



Functional importance and structure of small ribosomal protein RACK1

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Received 05 July 2021; revised 15 August 2021;
accepted 22 August 2021; available online 15 October 2021

[doi:10.24271/psr.34](https://doi.org/10.24271/psr.34)

ABSTRACT

The Receptor for Activated C Kinase 1 (RACK1) protein is one of the ribosomal proteins that is located in the small subunit which is maintained across most of the eukaryotes and functions as a flexible scaffold protein involved in multiple signaling pathways. It is considered as a highly conserved protein that found in a wide range of tryptophan-aspartate (WD40) repeat proteins of eukaryotic organisms, from *Chlamydomonas* to plants and mammals. RACK1 adopts a propeller structure with seven blades structures, enabling the binding capability of the protein. RACK1 participates in shuttling and anchoring of proteins around the cells at certain positions and it stabilizes protein production during translation. RACK1 is a member of the protein family WD repeat that consists of seven-bladed β -propeller structure which shares important homology to the G-proteins (Gb) β -subunit. It interacts with the ribosomal machinery, multiple receptors of the cell surface and the nuclear proteins. RACK1 is a key mediator of different pathways and contributes to a variety of cellular functional aspects. This review discusses the main function of RACK1 protein in eukaryotes including animals and plants. Furthermore, we will show the recent study on RACK1 function in different organisms.

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Keywords: Ribosomal subunit, RACK1 protein, tryptophan-aspartate (WD)-40, prokaryotes, eukaryotes, *Arabidopsis thaliana*.

1. Introduction

The small ribosomal subunit (40S) in eukaryotic cells contain 18S ribosomal RNA (rRNA) and 33 ribosomal proteins (rProteins); one of these proteins known as the Receptor for Activated C Kinase 1 (RACK1) is near the mRNA exit channel on the small ribosomal subunit [1]. The RACK1 belongs to the Trp-Asp 40 (WD40) domains family with its sequence similarity to the guanine nucleotide-binding protein subunit [2] that is devoted to protein-protein interaction with a molecular mass of about 30kDa. It was initially cloned from the liver of chicken [3] and it found to act as a shuttling protein for activated PKC β II and also involved in multiple cellular signaling pathways in all eukaryotic cells [4]. RACK1 is considered to act as an adaptor or hub between ribosomes and many signaling pathways, which makes a key regulator protein of cellular homeostasis [5]. Furthermore, its localization in the small ribosomal subunit has been confirmed through the determination of the crystal structure of ribosomal subunit in *Tetrahymena thermophila* [6] and yeast [7].

When RACK1 was first found in the 1990s it has been considered as a non-ribosomal protein and a homologue of the β subunit of G protein which has role in protein kinase C (PKC) mediated signal transduction in the existence of PKC activators and hence termed as a receptor for activated C-kinase [8]. Later, it was termed anchor protein because it adapts different signal transduction components including receptors or kinases into a stable complex [9]. RACK1 is a key mediator that involves in several cellular process, including cell growth and division [10], apoptosis [11], regulation of cell adhesion [12] and migration [13], developmental pathway [14], stress response [15], translation and transcription [16], neuronal remodeling [17] and activity, signaling pathway [18] and circadian clock oscillatory mechanism [19]. It has been shown that PCK elaborates in several cellular processes such as regulating cell-cycle, differentiation and apoptosis and several PKC isoforms were found in the mammalian cells which are divided into three groups based on their role in activation of PCKs (conventional PCKs, novel PCKs and typical PCKs) [20]. Previous studies have shown that PCKs interact with eukaryotic initiation factor 4E (eIF4E) and RACK1 through its phosphorylation by PKC either *in vivo* or *in vitro* [21]. The interaction of RACK1 protein with specific PKC isoform (PKC β II) has an essential role in regulating of protein translation independently through mechanistic Target Of Rapamycin (mTOR) pathway in HeLa and human embryonic kidney-293

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Peer-reviewed under the responsibility of the University of Garmian.

