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Rab1 in Cell Signaling, Cancer and Other Diseases

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Abstract

The ER and Golgi membrane system plays major roles in cell signaling and regulation of the biosynthesis/transport of proteins and lipids in response to environmental cues such as amino acid and cholesterol levels. Rab1 is the founding member of the Rab small GTPase family, which is known to mediate dynamic membrane trafficking between ER and Golgi. Growing evidence indicate that Rab1 proteins have important functions beyond their classical vesicular transport functions, including nutrient sensing and signaling, cell migration, and presentation of cell surface receptors. Moreover, deregulation of *RAB1* expression has been linked to a myriad of human diseases such as cancer, cardiomyopathy and Parkinson's disease. Further investigating these new physiological and pathological functions of Rab1 should provide new opportunities for better understanding of the disease processes and may lead to more effective therapeutic interventions.

Introduction

Rab1 was first identified as Ypt1 (yeast protein transport 1) in the budding yeast *Saccharomyces cerevisiae*⁴⁸. Rab1A and Rab1B were subsequently isolated as mammalian homologs of Ypt1^{55, 58}. Over the next three decades, a large number of Rab proteins have been identified and shown as key components of the intracellular vesicular transport system

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Conflict of Interest

The authors declare no conflict of interest.

that carries out vesicle docking and infusion, organelle motility and secretion of macromolecules²⁴. In mammals, there are over 60 Rab GTPase family members, representing the largest branch of the Ras superfamily²⁴. Rab1A and Rab1B have been found in 158 and 89 different organisms, respectively, ranging from yeast to humans, indicating that Rab1 is highly conserved during evolution. Rab1A and Rab1B contain a short N-terminal sequence, a conserved motif named “G box” essential for guanine nucleotide binding and guanosine 5'-triphosphate (GTP) hydrolysis, and a carboxyl (C)-terminal motif containing two conserved cysteine residues called “CC motif” that is the site for geranylgeranylation necessary for membrane binding⁵⁶ (Figure 1).

Active Rab proteins are localized to specific intracellular membranes. Rab1A and Rab1B are found predominantly at the membrane of endoplasmic reticulum (ER) and Golgi apparatus^{41, 46}. They have also been detected on lipid rafts⁵⁹ and autophagosomes⁷⁰, respectively. Rab1 proteins undergo several posttranslational modifications that regulate their functions. Ser-194 of Rab1A is phosphorylated by Cdk1 (Cdc2) kinase that affects its association with membranes during mitosis⁵. Phosphocholination at Ser-79 of Rab1A and Ser-76 of Rab1B by AnkX of the bacterial pathogen *Legionella pneumophila* leads to displacement of the GDP dissociation inhibitor (GDI)³⁵. AMPylation at Tyr-77 by *Legionella pneumophila* DrrA occurs in the switch 2 region of Rab1B protein, leading to moderate inactivation of the GTPase activity, while de-AMPylation by *L. pneumophila* SidD releases Rab1B from bacterial phagosomes^{36, 38}.

Like other Ras-related small GTPases, Rab1 activity is regulated by guanine nucleotide exchange factors (GEFs), GTPase-activating proteins (GAPs), GDP dissociation inhibitors (GDIs) and GDI-displacement factors (GDFs)⁹. GEF and GAP catalyze the conversion of Rab1 between the inactive GDP-bound and active GTP-bound forms, which regulates localization of Rab1 proteins to either cytosol or membranes⁹. GDI binds to Rab1-GDP, which maintains Rab1 in the inactive state and prevents Rab1 from binding to the membranes⁹. The inhibitory effect of GDI is relieved by GDF. TRAPP (transport protein particle) is a multimeric protein complex that serves as a GEF for Rab1. In yeast, there are three distinct TRAPP complexes, TRAPP I, II and III, which regulate Rab1 proteins in ER-to-Golgi traffic, intra-Golgi traffic, and autophagy, respectively⁷. However, only one TRAPP, the TRAPP II complex, has been identified in mammalian cells that regulates Golgi traffic⁷. Because Rab1 has low intrinsic GTPase activity, it relies primarily on GAP to accelerate GTP hydrolysis, which converts Rab1 from the GTP-bound to GDP-bound form, releasing Rab1 from the membranes⁷. Unlike the limited GEF proteins, there are over 40 Rab GAPs encoded by the human genome¹⁸. Rab GAPs are also known as TBC proteins that contain a conserved catalytic domain called the Tre2/Bub2/Cdc16 domain¹⁸. GDIs are relatively simple with only two isoforms that recognize geranylgeranylated Rab proteins and maintain them in the inactive, GDP-bound form⁹.

