Journal of Cell and Molecular Research (2021) 12 (2), 65-73 DOI: 10.22067/jcmr.v12i2.2102.1002

Review / Mini-Review

Signal Transduction of Unique RAS Family Member towards Cell Survival

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Received 3 February 2021 Accepted 21 February 2021

Abstract

Small GTPases of RAS act as central regulators of intracellular signal transduction and translate external stimuli to the various cellular responses. Embryonic stem cell-expressed RAS (ERAS) is a member of the RAS family that is specifically expressed in undifferentiated mouse embryonic stem cells, hepatic stellate cells and diverse human tumors, such as gastric, breast, brain, pancreatic, melanoma and colorectal tumors. Although ERAS belongs to GTPase family, it is an inefficient enzyme to hydrolyze GTP to GDP. Therefore, it remains mainly in its GTP-bound active form and contributes to sustained signal transduction. In comparison with classical members (HRAS, NRAS and KRAS4B), ERAS is known as a unique member, due to its temporal expression, remarkable amino acid sequence deviations and functional differences. Notably, ERAS has been recently proposed as a potential marker for drug resistance in several human tumors. In this minireview, I compare in great detail the biochemical properties of ERAS with conventional members of RAS family, and discuss the main ERAS function in the control of the PI3K-AKT-mTORC survival pathway. Targeting this pathway may sensitize ERAS expressing cell populations to chemotherapy.

***Keywords*:** Embryonic stem cell-expressed RAS, Signaling, Cancer, Oncogene, Effector, Survival

Hallmarks of ERAS

Embryonic stem cell-expressed RAS (ERAS) is a novel and unique member of small GTPase of RAS. Its expression has been first reported in undifferentiated mouse embryonic stem cells in 2003 (Takahashi et al., 2003). ERAS is meanwhile known as a unique member of RAS family due to its temporal expression and unusual biochemical properties. Unlike classical RAS proteins, it is not ubiquitously expressed in human tissues. In human cells, *ERAS* promotor is silenced by DNA methylation and histone deacetylation. Treatment of cells with inhibitors of DNA methyltransferase and histone deacetylase has been shown to restore *ERAS* expression (Nakhaei-Rad et al., 2016; Yashiro et al., 2009; Yasuda et al., 2007).

Biochemistry of ERAS

Regulation of RAS activity

Small GTPases of RAS act as nodes of intracellular signal transduction and convert external stimuli to the various cellular out-comes, including cell proliferation, differentiation, cell survival, migration, apoptosis and calcium signaling (Nakhaei-Rad et al., 2018). Although, RAS proteins are expressed and available for signal transduction at the cellular membranes, they remain as inactive proteins (GDP-bound) unless they receive external stimuli and transform to active protein (GDP-to-GTP exchange) (Fig. 1A). By the action of two main classes of regulatory proteins, namely guanine nucleotide exchange factors (GEFs) and GTPase activating proteins (GAPs), they cycle between an active (GTP-bound) and inactive (GDP-bound) forms, respectively (Fig. 1A). Oncogenic mutations of RAS proteins in three hotspot residues of G12, G13 and Q61 are found in more than 30% of human tumors (Pylayeva-Gupta et al., 2011). These point mutations are placed at the region of the protein where affect either the intrinsic GTPase activity (Q61) of enzyme or impair GAP function (G12 and G13). ERAS is an oncogenic protein without presence of any of these hotspot mutations. ERAS has a natural amino acid deviation at the position of G12S (HRAS numbering; ERAS S50) which renders it GAP insensitive (Takahashi et al., 2003) (Fig. 1B). Substitution of critical residue of glycine 12 for any other amino acids rather than glycine impairs GAP function on RAS proteins, which affects the cycle of RAS from active form (GTP-bound) to inactive form (GDP-bound) (Scheffzek et al., 1997) (Fig. 1A and

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B). Among amino acids, glycine possesses the smallest side chain and this small side chain provides a space for arginine finger of GAP proteins to enter the active site of RAS enzymes and accelerate hydrolysis of GTP to GDP (Ahmadian et al., 1997). Therefore, as soon as ERAS is expressed, translates to the active protein which cannot be inactive with conventional GAP proteins (Fig. 1B). Up-to-date, there is not any reports for ERAS specific GAP or inhibitory protein. Thus, the regulation of ERAS at the level of transcription is a critical step on its function.