(HEK-293) cells [20]. Other studies have shown that deletion of its ortholog Cpc2 in *Schizosaccharomyces* declines in the steady state level of several proteins and cause a reduced translation of ribosomal L25 mRNA [22]. Additionally, it has shown that there was a great conservation between RACK1 protein and 7 WD repeat heterotrimeric β -subunit of G proteins (G β) [23]. The intracellular localization of RACK1 protein among different organisms are slightly different, for instance in mammalian cells RACK1 is located in the nucleus, cytoplasm and endoplasmic reticulum [18], in maize (ZmRACK1) localized in the nucleus, cytoplasm and membrane [24], in rice (OsRACK1) located in the cytoplasm and microsomes [25], the kale (BoRACK1) localized in the cytoplasm, the nucleus and the cell membrane [26] and in *Arabidopsis thaliana* (AtRACK1) located in the chloroplast, cytoplasm, cytosol, nucleus and plasma membrane [27]. RACK1 protein has been shown to interact with several other proteins including tyrosine kinase of Sarcoma (Src) family through its SH2 domain protein in NIH 3T3 cells, which has a significant role in translation process [28]. Moreover, RACK1 interacts with phosphodiesterase 4D (PDE4D5) protein in HEK293 through a distinctive amino acid in the terminal region of PDE4D5 including amino acid 12-49 [29]. Interaction of RACK1 with the cyclic AMP-PDE4 demonstrates that it acts as an adapter protein that change PDE4D5 and other proteins into a signaling complex [9]. RACK1 plays specific roles in translational control through interaction between ribosomes and mRNA binding protein Scp160 [30]. Also, RACK1 interacts with Signal Transducers and Activators of Transcription (STATs) non-phosphorylated protein in human, through this interaction RACK1 protein act as a scaffold protein for activation of (STATs) via type I Interferon (IFN) receptor [31]. Moreover, RACK1 interaction was found with other targets in the cell, which includes binding with cytoplasmic domain β -subunits in eukaryotic cells including (β 1, β 2 and β 5) [32], association via Tyr-302 with protein phosphate 2A (PP2A) and β 1 integrin required for insulin-like growth factor I (IGF-I)-mediated cell migration and tumor cell proliferation in mouse [33, 34]. In addition, RACK1 protein acts as an activator for Jun-N-terminal kinase signaling cascade through with protein kinase C [4]. RACK1 mediate calcium (II) release through its contact with inositol 1,4,5-trisphosphate receptors (IP₃Rs) [35]. Also RACK1 protein mediates Brain-Derived Neurotrophic Factor (BDNF) expression in response to acute exposure to ethanol which may indicate that this pathway is crucial for regulating alcohol addiction [36]. In cancer cells RACK1 was found to interact with focal adhesion kinase (FAK) which is essential for nascent adhesions and cancer cell polarization [37]. RACK1 also may act as E3 ubiquitin ligase in proteasome degradation pathway that mediate the degradation of p63 α isoforms via 26S proteasome [38]. It has shown that RACK1 protein acts as a novel interaction partner with Autophagy-Related Gene 5 (ATG5) and mediate autophagy regulation [39]. The identification of binding sites of most of the proteins interacting with RACK1 were mapped as cartoons [40].

In this review we discuss the structure and properties of RACK1 protein in different organisms. Also, we will discuss the functional importance of RACK1 protein in plants and animals. Furthermore, we will show how different treatments affect the role of this protein.

2. Role of the RACK1 in different organisms

2.1 Role of RACK1 in mammalian and yeast cells

Several research studies have shown the essential role of RACK1 protein in different organisms including yeast (*Saccharomyces cerevisiae*) [41], *Drosophila melanogaster* [42], mouse [43], human [39] and plants such as (*Arabidopsis thaliana*) [44] and rice [45].

In yeast (*Saccharomyces cerevisiae*) Asc1p which is orthologous to ribosomal proteins RACK1 in mammalian cells is more than 50% similar in sequence identity with mammalian RACK1 [2] and each yeast cell contain about 100000 copies of Asc1p and this number is consistent with the abundance of most other ribosomal proteins [46]. In contrast to the RACK1 in human Hela cells which is located in the 40S small ribosomal subunit, the yeast RACK1 ortholog Asc1p is located in the 40S and 80S ribosomal complex [2]. In *Saccharomyces cerevisiae*, Asc1p acts as an adapter protein that is crucial for interaction of Scp 160p RNA binding protein with polysomes [47]. Asc1p also participates in the regulation of iron homeostasis and balancing of energy metabolism. However, its mutation of RACK1 gene leads to decreases iron concentrations within the cell followed by increasing the intracellular oxidative stress [41]. A study has shown the impact of Asc1 in the translation of short mRNAs encoding ribosomal proteins in cytoplasm and mitochondria. However, deficiency of Asc1 caused an alternation in translation activity for many mRNAs as well as reduced cellular respiration [48]. In addition, the fission yeast (*Schizosaccharomyces pombe*) Cpc2 protein is orthologous to ribosomal proteins RACK1 encodes a 314 amino acids of about 35kDa orthologue of the Asc1p in *Saccharomyces cerevisiae* with approximately 67% sequence similarity [49]. This protein plays crucial role in regulating sexual differentiation by its interactions with multiple Moc (Moc1, Moc2, Moc3 and Moc4) [50]. Moreover, Cpc2 was shown to participate in the modulation of stress response through its interaction with Msa2pRNA binding protein Msa2/Nrd1 [51]. Cpc2 also controls sexual differentiation as a positive regulator by its interaction with a key regulator Pat1p [52] and regulates the pheromone-induced cell cycle arrest [49]. The expression of RACK1 in the fruit fly (*Drosophila melanogaster*) has been studied in various developmental steps and results shown that RACK1 is functionally important in multiple developmental stages including embryonic, larval and pupal as well as in gamete production [42]. Furthermore, RACK1 participates in activation of autophagy in response to starvation and involves in glycogen synthesis [53]. Ribosomal RACK1 is essential for internal ribosome entry site (IRES)-mediated translation in *Drosophila* and in human after viral infection as well as it is important as an indicator for hepatitis C virus infection [54].