The ER and Golgi apparatus play a major role in the biosynthesis/transport of proteins and lipids. These organelles are highly dynamic and the rate of membrane trafficking between the two organelles rapidly changes in response to nutrient conditions and metabolic demands³⁰. Transport between the ER and Golgi is mediated by pre-Golgi structures or intermediate compartment where Rab1 proteins are enriched. The switch between GDP- and

GTP-bound states promotes Rab1 conformational changes and binding to effectors. Rab1-GTP regulates vesicular targeting and fusion to the Golgi complex by recruiting the tethering factor p115 and v-SNAREs to vesicles derived from the ER. The tethering protein is recruited to the coat protein complex II (COPII) on ER-derived vesicles, leading to formation of a *cis*-SNARE complex that promotes targeting to the Golgi membranes⁴. In addition, Golgi-84 binds to Rab1A/B-GTP, which contributes to the assembly of Golgi ribbon and the maintenance of Golgi structure^{14, 47}.

Rab1 Signaling Functions

The ER and Golgi apparatus are central to the synthesis, modification and transport of cell surface receptors and transporters. This membrane system also serves as a major hub for cell signaling and regulatory functions in response to extracellular and intracellular cues such as nutrients and ER stress. For examples, the transcription factors SREBP1 and ATF6 are anchored in the ER-Golgi system. Upon stimulation, they are proteolytically processed and translocated into the nucleus where they regulate gene expression^{22, 27}. As a key regulator of ER-to-Golgi transport, it is not surprising that Rab1 proteins have been increasingly linked to diverse cellular signaling pathways, including nutrient signaling, Notch signaling, integrin-dependent cell migration, autophagy and cell surface receptor expression. Figure 2 summarizes some of the key signal transduction pathways that are regulated by Rab1 GTPases. In contrast to Ras, Rho and Cdc42, the Ras family of small GTPases traditionally known for their role in signal transduction, Rab1 proteins do not appear to directly activate their effectors. Instead, they regulate the formation and/or targeting of active signaling complex on appropriate membranes. In this regard, Rab1 is similar to Rag in that both GTPases act as ‘unconventional’ signaling molecules.

mTOR Signaling

Nutrients such as amino acid (AA) are not only building blocks for the biosynthesis of proteins and other macromolecules, but also mitogenic signals that regulate cell growth and metabolism. Genetic screens in the budding yeast *Saccharomyces cerevisiae* identified several Golgi proteins important for trafficking the general amino acid transporter Gap1 from Golgi to the plasma membrane or vacuoles in response to AA availability. One of the genes isolated is *LST8* (known as *GBL* or *mLST8* in mammals), which later was shown to encode an essential subunit of mTORC1, a master regulator of nutrient signaling⁴⁴. Consistently, mTOR is enriched in the endoplasmic reticulum (ER) and Golgi membrane system, which is important for mTOR signaling to S6 kinase^{15, 33}. Another study shows that Golgi-endosome trafficking is crucial for TOR to regulate nuclear localization of Gln3 in yeast⁴³. The ER-Golgi system plays a central role in nutrient signal transduction into the nucleus. For example, Pik1, a phosphatidylinositol 4-kinase, shuttles between the Golgi and nucleus in a nutrient-dependent manner¹³. SREBP1 (Sterol regulatory element-binding protein 1), a master transcription factor for metabolic genes, is localized on the ER as an inactive precursor. In response to metabolic demands (e.g. insulin or cholesterol), it is transported to the Golgi apparatus where it is processed into the active form that transits to the nucleus and activates the expression of lipogenic or other metabolic genes²². mTOR has been shown to regulate the trafficking and processing of SREBP1c^{19, 42}. Collectively, these

observations indicate that the ER-Golgi system is especially important for mTOR to regulate signaling into the nucleus.