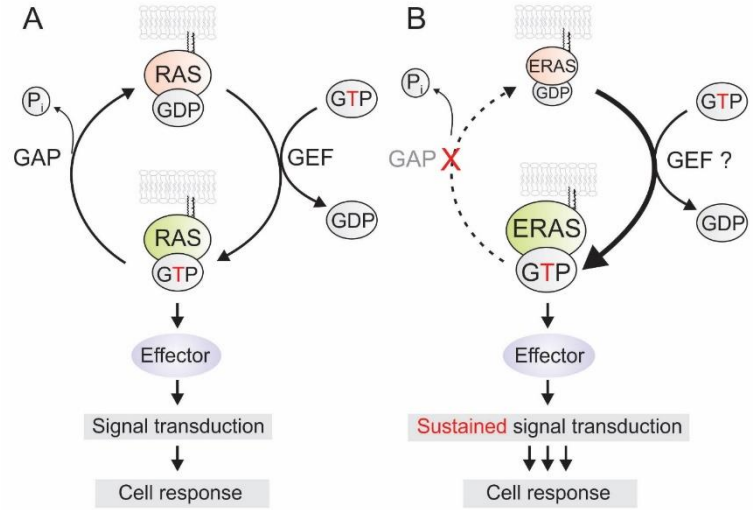

Figure 1. Schematic view of the RAS-GDP/GTP cycle and its comparison with ERAS. A) RAS proteins are cycling between GDP/GTP bound forms by the actions of two main regulatory proteins, GEF, and GAP. Through the interaction with effectors and switching ON the downstream pathways, RAS proteins exert their cellular functions, bottom in gray. B) ERAS harbors a deviation at G12 (S50 ERAS numbering) which impairs natural GTPase cycle to inactive form (GDP-bound) and makes it hyperactive protein with sustained signaling. GAP, GTPase-activating protein; GEF, guanine nucleotide exchange factor.

Structural fingerprints

RAS proteins harbor a conserved G domain with 5 motifs (G1-G5) that is responsible for a high-affinity binding to GTP (Fig1. B) (Bourne et al., 1990; Bourne et al., 1991). G1 with consensus sequence of GxxxxGKS binds to the phosphate groups of GTP, therefore it is known as P-loop (Saraste et al., 1990). Notably, critical residue of G12 is placed in this motif. G2 and G3 or switch I and switch II, respectively, are the flexible regions of the protein which upon binding to GTP or GDP move and provide a docking site for effector proteins (Vetter, 2001; Herrmann, 2003). G4 and G5 are differential motifs among GTPases and ATPases which covalently and specifically bind to the guanine base (Schmidt et al., 1996; Wittinghofer and Vetter, 2011). Although, ERAS protein as a member of RAS family owns conserved G domain with its essential motifs, it cannot efficiently hydrolyze GTP to GDP due to G12S (50 ERAS numbering) deviation in P-loop.

Effector selection by ERAS

Amino acid composition of switch I and switch II regions determine the specificity of RAS proteins for effector proteins (Wittinghofer and Vetter, 2011). Effector proteins are known as “effectors”, since RAS proteins alone cannot translate signals to the target proteins. These proteins are enzymes, scaffolds or modulators which upon RAS-GTP binding get activated or deactivated and diverge RAS signaling to the various cellular compartments and translate the RAS signaling to specific cellular out-comes (Nakhaei-Rad et al., 2018; Nakhaeizadeh et al., 2016). The specific RAS-effector interactions determine which pathways and where should be activated. Prototypes of RAS family, HRAS, NRAS and KRAS4B, possess similar sequences in their switch/effector regions which indicates, they could share the same set of downstream effectors (Nakhaeizadeh et al., 2016). In contrast, the sequence of switch regions of ERAS remarkably differs from HRAS, NRAS and KRAS4B. Therefore, ERAS may apply different set of effectors with different binding affinity and consequently emerges not overlapping cellular functions with classical RAS proteins. Among RASs, the phosphoinositide 3-kinase (PI3K) has the