RACK1 was found to be necessary for early stages of mouse embryonic development and for tissue growth, whereas knockout of RACK1 is lethal and caused deficits and reduction in protein synthesis in both the brain and liver and the appearance present of belly spot phenotype and pigmentation in paws and tail tips [43]. Moreover, it has been shown that RACK1 involves in autophagy activity and autophagosome biogenesis in mice through its involvement in the assembly of the Atg14L-Beclin 1-Vps34-Vps15 complex; however, lack of RACK1 may cause hepatosteatosis [55].

The role of the RACK1 orthologue, VdRACK1, in soilborne fungus (*Verticillium dahliae*) was also studied during its infection of cotton roots and it was found that VdRACK1 controls multiple growth and development-related traits in *V. dahliae*. VdRACK1 is required for root penetration and deletion of this gene may extremely affect the expression of other ribosomal protein genes [56].

In human, RACK1 protein is involved in many physiological functions. However, the role of this protein was also emphasized in pathological conditions such as breast cancer. In this regard, RACK1 expression was found to be increased in most of the breast carcinomas cells compared with the normal cells, therefore it may of diagnostic or prognostic value in breast cancer [57]. RACK1 was found to be involved in regulation of growing human colon cells and thus it might inhibit the growth of colonic cancer cells by controlling the Src tyrosine kinase activity [58]. Furthermore, increased expression of RACK1 was found in proliferating prostate cancer cells [59]. Additionally, it has been shown that RACK1 is preferentially expressed in normal liver cells and an upregulated expression was found in hepatocellular carcinoma (HCC) which may have a prognostic role in treatment of HCC [60]. RACK1 is important in autophagy pathway by its interaction with ATG5, an ubiquitin E3 ligase [39].

Since RACK1 proteins are connected to ribosomes in mammals and yeasts, therefore the role of RACK1 among different organisms may be evolutionary conserved.

2. 2 Role of RACK1 protein in *Arabidopsis thaliana*

In plant cells RACK1 protein is considered as a scaffold protein and belongs to WD-40 repeat which interacts with many proteins. For the first time it has been found an auxin-inducible gene such as *arcA* mediated cell division in tobacco BY-2 cells that belongs to a homologue RACK1 in *Arabidopsis* [61]. Later, RACK1 protein was also found in other plants such as rice [62],

Arabidopsis thaliana [63] rape (*Brassica napus*) [64] and alfalfa [65].

It has been revealed that RACK1 in rice (OsRACK1A) acts as a positive regulator in reactive oxygen species (ROS) production and defense gene expression, as well as it plays a significance role in rice innate immunity and response to pathogen [25]. Wang et al. (2014) has shown that overexpression of RACK1 in maize (ZmRACK1) led to a reduction in symptoms caused by *Exserohilum turcicum* on maize leaves and also regulated oxidative stress production and pathogenesis-related genes expression [24]. In kale (*Brassica oleracea* var. *acephala* *f. tricolor*) it has demonstrated that RACK1 protein (BoRACK1) has a significant role in response to salt stress and pathogen diseases. Moreover, they showed that overexpression of BoRACK1 in transgenic kale plant was involved in disease resistance caused by fungal pathogen (*Peronospora brassicae* Gaumann) in addition to its involvement in improving salt tolerance in comparison with the wild type (WT) line (CK) [26]. In contrast to most organisms where RACK1 protein is encoded by one gene, plant RACK1 is encoded by more than one gene, for instance in rice RACK1 protein (OsRACK1) is encoded by two genes OsRACK1A and OsRACK1B [25]. The *Arabidopsis thaliana* genome contain three RACK1 orthologues including AtRACK1A (At1g18080), AtRACK1B (At1g48630) and AtRACK1C (At3g18130) respectively [5]. It has been shown that the *Arabidopsis* RACK1 genes like mammalian RACK1 are ubiquitously expressed [66]. These three genes have high degree of sequence identity (87-92%) as shown in Figure 1. However, the distinct sequence difference among these three RACK1 proteins genes can be seen in their C-terminus sequence at which about 10 amino acids show mismatch or non-similarity to each other starting from amino acid 286 to 295 in the region of the sixth and seventh conserved region on the GH-WD sequences [66].