AA is a key activating signal for mTORC1^{2, 45}. Genetic screens in *Drosophila*³² and yeast⁵⁴ identifies Rab1 as an essential factor for activation of mTORC1 by AA. Rab1A knockdown in human embryonic kidney (HEK) 293, colorectal (CRC) and hepatocellular carcinoma (HCC) cells attenuates the ability of AA to stimulate mTORC1, while overexpression of Rab1A potentiates mTORC1 signaling^{54, 66}, indicating that this Rab1 function is evolutionarily conserved. Mechanistically, AA stimulates GTP loading onto Rab1 proteins and GTP-dependent interaction with mTORC1 in the Golgi. Rab1 does not appear to directly activate mTORC1 kinase activity. Instead, it regulates the interaction of mTORC1 with another small GTPase Rheb, which activates mTORC1 activity on the Golgi surface. It is interesting to note that the mechanism of mTORC1 activation by Rab1 on the ER-Golgi system is similar to that by Rag GTPases on the lysosomes¹⁶. Because mTOR is localized in both Golgi and nucleus^{31, 57}, it will be interesting to see whether the Golgi anchored signaling mechanism is especially important for mTOR shuttling into the nucleus.

Notch Signaling

Notch Signaling is an evolutionarily conserved pathway that regulates cell proliferation and developmental processes such as cell fate determination and differentiation in metazoans. Notch is a cell-surface receptor interacting with transmembrane ligands from neighboring cells. Notch receptors are processed in the ER and Golgi in the signal-receiving cell through cleavage, glycosylation and other posttranslational modifications, generating a membrane-attached heterodimer that is transported to the plasma membrane²⁸. In a *Drosophila* genetic screen for modulators of Notch signaling, a novel protein prenyltransferase (PPT) named Tempura was identified⁸. Tempura functions as a subunit of a previously uncharacterized geranylgeranyl transferase complex for Rab1. Loss of *Tempura* or *RAB1* leads to mis-localization of Delta and Scabrous, two important Notch signaling components, and Notch signaling defects⁸. These results demonstrate that Rab1 and Tempura play an important role in Notch signaling.

Regulation of Integrin-dependent Cell Migration

The heterodimeric complex of integrin α and β is the major receptor for extracellular matrix. It play essential roles in cell adhesion, migration and proliferation²⁵. Cell-surface integrins undergo dynamic internalization and recycling processes. In a focused RNAi screen for essential GTPases in cell migration in *Drosophila* S2 cells, Rab1A was identified as a novel regulator of cell migration⁵⁹. *RAB1A* knockdown inhibits integrin-mediated cell adhesion and spreading on fibronectins, integrin β 1 localization to lipid rafts, and recycling of integrin β 1 to the plasma membrane regions at the leading edge of migrating cells. Among Rab1A effectors, the tethering factor p115 is selectively involved in Rab1a regulation of integrin recycling and lipid raft localization in cell migration. Interestingly, p115 knockdown also affects Rab1A localization to the lipid raft, suggesting that p115 is a specific effector and a co-factor for Rab1A in this regard. These results reveal a novel function for Rab1A that controls cell motility through regulation of integrin β 1 recycling and targeting to lipid rafts at the leading edge of migrating cells.

