

Recent advances in understanding of amino acid signaling to mTORC1 activation

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1. ABSTRACT

The mechanistic target of rapamycin complex 1 (mTORC1) is a master controller of cell growth and metabolism which integrates diverse bio-signaling inputs to coordinate various fundamental biological processes. Amino acids, especially leucine, arginine and glutamine, signal to mTORC1 activation. Classically, Rag GTPases play a crucial role in amino acids-induced mTORC1 activation in the lysosome and Golgi apparatus. More recently, multiple amino acid sensors have been identified and most of them indirectly associate with Rag GTPases. As a result, the mechanistic details on how amino acids are sensed and activate mTORC1 are rapidly evolving. This review discusses current understanding of mTORC1 activation and provides a brief and up-to-date narrative on the progress of amino acid sensors regulating mTORC1 activation.

2. INTRODUCTION

Eukaryotic cells have evolved mechanisms for integrating signals from the environment to ensure efficiently transitioning between anabolic and catabolic states, allowing them to survive and grow. The studies of the past decades have revealed that the mechanistic/mammalian target of rapamycin complex 1 (mTORC1) has played a central role in integrating signals and regulating fundamental cell process(1-5). The mTORC1 is an evolutionary conserved atypical serine/threonine protein kinase that belongs to phosphoinositide protein kinases family (PIKKs). The mTORC1 is a key integrator of environmental cues, such as growth factors, energy status, and an array of stress(6), which control many processes from cell growth to apoptosis, and deregulated mTORC1 activation is associated with many human diseases (4, 7-9).

Among these signals, amino acids act as crucial nutrient signals to activate the mTORC1 pathway in addition to their role as protein building blocks. Amino acids are also precursor substrates to synthesize many low-molecule substances which feature enormous physiological functions. In addition, there is increasing evidence that multi-amino acids (leucine, arginine, serine, glutamine) can participate in or regulate key metabolic mTORC1 pathway to improve animal health, survival, growth, development and reproduction of organisms(10-13), even though the essential amino acid leucine has been considered as a crucial mTORC1 activator in many cell types. Therefore, in this review, we attempt to provide a brief and up-to-date narrative on key mediators of amino acid sensing pathway in the regulation of mTORC1.

3. AMINO ACID SENSING TO mTORC1

3.1. Extracellular amino acid transport into cells

The phospholipid bilayer in the cell surface is a selective barrier to signals and nutrients, and numerous receptors and transporters are embedded in cell membrane and participate in signaling and nutrient transportation(14). Amino acids do not directly diffuse across cell membrane or organelle membrane, and it require membrane-spanning transporter proteins to help transfer them into or out of cells and organelles(15, 16). Recent studies have shown that the solute carrier (SLC) superfamily has been thought to be the major group of amino acid transporters. The SLC superfamily genes include the classical transporter families which contain ion-coupled transporters, exchangers, passive transporters, etc(16, 17). The detailed information of the SLC genes is described in Table 1. Amino acid transporters have a similar structure that features several transmembrane domains organized around a central pore region which can recognize a range of structural or physico-chemical property similar amino acids(18, 19). Likewise, the monocarboxylate transporter SLC16 can transport aromatic amino acids including tyrosine, phenylalanine and tryptophan (20). In mammalian cells, some amino acid transporters are expressed in specific tissues but in most types of tissues expressing several amino acid transporters coupled with overlapping function in transporting amino acids. In epithelial cells, SLC6A19 and SLC6A14 belong to broad-scope Na⁺-coupled amino acid symporters that are able to transport neutral amino acids. However, in nonepithelial cells, large neutral amino acids are transported into cells by exchange or facilitative mechanisms (19, 21).