Figure 1: Multiple sequence alignment of *Arabidopsis thaliana* RACK1 protein paralogs, the seven WD40 repeats are underlined and the yellow rectangular shows the amino acid difference among these three RACK1 paralogs (RACK1A_At (*Arabidopsis thaliana*, NP_173248))

Moreover, *Arabidopsis thaliana* RACK1 genes are very similar in their gene structure at which each of these genes contains two exons and one intron as shown in Figure 2. Several researches works have studied the mechanism, relationship and function of these three different RACK1 protein orthologues in *Arabidopsis*

thaliana and most of them have shown that although there is a high conservation among these paralogues, defect or mutation in one of these genes may affect the plant response in comparison with wild types.

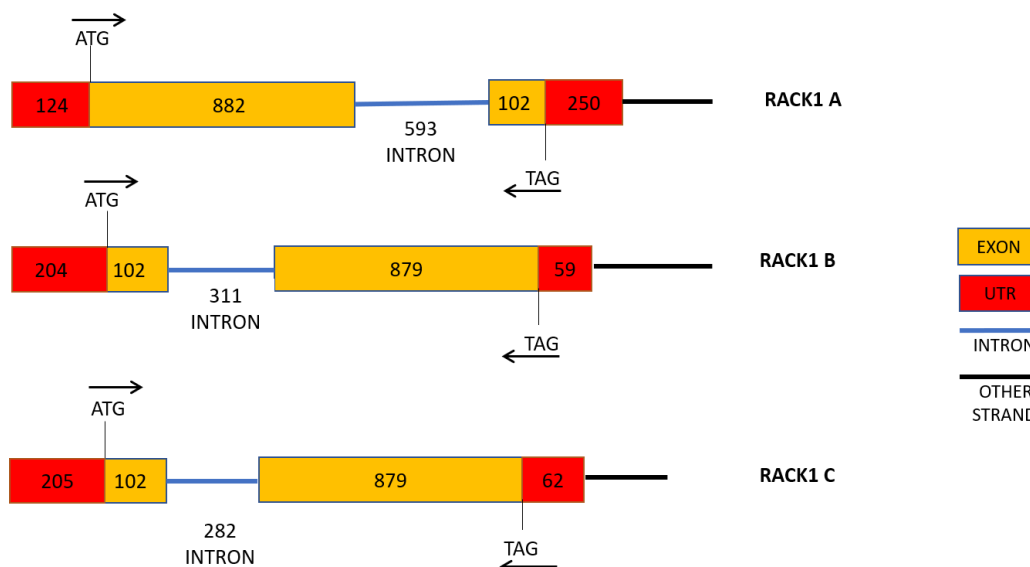


Figure 2: The composition of RACK1 homologues in *Arabidopsis thaliana*, the numbers represent the amino acid numbers.

Chen and co-workers have shown that RACK1A is important for developmental process and hormonal response in *Arabidopsis thaliana* and its mutation causes loss of their function. They further showed that the knockout of RACK1 alleles may affect the production of rosette leaves that reduced approximately by 50% in *rack1a* mutant followed by late flowering [66]. Moreover, mutation in RACK1A changed the sensitivity of *Arabidopsis* to several hormones response like gibberellin (GA), brassinosteroid and auxin [66]. RACK1 also acts as a negative regulator of abscisic acid (ABA) response and its expression level was down-regulated during ABA treatment at different concentrations as well as mutation in all three RACK1 genes showed hypersensitivity to ABA [67]. It has been shown that both RACK1B and RACK1C paralogous participate in the regulation and function of RACK1A in *Arabidopsis thaliana* [14]. Single mutation of either *rack1b* or *rack1c* or even double mutation such as *rack1b rack1c* have not any affected the root development and rosette leaves production in comparison to wild type morphology in *Arabidopsis* plant as it has seen in mutation in *rack1a*. Furthermore, double mutation *rack1a rack1b* and *rack1a rack1c* as well as triple mutation *rack1a rack1b rack1c* have shown a clear effect on the length of the roots and number of their rosette leaves [14]. RACK1 sensitivity has been studied with regard to tolerance to saline in different NaCl concentrations, and the results have shown hypersensitivity to NaCl in each of single mutant *rack1a*, double mutants *rack1a rack1b* and *rack1a rack1c* [67].