Regulation of Autophagy

Autophagy (also known as macroautophagy) is an evolutionarily conserved intracellular and lysosome-dependent degradation process in eukaryotic cells²⁰. During autophagy, cytoplasmic contents, including ribosomes and mitochondria, are enclosed by double-membrane vesicular structures called autophagosomes that are then delivered to the lysosomes for degradation. This process generates an internal supply of nutrients essential for maintaining basic cellular functions and survival during starvation. siRNA-mediated knockdown of *RAB1B* or overexpression of dominant negative Rab1B in CHO cells inhibits autophagosome formation, resulting in accumulation of immature autophagosomes⁷⁰. The same work suggests that Rab1B-mediated ER vesicular transport, independently of Golgi, is important for initiation of autophagosomal formation. Consistent with a role of Rab1 in autophagy, Trs85, a component of the TRAPP complex, the GEF for Rab1, was shown to be necessary for formation of proper pre-autophagosomal structure (PAS)³⁴. It was further shown that that activated Ypt1/Rab1 recruits Atg1 to the PAS, bringing it to the proximity of its binding partner Atg17⁶⁰. The same study further showed that Ypt1/Rab1 binds and activates casein kinase (CK) 1 delta, which in turn regulates membrane trafficking and autophagosome biogenesis⁶¹. Overexpression of α -synuclein has been implicated in the pathogenesis of Parkinson's disease (PD). It was shown that in cultured cells and transgenic mice, α -synuclein overexpression inhibits autophagy in a Rab1A-dependent manner because this blockage can be readily reversed by Rab1A overexpression⁶³.

Other Notable Rab1 Signaling Functions

Rab1 proteins are known to modulate several cellular processes through targeted cargo delivery. In addition to the aforementioned integrin β 1 recycling and plasma membrane targeting of Notch receptors, several other cell surface molecules have been shown to be Rab1-dependent, including human calcium-sensing receptor (hCaR) that controls cellular sensitivity to extracellular calcium⁶⁹, the G protein-coupled receptors (GPCRs) angiotensin II type 1A receptor (AT1R), and adrenergic receptor (AR)⁶⁵. Of a large number of cell surface proteins, only a small number are known to be regulated by Rab1. It would be of great interest to determine whether Rab1 is broadly involved in the presentation of receptor proteins on the cell surface or it has a more selective role.

Rab1 and Cancer

Aberrant *RAB1* expression in cancer

Given their important regulatory functions in growth, migration and survival, it is not surprising that elevated expression of *RAB1A* and *RAB1B* has been reported in multiple cancer types, including colorectal cancer (CRC)⁵⁴, gliomas⁶, hepatocellular carcinomas (HCC)⁶⁶, prostate cancer¹, and tongue squamous carcinomas⁵¹ for *RAB1A*, and CRC⁶⁸, HCC^{21, 37} and prostate cancer¹ for *RAB1B*. Alternative splicing of *RAB1B* has also been detected in cervical cancer, although the pathological significance is not known³⁹. In CRC and HCC, analysis of large cohorts of human primary tumor samples indicate that *RAB1A* overexpression is strongly associated with disease progression and poor prognosis^{54, 66}. Interestingly, *RAB1A* and *RAB1B* was reported to be down-regulated in metastatic prostate⁵³ and triple negative breast cancers²⁶, suggesting that loss of *RAB1* expression is

associated with metastasis. However, these observations contradict aforementioned studies in CRC, HCC and breast cancer in which *RAB1A* overexpression was found to promote tumor invasion and metastasis. A possible explanation for the discrepancies is that the role of *RAB1* in metastasis is dependent on specific tumor type and/or other oncogenic events. In HCCs, *RAB1A* overexpression can be attributed in part to gene amplification, rather than epigenetic changes by DNA methylation⁶⁶. MicroRNAs (miRs) may contribute to the dysregulated *RAB1* expression of in human cancer. miR-15b-5p was reported to be down-regulated in HCC, which results in overexpression of its target gene *RAB1A* in HCC⁶⁷. On the other hand, Rab1A was reported to be negatively regulated by miR-221 in androgen independent prostate cancer⁵³.