There is emerging evidence to show that amino acid transporters own a dual transporter/receptor function. Firstly, the amino acid transporters at the surface of cells act as gate keepers of nutrient exchange (18). Secondly, mammalian amino acid

transporters may regulate nutrient signaling (eg. mTORC1 activation) and become a limiting factor for mTORC1 activation. In addition, the glutamine transporter (SLC1A5) in combination with the heterodimeric amino acid transporter CD98, solute-linked carrier (SLC)3A2-SLC7A5 (CD98hc-LAT1) can activate mTORC1 by transporting leucine into cells. SLC7A5 can directly mediate leucine-induced mTORC1 activation in fibroblasts(22). Moreover, there is emerging evidence to suggest that arginine transporters SLC7A1-4 may directly influence mTORC1 activation (23).

3.2. Intracellular amino acid signaling to mTORC1

3.2.1. Organization of mTORC1

mTORC1 is comprised of mTOR, mammalian lethal with SEC13 protein 8 (mLST8, also known as GβL), the regulatory associated protein of mTOR (RAPTOR), DEP domain containing mTOR-interacting protein (DEPTOR), PRAS40 and recently identified telomere maintenance Tti1/Tel2(24-26). Among the proteins in the complex, mTOR is the core kinase, and RAPTOR and Tti1/Tel2 are scaffold proteins regulating the assembly and stability of the mTORC1. The RAPTOR interaction with mTOR can be either loosened or tightened depending on various stimuli. For example, amino acid deprivation reinforces the RAPTOR-mTOR interaction, whereas rapamycin can disrupt the interaction(26). The function of mLST8/GβL is still unknown, but it may stabilize and positively regulate mTORC1. However, this view is challenged by the observation that knockout of mLST8 does not impair the stability of mTORC1(27). RRAS40 and DEPTOR are negative regulators of mTORC1(28). PRAS40 directly interacts with RAPTOR and can block its binding to mTOR. Similarly, DEPTOR can bind to the FRAP-ATM-RRAP (FAT) domain of mTOR(29). mTORC1 activation is regulated by two types of mechanisms: one is direct modification of mTORC1 components, and the other one is that growth factor through IRS1-PI3K or AMPK pathway signal regulation the upstream factors of mTORC1 signaling pathway (30, 31). Recent studies have showed that mTORC1 can maintain cell metabolism through regulating various key mediators or transcription factors, and this section has been well described in the review of Duan et.al(32). Thus, in this review, we will focus on the proteins that participate in amino acid sensing to mTORC1.

3.2.2. Rag GTPases in amino acid signaling to mTORC1

Recent studies have suggested that the lysosome has been recognized as a major effector and serves as a platform for mTORC1 activation by amino acids or growth factors. Intracellular amino

Table 1. The principal amino acid transporters expressed in mammalian cells

SLC name	Transporter name	Transport types [*]	Substrates	Distribution
SLAC1A1	EAAC1, EAAT2	B A	L-Glu, D/L-Asp	Intestine, kidney, liver, heart, brain
SLC1A2	GLT-1, EAAT2	B A	L-Glu, D/L-Asp	Brain, Liver, Pancreas
SLC1A3	GLAST, EAAT1	B A	L-Glu, D/L-Asp	Brain, Skeletal Muscle
SLC1A4	ASCT1, SATT	B C	L-Ala, L-Ser, L-Cys, L-Thr	In Most Tissue
SLC1A5	ASCT2	B	L-Ala, Ser, Cys, Thr, Gln	Lung, Skeletal Muscle, Large Intestine,
SLC1A6	EAAT4	A and B	L-Glu, D/L-Asp	Cerebellum
SLC1A7	EAAT5	A and B	L-Glu, D/L-Asp	Retina
SLC3A1	rBAT	C	Cationic Amino Acids, Neutral Amino Acids	Kidney, Small Intestine, Liver, Pancreas
SLC3A2	4F2hc	C	Neutral L-Amino Acids, Cationic Amino Acids	In Most Tissue
SLC6A5		UN	Glycine	Brain
SLC6A9		UN	Glycine	Liver, Spleen, Kidney, Stomach, Intestine
SLC6A14		UN	Neutral, Cationic Amino Acids	Lung, Trachea, Salivary Gland, Mammary Gland, Stomach,
SLC6A15		UN	Large, Neutral Amino Acids	Brain, Kidney
SLC6A17-19		UN	Neutral Amino Acids	Brain, Heart, Skeletal Muscle
SLC7A1	CAT-1	C	Cationic L-Amino Acids	Ubiquitous Except For Liver,
SLC7A2	CAT-2	C	Cationic L-Amino Acids	Liver, Skeletal Muscle, Pancreas
SLC7A3	CAT-3	C	Cationic L-Amino Acids	Thymus, Ovary, Testis, Brain
SLC7A5	LAT-1	C	Neutral L-Amino Acids	Brain, Testis, Placenta, Spleen, Colon, Fetal Liver
SLC7A6	y+LAT2	C	Cationic Amino Acids, Neutral L-Amino Acids	Brain, Small Intestine, Heart, Kidney, Lung, Thymus
SLC7A7	y+LAT1	E	Cationic Amino Acids, Neutral L-Amino Acids	Small Intestine, Kidney, Spleen, Leucocytes, Placenta
SLC7A8	LAT2	C	Neutral L-Amino Acids	Small Intestine, Kidney, Lung, Heart, Spleen, Liver, Brain
SLC7A9	b ⁰ , +AT	C	Cationic Amino Acids, Neutral Amino Acids	Kidney, Small Intestine, Liver, Placenta
SLC7A10	Asc-1	C	Neutral Amino Acids	Brain, Small Intestine, Muscle