3. Structure and localization of RACK1

RACK1, approximately 36000Da cytosolic protein, considered of a varying number of amino acids among different organisms ranging from 240 to 328 amino acids that divided into seven bladed β - propeller and each blade consists of four strand of β -

sheet antiparallel A to D (Figure 3). The conserved repeating units referred to tryptophan-aspartic acid (WD) 40 motifs allow RACK1 to act as a signaling hub. Each of these seven blades contain 11-24 amino acid with two internal dipeptide sequences that begin with N-terminus glycine-histidine (GH) dipeptide and ends with C-terminus tryptophan-aspartic acid (WD) dipeptide [68]. RACK1 interacts either directly or indirectly as part of a complex with more than 100 proteins to mediate protein-protein interaction and contribute in many different functional categories [69, 70]. It has been shown that a big part of RACK1's surface area is interacting with three ribosomal protein including S3 via blades 4 and 5, S9 through blades 1 and 2 and S17, as well as RACK1 binds to 18S rRNA in its helices 39 and 40 [40].

Cryo-Electron Microscopy (Cryo-EM) study have shown that RACK1 is located at the back of the head region of 40S small ribosomal subunit near the entry channel of the mRNA which is surrounded by uS3, uS4, uS5 and eS30 proteins [71]. Furthermore, ribosomal RACK1 is located near the mRNA exit channel which has been proposed to involve in the initiation process through its binding to eIF3. Also RACK1 interacts through its N-terminates region with helices 39 and 40 of 18S ribosomal RNA (rRNA) [1, 72]. Moreover, RACK1 protein interacts with several ribosomal proteins including uS3, uS9 and eS17 [40].

The multiple sequence alignment of ribosomal proteins S3, S7, S9 and RACK1 has shown that they have high degree conservation among mammals and plants which suggests that RACK1 is highly conserved through evolution. The phylogenetic tree shows the evolutionary relationship of RACK1 among most of the organisms are close to each other (Figure 4) [40] from which it can be inferred that RACK1 proteins in *Arabidopsis* shares the highest degree of conservativity to RACK1 in rapeseed (*Brassica napus*).