Role of Rab1 in cancer

The consequence of aberrant *RAB1* expression has been investigated. Ectopic *RAB1A* overexpression is sufficient to transform NIH3T3 cells at a potency stronger than the oncogene H-RAS^{V12} in colony and xenograft tumor formation assays⁵⁴. Ectopically expressed Rab1A activates mTORC1 and promotes tumor growth, invasion and progression. Consistently, CRC and HCC tumors with high *RAB1A* expression exhibit hyperactive mTORC1 signaling and poor overall survival^{54, 66}. Conversely, *RAB1A* knockdown in CRC and HCC cell lines with high endogenous Rab1A level attenuates mTORC1 signaling, and tumor growth and invasiveness^{54, 66}. Interestingly, growth of CRC cells with high *RAB1A* levels is more dependent on AA, suggesting that aberrant *RAB1A* expression elevates AA-mTORC1 signaling and renders cancer cells addictive to AAs. Consistently, CRC and HCC cells with high Rab1A levels are also very sensitive to rapamycin, the highly selective mTORC1 inhibitor, further supporting the notion that such cancer cells are addictive to hyperactive AA-mTORC1 signaling for their oncogenic growth.

Compared with Rab1A, the role of Rab1B in human cancer is less well studied. In CRC cells, *RAB1B* was shown to be a target for miR-502⁶⁸. miR-502 is frequently down-regulated, which is correlated with high *RAB1B* expression. Ectopic expression of miR-502 causes down-regulation of *RAB1B*, resulting in blockage of autophagy flux, tumor growth and proliferation, while knockdown of miR-502 enhances *RAB1B* expression, autophagy and tumor growth⁶⁸. In another study, increased expression of *RAB1A* and *RAB1B* was found to be associated with neoplastic reprogramming of adipose-derived stem cells (pASCs), which may be important for prostate cancer development¹. More recently, loss of *RAB1B* expression was found in triple-negative breast cancer (TNBC), which is correlated with enhanced metastasis²⁶. The altered metastasis appears to be mediated by the TGF- β /Smad pathway. Thus, Rab1 proteins may have distinct roles in different types and subtypes of tumors, which appears to be mediated by distinct downstream oncogenic signaling pathways.

Cardiomyopathy

Cardiac hypertrophy is the thickening of heart muscle in response to extrinsic and intrinsic stimuli. In a dilated cardiomyopathy mouse model with cardiac muscle-specific overexpression of β 2-adrenergic receptor (AR), *RAB1* was found to be highly expressed⁶⁴.

To investigate the significance of *RAB1*, the authors generated heart-specific *RAB1A* transgenic mice and found that the animals develop dilated cardiomyopathy in a *RAB1A* dosage-dependent manner. The hearts of mice carrying high copy number of *RAB1A* transgene are dilated with prominent signs of cardiac hypertrophy within 6 weeks⁶⁴. The level of MAP kinases did not change but the expression of several protein kinase C (PKC) isoforms increases. In cardiac myocytes, increased Rab1A level facilitates cardiomyocyte hypertrophic growth in response to stimulation by angiotensin II (Ang II) and phenylephrine (PE)¹⁷. More recently, it was shown that up-regulation of miR-101 in a rat model of cardiac hypertrophic model protects against Rab1A-induced myocardial hypertrophy and heart failure, suggesting that miR-101 is potentially useful for therapeutic intervention of cardiomyopathy⁶². Thus far, the precise mechanism of Rab1A in cardiac pathogenesis remains unclear. Because hyperactive mTORC1 is known to cause cardiac hypertrophy⁴⁹, it would be interesting to determine if Rab1A-driven cardiac hypertrophy is mediated through activated mTORC1 signaling.

Parkinson's Disease (PD)

PD is the second most common neurodegenerative disease, which is characterized by over-accumulation of the presynaptic protein α -synuclein in neurons¹². In a yeast genomic screen, Ypt1 was identified as a suppressor of α -synuclein-induced toxicity¹⁰. It was subsequently shown that α -synuclein overexpression impairs Rab1A activity and thus hinders the formation of autophagosome by interfering with Atg9 function⁶³. Moreover, increased Rab1 production is sufficient to correct α -synuclein-mediated Golgi fragmentation, dopaminergic (DA) neuron loss, and motor deficits in mammalian animal models of PD^{10, 11}. These observations suggest that Rab1A plays a crucial role in the pathogenesis of PD and is a potential therapeutic target for a disease currently lacking effective medicine.