*Note: The sequential relationship between primary, secondary and tertiary active transport systems (denoted A, B and C, respectively), the same denotation is described in Figure 1.

acids can induce the movement of mTORC1 to the lysosome membranes and lead to mTORC1 activation(33-35). Rags and Rheb, two different types of small GTPases cooperate to accurately regulate mTORC1 activity. The Rags is involved in the translocation of mTORC1 to the lysosome surface in response to amino acids. Full activation of mTORC1 requires Rheb, which is activated under conditions of high energy status and growth factor signals(36, 37). Together, the GTPases act as coincidence detectors, which integrate signals relating to nutrients, energy status, and growth factors.

The Rag proteins are obligate heterodimers of functionally redundant small GTPases composed of either RagA or RagB and RagC or RagD. The heterodimers RagA/B in the GTP bound state (RagA/B^{GTP}) and RagC/D in GDP bound state (RagC/D^{GDP}) are conceived as active forms in terms of mTORC1 activation(38-40). Multiple studies have provided insights into the complex machinery implicated in the regulation of Rag nucleotide status that convey amino acid signals to mTORC1(41). The activity of Rag GTPases is regulated by GTPase-activating proteins (GAPs) and guanine nucleotide exchange

factors (GEFs)(42). GEFs activate Rag GTPases by exchanging their nucleotide status, while GAPs can inactivate Rag GTPases by stimulating GTP hydrolysis (43).

Extensive works have suggested that a large protein complex activates Rag GTPases' activity on the lysosome surfaces in response to amino acids(44-46). Within this complex, Vacuolar H⁺-adenosine triphosphatase ATPase (v-ATPase) interacts with Ragulator(47), which is anchored in the lysosomal surfaces and functions as a guanine nucleotide exchange factor (GEF) for RagA/B to facilitate the exchange of the heterodimer RagA/B^{GDP} to the active form (RagA/B^{GTP})(10, 48). V-ATPase plays a role in positively regulating the mTORC1 pathway through an unknown mechanism, while it is believed to regulate Ragulator's GEF activity towards RagA/B.

A multiprotein complex known as GAP activity toward Rags 1 (GATOR1) was identified by immunoprecipitation and mass spectrum (IP-MS) analysis using RagB as a bait(49). GATOR1 is a trimeric protein complex composed with DEPDC5, Nprl2, and Nprl3, and functions as a GTPase-activating protein toward RagA/B. In this study, a second complex named CASTOR2 was also identified by IP-MS analysis. GATOR2 interacts with GATOR1 and negatively regulates GATOR1 activity (50). Recently, the KICSTOR complex is composed with KPTN, C12orf66, ITFG2 and SZT2-containing regulator of mTORC1, and function as a scaffold protein for GATOR1 binding to the lysosome(51). As mentioned above, FNIP1/2 complex with Folliculin acts as a GTPase-activating protein for RagC/D(52) that can regulate Rag GTPases' activity. Thus, FICN-FINP1/2 is a positive regulator of mTORC1 in a Rag GTPase-dependent manner(53).