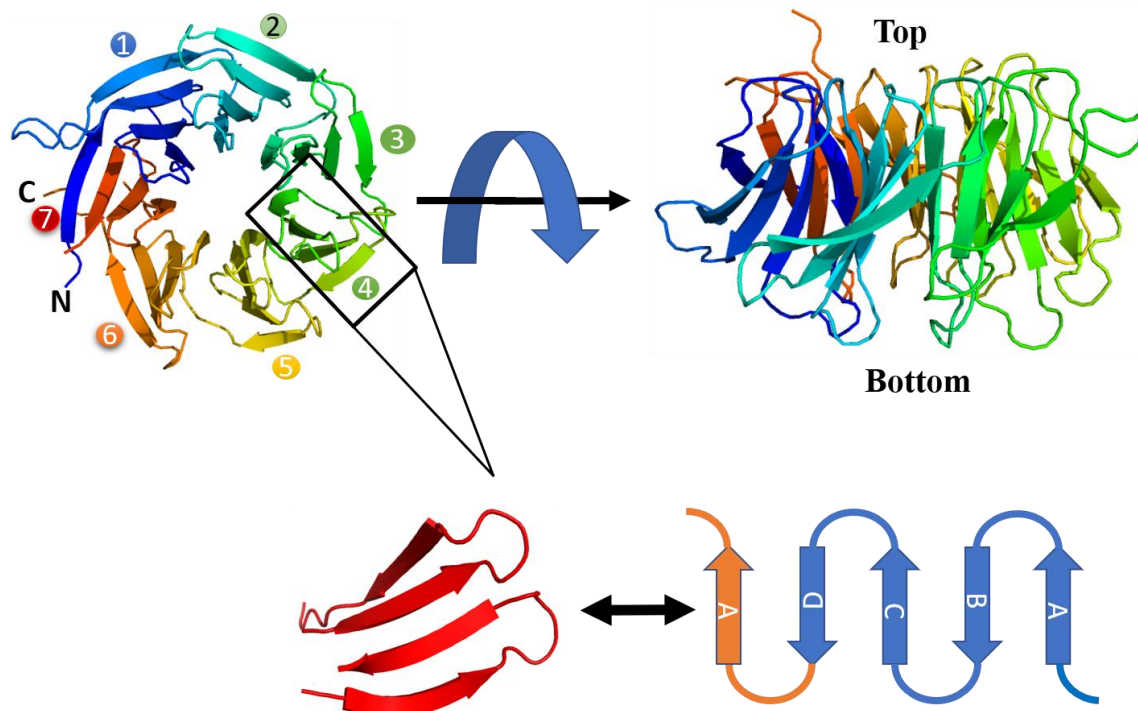


Figure 3: Arabidopsis RACK1A surface view, seven bladed β -propeller are numbered (1-7) and each blade consists of four β -sheet antiparallel strands from A to D. PDB: (3DM0).

A recent study in mice has shown that RACK1 contributes to regulation mechanism in asthma pathogenesis [73]. RACK1 as part of the small ribosomal subunit (40S), has been found enhance translation process in poliovirus. However, mutation in RACK1 resulted in a significant decrease in the poliovirus plaque size [74]. Among the three isoforms of RACK1 protein in *Arabidopsis thaliana* we found that RACK1C ribosomal protein has the highest degradation rate (K_D) followed by RACK1B and

RACK1A ($K_D = 0.61, 0.45$ and 0.20 per day) with half-lives from 1 to 1.4 days [75]. This could suggest that RACK1A, RACK1B and RACK1C compete in being assembled to be a functional ribosome. RACK1A might have the priority to be assembled while RACK1B and RACK1C are not thus degraded once synthesized. This result could support the previous published research [67, 76] in which they found that mutation in RACK1A had an obvious phenotype but RACK1B and RACK1C were not.

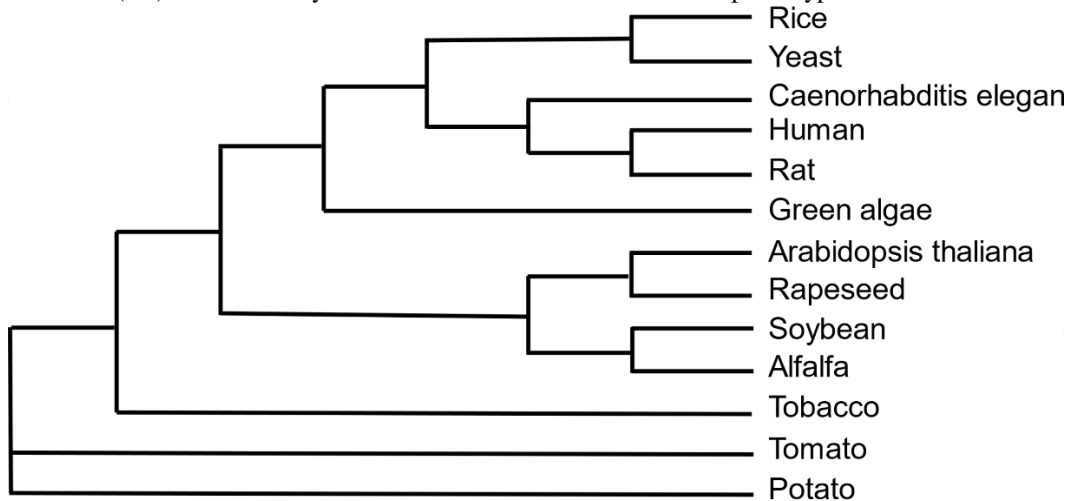


Figure 4: Phylogenetic tree for RACK1 protein in *Arabidopsis thaliana* and other organisms

4. Conclusion

Ribosome is a large protein complex that synthesizes protein within the cell. In eukaryotes, the size and the of protein constituents of ribosomes are different from prokaryotes and have a variety of physiological roles in eukaryotic cells, especially in mammals. RACK1 is one of the small ribosomal proteins that is

located in the 40S small subunit and is a repeat unit protein of the tryptophan-aspartate (WD) that has multiple roles in most animals and plants. It interacts with multiple cell surface receptors, ribosomal machinery and proteins in the nucleus. Also, RACK1 protein acts as an adaptor for many proteins along the signaling pathways.

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