Other Rab1-related Diseases

Infections of Intracellular Pathogens

Pathogenic intracellular bacteria such as *Legionella pneumophila* residing in host membrane vesicles have evolved survival mechanisms by targeting Rab1 proteins. This allows alteration of the destination of pathogen-occupied vacuole to avoid fusion with lysosomes for destruction, and to acquire nutrients to support bacterial propagation. These processes are the subjects of several excellent reviews that detail the role of Rab1 proteins in bacteria-host cell interactions^{50, 52}.

Retinitis pigmentosa (RP)

RP is a degenerative retinal disease characterized by progressive loss of vision caused by photoreceptor degeneration followed by retinal pigment epithelium abnormalities. Genetic linkage analysis of autosomal recessive RP in an Indian family mapped the susceptibility locus to Chromosome 2p14-15 that contains the *RAB1A* gene²⁹. Interestingly, a recent study showed that Rab1A is selectively expressed in the rod bipolar cells in the inner retina, which is highly dependent on ambient light²³. This finding suggests a role of Rab1A in dark

adaptation, which is consistent with the pathological phenotype of defective dark adaptation in RP patients³.

Aspirin-exacerbated respiratory disease (AERD)

AERD is a type of asthma triggered by aspirin (acetyl salicylic acid) and other nonsteroidal anti-inflammatory drugs (NSAIDs). A recent study analyzed a large cohort of 1,197 asthmatic patients. Single-nucleotide polymorphisms (SNPs) in *RAB1A* gene, +14444 T > G and +41170 C > G, were found to be significantly associated with the AERD group compared with the aspirin-tolerated asthmatic group⁴⁰. The molecular basis for *RAB1A* in this disease association is currently unknown.

Concluding Remarks

Over the past decade or so, progress has been made in the understanding of Rab1 functions beyond its canonical role in ER-Golgi membrane trafficking, showing that Rab1 is also involved in a myriad of cell signaling and regulatory functions. Moreover, Rab1 proteins have been implicated in human diseases such as cancer, cardiomyopathy and Parkinson's disease. These new findings provide new insights into their physiological and pathological functions. Importantly, modulation of Rab1 expression/activity has been shown to have therapeutic benefits toward Parkinson's disease, colorectal cancer and hepatocellular carcinoma, suggesting that Rab1 is a potentially useful drug target. Despite of these advances, research on Rab1's non-canonical functions is still limited and many basic questions remain. For examples, Rab1 have two isoforms, Rab1A and Rab1B, which share 92% amino acid sequence homology. It is unclear whether they are merely functionally redundant or have unique functions. Targeted deletion of *RAB1A* or *RAB1B* has not been reported in animals. Their roles in development and organ/tissue functions are largely unknown. Because Rab1 proteins play key roles in cancer, cardiomyopathy and Parkinson's disease, it would be of great interest to identify small molecule agonists and/or antagonists, which would be useful for therapeutic development or as chemical probes to study Rab1-dependent cellular and physiological processes. Addressing these questions may open up new research frontiers in biology and medicine.

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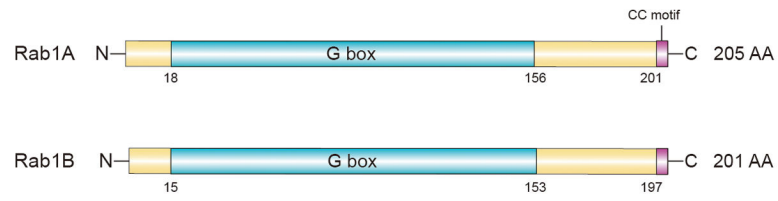


Figure 1. Domain Structure of Rab1A and Rab1B

Shown is the domain structure of Rab1A and Rab1B. The G box is involved in guanine nucleotide binding and GTP hydrolysis domain. The CC motif, containing two cysteine residues, targets membranes through geranylgeranyl modification. .