Overall, multiple regulatory proteins, including GAPs, GEFs, and scaffold proteins, have been characterized to directly or indirectly modulate the activity of Rag GTPases, which play a central role in the activation of mTORC1(54).

3.2.3. Other GTPases in amino acid signaling to mTORC1

The discovery of Rag GTPases is a milestone in understanding of mTORC1 activation by nutrients. However, recent studies have shown that another two small GTPases are also essential for mTORC1 activation in cells. Glutamine, a nitrogen source and energy substance, can promote the translocation of mTORC1 to the lysosome and its activation in a Rag GTPases-independent mechanism. A small GTPase named ribosylation factor1 (ARF1) has been characterized to have a similar function as Rag which involves glutamine-induced mTORC1 activation(10,

55, 56). Knockdown of ARF1 in mammalian or *Drosophila* S2 cells can block glutamine signaling to mTORC1 in the absence of Rags(10). Overexpression of constitutively GTP-bound Arf or treatment with brefeldin A, an inhibitor for ARF1, can inhibit mTORC1 translocation and activation even in the presence of glutamine(57, 58). Overall, ARF1 seems to be specific to glutamine-induced mTORC1 activation(58).

Recent studies have revealed that amino acids can activate mTORC1 via Rab GTPase in the surface of Golgi apparatus(59, 60). Thomas *et al* have identified Rab1 as a conserved regulator of mTORC1 and elucidated a Golgi-based mechanism by which Rab1 engages mTORC1 interaction with RheB(61, 62). In addition, overexpression of Rab1A promotes mTORC1 signaling. Furthermore, Fan *et al* have revealed that SLC36A4, known as PAT4, is predominantly localized in the Golgi apparatus and engages mTORC1 interaction with Rab1A(63).

4. INTRACELLULAR AMINO ACID SENSORS

4.1. Sestrin2: a leucine sensor in the cytoplasm

Sestrins have been initially identified as a family of stress-inducible proteins, which are capable of attenuating various stresses, stimulating autophagy, and regulating cell metabolism(64, 65) (Figure 1). Sestrins family contains three homologs (Sestrin1-3) sharing nearly 50% amino acid sequence similarity. Apart from the function of redox regulation, Sestrin 1-3 have been characterized as negative regulators of mTORC1 and positive regulators of AMPK through TSC2(66-69). The Sestrins have been proposed to interact with and function as guanine nucleotide dissociation inhibitor for the Rag GTPases(70). More recently, Sestrin1 and Sestrin2 showed a high affinity (K_d) of 10~15 and ~20 μ M to physically bind to leucine(71). Moreover, Sestrin2 which purified from prokaryotic cell, has ability to directly bind to leucine but not arginine *in vitro*. And the assay of mutation Sestrin2 and crystalized Sestrin2 strongly indicated residues of Sestrin2 directly bind leucine and importance for binding leucine capacity of the protein. Sestrin2 interacts with GATOR2 to inhibit mTORC1 under leucine deprivation, not arginine deprivation(72, 73). When leucine added in media, it binds to Sestrin2 to dissociate the complex of Sestrin2-GATOR2. Leucine must bind to Sestrin2 in order for leucine to activate mTORC1 in mammalian cells. Overall, Sestrin2 acts as a leucine sensor in the cytoplasm(74).