highest affinity for ERAS (Fig. 3). Our mutational analysis of switch I, switch II and interswitch regions of ERAS to HRAS like sequence had revealed that tryptophan 79 of ERAS (arginine 41 of HRAS), within the interswitch region, is a main modulator for the effector selectivity of ERAS not its switch regions themselves (Nakhaei-Rad et al., 2015).

Prominent components of ERAS signal transduction towards cell survival

ERAS selectively and effectively activates PI3K signaling and this is due to the structural features of ERAS (see above). How dose PI3K support ERAS for its oncogenic function? To address this issue, we need to review in great details the components of this signaling pathway.

Lipid kinases

The RAS effector of PI3K belongs to the family of lipid kinases which phosphorylates phosphatidylinositol and phosphoinositides at inner leaflet of cellular membranes. According to the sequence homology and lipid substrates, three classes of PI3Ks are recognized: Class I, II and III. These kinases get activated either upon ligand binging to the receptor tyrosine kinases and G protein-coupled receptors or direct interaction with RAS proteins which targets them to the plasma membrane where they can interact with their substrates (Vanhaesebroeck et al., 2010). Class I PI3K consists of four heterodimeric proteins with two different functional subunits: catalytic and regulatory subunit. Based on the regulatory subunit, class I PI3K is subdivided in two categories; class IA p110α, p110β and p110δ that are associated with p85-like regulatory subunit (p85α/β, p50α and p55α/γ); class IB has a unique member, p110γ, which forms a heterodimer with regulatory subunits of p101 and p84 (Jean and Kiger, 2014; Vadas et al., 2011; Vanhaesebroeck et al., 2010). The catalytic subunits of class I, p110, exhibit differential expression patterns where p110α and β are ubiquitously expressed in human tissues but expression of p110γ and δ are imitated mainly to the hematopoietic lineages (Fritsch et al., 2013; Fritsch and Downward, 2013; Kok et al., 2009; Vanhaesebroeck et al., 2005).

The phosphorylates 3-hydroxyle of the phosphoinositide (4,5) bisphosphate (PIP_2) is a substrate of p110 catalytic subunit. Upon phosphorylation it is converted to a second messenger of phosphoinositide (3,4,5) trisphosphate (PIP_3) (Fig. 3). PIP_3 acts as a docking site for recruiting the proteins which harbors pleckstrin homology (PH) domain to the membrane. These PH containing proteins include adaptor proteins, protein kinases (*e.g.*, AKT and PDK1), RAS regulatory proteins of GEFs or GAPs (Vanhaesebroeck et al., 2001). Spatial localization of these protein through PH-PIP3 interactions, place them to the specific membrane nanoclusters where they could be in close approximately to their substrates.

Protein kinase B (PKB)

Protein kinase B (PKB) or AKT is a member of AGC subfamily of protein kinases and the most investigated target of PI3K-PIP3 axis. PI3K-PIP3-AKT activation results in cell proliferation, metabolic changes, cell growth, autophagy inhibition, and cell survival (Hers et al., 2011; Pearce et al., 2010). Activity of AKT is regulated by two critical posttranslational covalent modifications on its active site (T308) and hydrophobic motifs, S473 (Andjelkovic et al., 1997). AKT gets phosphorylated at position T308 by PDK1 enzyme (Alessi et al., 1997). Notably, both PDK1 and AKT share a PH domain that cluster them at the same membrane region via binding to PIP3. Phosphorylation of AKT at T308 position activates its kinase activity towards tuberous sclerosis 1/2 (TSC1/2) proteins (Fig. 3). TSC1/2 are GAP for a member of RAS family, RHEB, and their phosphorylation by AKT inhibits their GAP function. Consequently, RHEB could bind to its effector known as mammalian target of rapamycin (mTOR) complex 1 (Fig. 3) (Inoki et al., 2003; Inoki et al., 2002). A kinase for second key phosphorylation site of AKT (S473) is second mTOR complex (mTORC2) (see below for further information).