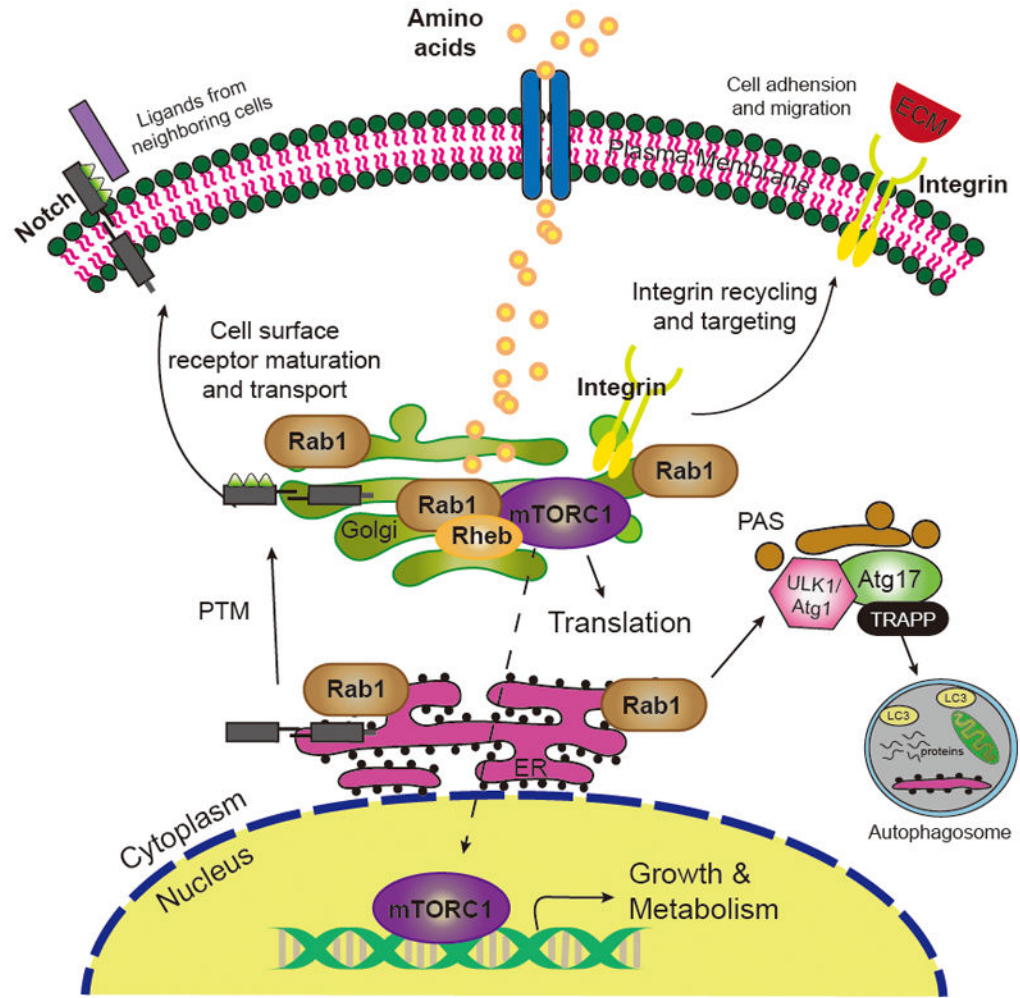


Figure 2. Role of Rab1 in Cell Signaling and Regulatory Functions

Rab1 has key roles in regulating mTORC1, Notch and integrin cell signaling pathways, as well as autophagy and localization of cell surface receptors. The ER-Golgi system appears to be particularly important for amino acid (AA) signaling into the nucleus and regulating gene expression. During carcinogenesis, *RAB1* is up-regulated in part by copy number variation (CNV) or microRNAs, which promotes cancer initiation and development through activation of mTORC1 signaling and other mitogenic pathways.