4.2. CASTOR1: an arginine sensor in the cytoplasm

GATOR2 have been characterized as integrating multiple amino acid inputs to mTORC1, and thus specific amino acid sensors may interact

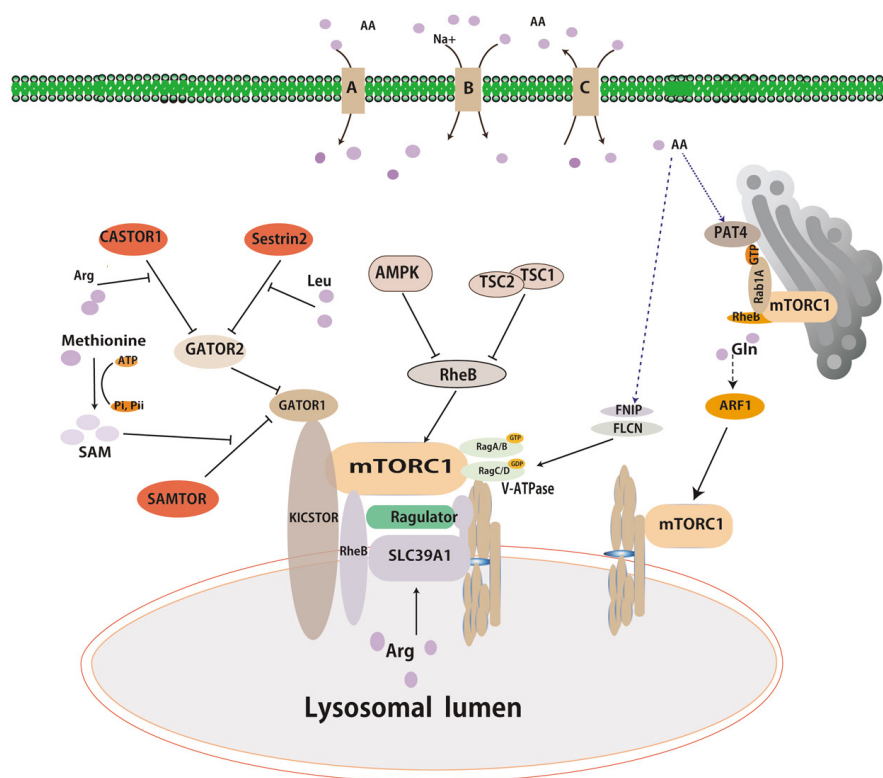


Figure 1. Overview of multiple signals activating mTORC1. Amino acids, growth factors and energy signals can lead to mTORC1 activation. Growth factors and energy signals activate mTORC1 primarily through the PI3K pathway and AMPK pathway, respectively. Amino acids signal to mTORC1 in Rag-dependent and Rag-independent pathway. Sestrin2, CASTOR1 and SAMTOR (shown in red box) are reported to be cytosolic amino acid sensors for leucine, arginine, and s-adenosyl-L-methionine, respectively. Arrows and bars represent activation and inhibition, respectively, of downstream proteins.

with GATOR2, analogous to that of SESN2 (Figure 1). Chantranupong and his colleagues searched a protein interaction database named BioPlex to identify potential GATOR2-interacting partners, and they found that CASTOR1 encoded by GATS protein-like 3 (GATSL3) gene is one of putative GATOR2 interactors(75). Subsequently, CASTOR1 has been characterized as a cytosolic arginine sensor. The homodimeric CASTOR1 protein can interact with GATOR2 under the arginine deprivation condition to inhibit mTORC1 activation. *In vitro* binding assays showed that CASTOR1 can directly and specifically bind to arginine at a highly affinity of $\sim 30 \mu\text{M}$ (76). Arginine-bound CASTOR1 can lead to dissociation of CASTOR1 from GATOR2, leading to mTORC1 activation. Thus, CASTOR1 acts as an arginine sensor in the cytoplasm(75, 77).