Composition of mammalian target of rapamycin (mTOR) complex 1 and 2

Two separate protein complexes of mTORC1 and mTORC2 share a same kinase, mTOR that is responsible for their catalytic activities (Zoncu et al., 2010). In addition to mTOR, these complexes have some negative and positive regulatory proteins in common such as DEP domain-containing mTOR-interacting protein (DEPTOR) and mammalian lethal with SEC13 protein 8 (mLST8), respectively (Loewith et al., 2002; Peterson et al., 2009)(Fig. 3). The main differences and accordingly specificity of mTORC1 and mTORC2 emerge from their accessory proteins of regulatory-associated protein of mTOR (RAPTOR) (Hara et al., 2002) and

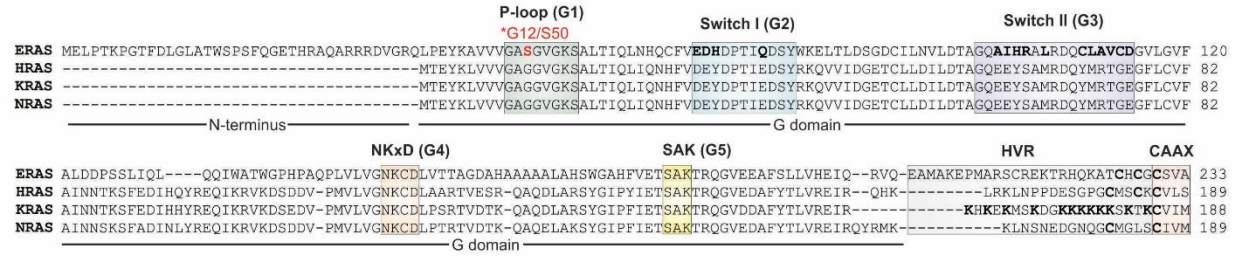

Figure 2. Overall sequence comparison of ERAS protein and classical RAS paralogs. ERAS contains an extended N-terminus (aa 1-38), which is not present in H, K, and NRAS. The P-loop (G1) of ERAS contains a serine (red) instead of a glycine (codon 12, HRAS numbering). Several residues in switch I (G2) and switch II (G2) regions that are responsible for effector recognition are different between ERAS and HRAS (bold letters). ERAS contains, like HRAS, a CAAX motif and two cysteines at the C-terminal hypervariable region (HVR), which is the site for posttranslational modifications by farnesylation and palmitoylation, respectively.

rapamycin-insensitive companion of mTOR (RICTOR), respectively (Sarbassov et al., 2004) (Fig. 3).

