstein *et al*, 2002). In summary, it is conceivable that PKC could phosphorylate other proteins that are involved in translational regulation besides eIF6.

In yeast, the RACK1 protein is not essential, which has allowed the genetic characterization of its role in translation. Although depletion of the protein leads to an increase in free 40S and 60S subunits, and a decrease in 80S subunits (Chantrel *et al*, 1998; Shor *et al*, 2003), it has only a minor effect on global translation (Shor *et al*, 2003). The deletion of the *RACK1* gene in *S. cerevisiae* led to the presence of stalled initiation complexes, which indicated a defect in the initiation of translation (Chantrel *et al*, 1998), but this behaviour was not observed in *S. pombe* (Shor *et al*, 2003). Therefore, the role of RACK1 in general translation initiation in yeast is still uncertain.

Regulated translation of specific mRNAs

Studies on *S. pombe* showed that the amount of the ribosomal protein rpl25 was specifically reduced in RACK1-depleted cells owing to a reduction in the recruitment of the rpl25 mRNA to

ribosomes (Shor *et al.*, 2003). Importantly, the other mRNAs that were analysed in the study were not affected. By contrast, a greater abundance of specific proteins was observed when RACK1 was deleted in *S. cerevisiae* (Gerbas *et al.*, 2004); however, whether the ribosomal binding of the mRNAs that encode these proteins was affected remains unknown.

In agreement with a role for RACK1 in regulating the translation of specific mRNAs, the binding of the KH-domain-containing protein Scp160p to ribosomes requires RACK1 in *S. cerevisiae* (Baum *et al.*, 2004). Scp160p, which is a member of the vigilin family of RNA-binding proteins, binds to a subset of mRNAs and might recruit them to the ribosome through its interaction with RACK1. Consistent with this hypothesis, the location of RACK1 on the ribosome is close to the mRNA-binding site on the small subunit (Fig 1C).

Does RACK1 regulate the translation of specific mRNAs in mammals? It might, indirectly, by regulating the Src phosphorylation of RNA-binding proteins, such as Src-associated in mitosis (Sam)68 and the heterogeneous ribonucleoprotein K (hnRNPk). RACK1 is known to control the phosphorylation of Sam68 (Miller *et al.*, 2004), which binds specifically to the 3' untranslated region of certain mRNAs, such as β -actin. Sam68 is a Src substrate and RACK1 prevents its phosphorylation by inhibiting the Src kinase. Whether this reduction in Sam68 phosphorylation regulates the translation of its associated mRNAs is not known, although phosphorylation reduces its affinity for RNA (Wang *et al.*, 1995). By contrast, in the case of the hnRNPk protein, Src phosphorylation has been shown to stimulate the translation of hnRNPk-bound mRNAs (Ostareck-Lederer *et al.*, 2002). Therefore, the ability of RACK1 to inhibit the Src kinase could regulate the translation of specific mRNAs that are bound to hnRNPk and Sam68. Whether Src can bind to ribosomes through RACK1 remains to be established, but the cryo-EM data clearly show that the Src-interacting residues on ribosome-bound RACK1 are exposed. Interestingly, hnRNPk and Sam68 are both found in SICs, and, therefore, could potentially regulate the mRNAs that are being translated in these centres.

Recruiting ribosomes for local translation

Does mammalian RACK1 have other functions in translation? There are no data at present to help answer this question, although some interesting possibilities await investigation. As mentioned above, a role for translation in focal-adhesion establishment is emerging, owing to the localization of ribosomes, RNA and mRNA-binding proteins at sites of adhesion. An important question is how such an area of local translation is established. Are ribosomes moving with the mRNA or are they independently and specifically recruited? In this regard, it is interesting that RACK1 is able to bind integrin- β receptors, PKC and ribosomes, thereby linking the cues for localization and translational activation to the ribosome (Fig 1D). The cryo-EM results show that repeat 5 of RACK1, which is the site of integrin- β binding (Liliental & Chang, 1998), is exposed on the ribosome; this indicates that RACK1 might indeed recruit ribosomes to integrin- β receptors and thereby establish an area with a large translational capacity. However, the hypothesis that RACK1 is involved in localizing ribosomes to membranes through these receptors awaits experimental verification. From the location of RACK1 on the ribosome, it can be noted that the binding of a membrane-bound receptor to the ribosome through RACK1 would not interfere with the binding of functional ligands, such as transfer RNA, mRNA and elongation factors, and so translation could occur in this configuration (Fig 1D).

The challenge ahead is to establish which of the many known RACK1 interactions take place on the ribosome, and to define the role of these interactions in the regulation of translation and ribosome localization.

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