4.3. SMATOR: an s-adenosyl-L-methionine sensor in the cytoplasm

As the mentioned above, GATOR2 plays a role in integrating multiple amino acid inputs to mTORC1. The function of GATOR2 remains known, however it might be upstream of CATOR1 which are GAPs for RagA/B(49), and the KICSTOR complex bound with GATOR1 is necessary for amino acid deprivation to inhibit mTORC1 activation (51)(Figure

1). Xin Gu et, al found that SAMTOR, previously named C7orf60, interacts with GATOR1 and KICSTOR through searching the BioPlex database and co-immunoprecipitation assays(78). Methyl donor S-adenosylmethionine (SAM) can directly bind to GATOR1 and then disrupt the SAMTOR-GATOR1 at the constant of approximately $7 \mu\text{M}$ in media (78). SAMTOR senses SAM to signal methionine sufficiency to mTORC1, while methionine may translate into SAM to activate mTORC1. Thus, SAMTOR acts as a SAM sensor in the cytoplasm (78).

4.4. SLC38A9: a putative arginine sensor in the lysosome surface

SLC38A9, an uncharacterized protein with sequence homology to amino acid transporters, functions as a positive regulator of mTORC1 in an amino acid-sensitive manner (79, 80) (Figure 1). SLC38A9 has been characterized as a lysosomal transmembrane protein that interacts with GTPases and Ragulator which can regulate mTORC1 activation (12). SLC38A9 binds to arginine with a high Michaelis constant (81). Knockout of SLC38A9 inhibits mTORC1 activation by arginine, and overexpression of SLC38A9 makes mTORC1 activation more sensitive by arginine. Thus, SLC38A9 is an excellent candidate for being

an arginine sensor in the lysosome for activating mTORC1(82).

5. CONCLUSION AND NEW PERSPECTIVE

Amino acids act as protein building blocks, precursor substrates for signaling molecule, and crucial nutrient signals to mTORC1 activation. In the past few years, our understanding of amino acid sensing to mTORC1 has increased tremendously(8, 28, 29, 33, 51). Of note, mTORC1 acts as a critical regulatory node that controls cell metabolism, including cell proliferation, cycle and death. Dysfunction of mTORC1 is highly associated with many diseases such as insulin resistance(83-85), diabetes(86) and various types of cancer(87-89). the discovery of Rag proteins is a breakthrough in understanding of mTORC1 activation by nutrients, and it helps researchers identify other key components in the mTORC1 signaling pathway, especially amino acid sensors. Recently, Sestrin2, CASTOR1, SMATOR and SLC39A1 have been identified as amino acid sensors. However, sensors for other amino acid such as serine and glutamine remain to be identified. Overall, the molecular mechanisms of amino acid sensing to mTORC1 is quite complex, and more regulatory components of mTORC1 require further investigation.