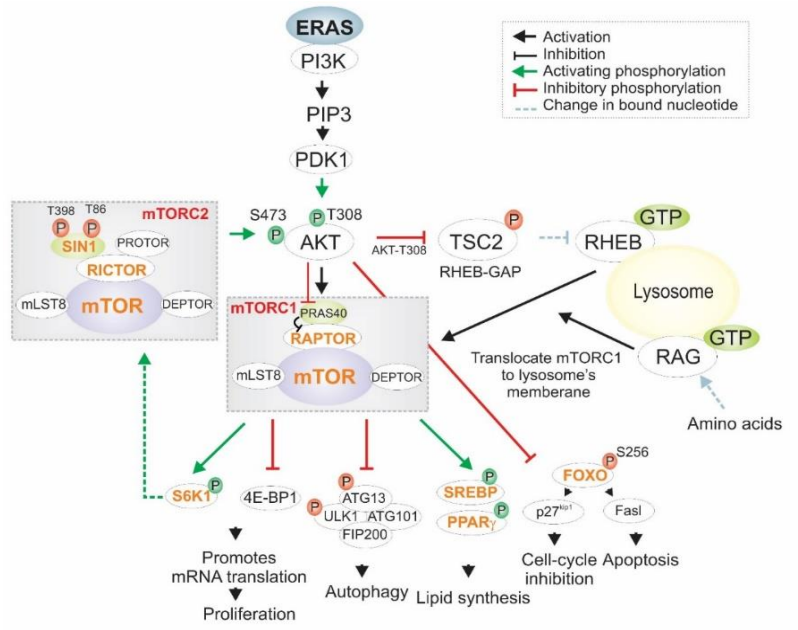

Figure 3. Schematic view of ERAS signaling towards mammalian target of rapamycin (mTOR) complexes. ERAS-PI3K-PDK1-AKT-mTORC signaling, its stimulation, regulation, substrates and cellular outcomes are illustrated. DEPTOR, DEP domain-containing mTOR-interacting protein; FIP200, FAK family kinase-interacting protein of 200 kDa; 4E-BP1, eukaryotic translation initiation factor 4E binding protein 1; FOXO1, forkhead transcription factor; GAP, GTPase activating protein; mLST8, mammalian lethal with SEC13 protein 8; mSIN1, mammalian stress-activated MAP kinase-interacting protein 1; mTORC, mammalian target of rapamycin; PDK1, 3-phosphoinositide-dependent protein kinase; PI3K, phosphoinositide 3-kinase; PKC, protein kinase C; PPARγ, peroxisome proliferator-activated receptor γ; PRAS40, 40 kDa Pro-rich AKT substrate; PROTOR, protein observed with RICTOR; RAPTOR, regulatory-associated protein of mTOR; RAS, rat sarcoma; RHEB, RAS homologue enriched in brain; RICTOR, mTORC2 rapamycin-insensitive companion of mTOR; TSC, tuberous sclerosis; ULK, Unc-51 like autophagy activating kinase 1.

Moreover, they are associated with other regulatory subunits, 40-kDa Proline-rich AKT substrate (PRAS40; mTORC1), mammalian stress-activated MAP kinase-interacting protein 1 (mSIN1/MAPKAP1; mTORC2) and protein observed with RICTOR (PROTOR; mTORC2) (Frias et al., 2006; Pearce et al., 2007; Sancak et al., 2007; Yang et al., 2006).

Regulators and targets of the mTOR complex 1

Since ERAS-PI3K-PDK1 signaling converges on mTORCs, here as cellular outputs of ERAS signaling, we specifically discuss targets of mTORC1/2. Signal transduction from PI3K-PDK1 towards mTORC1 occurs through inhibitory phosphorylation of TSC1/2 by AKT (phosphorylated at position T308) (Huang and Manning, 2008; Sancak et al., 2008). As a GAP, TSC1/2 is the negative regulator of RHEB GTPase (Tee et al., 2003) (Fig. 3). mTORC1 is an effector of RHEB, however, in physiological conditions mTORC is not located on the lysosomes. Therefore, one requirement of RHEB-mTORC1 interaction and its activation is translocation of mTORC1 to the endomembrane. Another GTPase, RAG resides together with RHEB on the lysosome/endosome surface. Changes in amino acid concentrations provide signals to stimulate RAG, which is responsible for endomembrane localization of mTORC1 (Sancak et al., 2008). Upon the TSC1/2 inactivation, RHEB stays in its GTP-loaded form and interacts and activates mTORC1 (Avruch et al., 2009; Inoki et al., 2003; Zoncu et al., 2010). mTORC1 phosphorylates wide range of substrates and regulates the ribosome biogenesis, mRNA translation, lipid synthesis and autophagy (Fig. 3) (Gentilella et al., 2015; Iadevaia et al., 2012; Kim and Chen, 2004; Porstmann et al., 2008; Yu et al., 2010). The best studies kinase downstream of mTORC1 is S6 kinase 1 (S6K1). S6K1 phosphorylates ribosomal protein S6, mTOR itself at position S2448, eukaryotic elongation factor 2 kinase (eEF2) and eIF4B (Hara et al., 1997; Ma and Blenis, 2009; Ma et al., 2008; Wang et al., 2001).

Regulators and targets of mTOR complex 2

Although, the growth factor signaling and mTORC2 association with ribosome are reported to control mTORC2 activity and assembly, the main upstream regulators of mTORC2 still remain as big puzzles (Zinzalla et al., 2011). Upon activation by mTORC1, p-S6K phosphorylates mSIN1 at two positions. mSIN1 is regulatory subunit of mTORC2 and it is essential for the integrity and substrate recruitment by mTORC2 (e.g. AKT) (Fig. 3). Therefore, mTORC1 through S6K regulates mSIN1-mTORC2 (Liu et al., 2013; Liu et al., 2014; Xie and Proud, 2013). Activated mTORC2 has a wide range of substrates rather than AKT (p-AKT473) and phosphorylates AGC kinases, serum and glucocorticoid-regulated kinase (SGK) and protein kinase C (PKC) (Garcia-Martinez and Alessi, 2008; Ikenoue et al., 2008; Sarbassov, 2005; Su and Jacinto, 2011). mTORC2 regulates cellular processes such as cell survival, cell cycle progression, anabolism and actin cytoskeleton organization (Jacinto et al., 2004). Second phosphorylation of AKT kinase at the hydrophobic motifs (S473) stimulates its full activity towards special substrates rather than TSC1/2, such as FOXO1 and 3. FOXO1/3 are two transcription factors that induce the expression from apoptotic genes (Fig. 3). Phosphorylation of FOXO1/3 by p-AKT (S473) sequester them in the cytoplasm. In this regards, it impairs nuclear translocation of FOXO1/3 and prevents their binding to the apoptotic gene promoters and induction of apoptosis. Therefore, mTORC2-AKT473-FOXO1/3 axis favorites the cell survival by inhibiting apoptosis (Wang et al., 2014). Co-immunoprecipitation analysis of the p110 isoforms with overexpressed ERAS and HRAS in Cos-7 cells indicted ERAS has highest affinity for p110α where HRAS binds mainly to p110δ isoform (Nakhaei-Rad et al., 2016). Cells which endogenously or exogenously express ERAS, have significantly higher levels of p-AKT308, p-mTORC, p-S6K, p-S6, p-mSIN1, p-AKT473 and p-FOXO1 (Nakhaei-Rad et al., 2016; Nakhaei-Rad et al., 2015). Collectively, ERAS through binding to PI3K and activation of this axis could regulate stem cell and cancer cell survival.

Concluding remarks

ERAS has been originally detected in undifferentiated embryonic stem cells and later in hepatic stellate cells as well as in several human tumors, including gastric, breast, brain, pancreatic, and colorectal tumors. Functional analysis of ERAS in tumors and stem cells, revealed its expression and signal transduction are important for tumor growth and cell survival responses. ERAS is a candidate gene for drug resistance in various human Establishes Cancer Cell Lines (ECCLs) as well as primary tumors derived from human tissues. To learn more about ERAS function in stemness and drug resistance in tumors, we need comprehensive

studies of ERAS binding partners in various cellular concepts. PI3K-AKT signaling pathway is one of the best-studied pathway controlled by ERAS, however, ERAS-specific effectors and upstream regulators remain unclear. Studying ERAS functions in the human stem cell pluripotency, and cancer cell growth will provide valuable insights into the control mechanisms of ERAS signaling during development, cancerogenesis and resistance to chemotherapies.

Acknowledgement
This study was supported by Ferdowsi University of Mashhad (grant numbers 49795) and Institute of Biotechnology (letter number, 4772474). I am grateful to Prof. Dr. Reza Ahmadian from the Institute of Biochemistry and Molecular Biology II of the Medical Faculty of the Heinrich-Heine University Düsseldorf for his helpful advices, and stimulating discussions.

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