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7. REFERENCES

1. V. P. Tan and S. Miyamoto: Nutrient-sensing mTORC1: Integration of metabolic and autophagic signals. *J Mol Cell Cardiol*, 95, 31-41 (2016)
DOI: 10.1016/j.yjmcc.2016.01.005
PMid:26773603 PMCID:PMC4909545
2. A. Philp, D. L. Hamilton and K. Baar: Signals mediating skeletal muscle remodeling by resistance exercise: PI3-kinase independent activation of mTORC1. *J Appl Physiol* (1985), 110(2), 561-8 (2011)
DOI: 10.1152/japplphysiol.00941.2010
PMid:21071597
3. R. J. Flinn and J. M. Backer: mTORC1 signals from late endosomes: taking a TOR of the endocytic system. *Cell Cycle*, 9(10), 1869-70 (2010)
DOI: 10.4161/cc.9.10.11679
PMid:20436274 PMCID:PMC4082334
4. H. Kassai, Y. Sugaya, S. Noda, K. Nakao, T. Maeda, M. Kano and A. Aiba: Selective activation of mTORC1 signaling recapitulates microcephaly, tuberous sclerosis, and neurodegenerative diseases. *Cell Rep*, 7(5), 1626-1639 (2014)
DOI: 10.1016/j.celrep.2014.04.048
PMid:24857653
5. P. Bond: Regulation of mTORC1 by growth factors, energy status, amino acids and mechanical stimuli at a glance. *J Int Soc Sports Nutr*, 13, 8 (2016)
6. N. Sulaimanov, M. Klose, H. Busch and M. Boerries: Understanding the mTOR signaling pathway via mathematical modeling. *Wiley Interdiscip Rev Syst Biol Med*, 9(4) (2017)
7. M. Palmieri, R. Pal, H. R. Nelvagal, P. Lotfi, G. R. Stinnett, M. L. Seymour, A. Chaudhury, L. Bajaj, V. V. Bondar, L. Bremner, U. Saleem, D. Y. Tse, D. Sanagasetti, S. M. Wu, J. R. Neilson, F. A. Pereira, R. G. Pautler, G. G. Rodney, J. D. Cooper and M. Sardiello: Corrigendum: mTORC1-independent TFEB activation via Akt inhibition promotes cellular clearance in neurodegenerative storage diseases. *Nat Commun*, 8, 15793 (2017)
8. D. M. Sabatini: Twenty-five years of mTOR: Uncovering the link from nutrients to growth. *Proc Natl Acad Sci U S A*, 114(45), 11818-11825 (2017)
DOI: 10.1073/pnas.1716173114
PMid:29078414 PMCID:PMC5692607
9. A. Efeyan, R. Zoncu and D. M. Sabatini: Amino acids and mTORC1: from lysosomes to disease. *Trends in Molecular Medicine*, 18(9), 524-533 (2012)
DOI: 10.1016/j.molmed.2012.05.007
PMid:22749019 PMCID:PMC3432651
10. J. L. Jewell, Y. C. Kim, R. C. Russell, F. X. Yu, H. W. Park, S. W. Plouffe, V. S. Tagliabracci and K. L. Guan: Metabolism. Differential regulation of mTORC1 by leucine and glutamine. *Science*, 347(6218), 194-8 (2015)
DOI: 10.1126/science.1259472
PMid:25567907 PMCID:PMC4384888

11. D. W. Wang, L. Wu, Y. Cao, L. Yang, W. Liu, X. Q. E, G. Ji and Z. G. Bi: A novel mechanism of mTORC1-mediated serine/glycine metabolism in osteosarcoma development. *Cell Signal*, 29, 107-114 (2017)
DOI: 10.1016/j.cellsig.2016.06.008
PMid:27297361
12. S. Wang, Z. Y. Tsun, R. L. Wolfson, K. Shen, G. A. Wyant, M. E. Plovanich, E. D. Yuan, T. D. Jones, L. Chantranupong, W. Comb, T. Wang, L. Bar-Peled, R. Zoncu, C. Straub, C. Kim, J. Park, B. L. Sabatini and D. M. Sabatini: Metabolism. Lysosomal amino acid transporter SLC38A9 signals arginine sufficiency to mTORC1. *Science*, 347(6218), 188-94 (2015)
DOI: 10.1126/science.1257132
PMid:25567906 PMCID:PMC4295826
13. R. V. Duran and M. N. Hall: Glutaminolysis feeds mTORC1. *Cell Cycle*, 11(22), 4107-8 (2012)
DOI: 10.4161/cc.22632
PMid:23095634 PMCID:PMC3524199
14. N. Poncet and P. M. Taylor: The role of amino acid transporters in nutrition. *Curr Opin Clin Nutr Metab Care*, 16(1), 57-65 (2013)
DOI: 10.1097/MCO.0b013e32835a885c
PMid:23196813
15. S. Broer: Amino acid transport across mammalian intestinal and renal epithelia. *Physiol Rev*, 88(1), 249-86 (2008)
DOI: 10.1152/physrev.00018.2006
PMid:18195088
16. F. Verrey, E. I. Closs, C. A. Wagner, M. Palacin, H. Endou and Y. Kanai: CATs and HATs: the SLC7 family of amino acid transporters. *Pflugers Arch*, 447(5), 532-42 (2004)
DOI: 10.1007/s00424-003-1086-z
PMid:14770310
17. B. Mackenzie and J. D. Erickson: Sodium-coupled neutral amino acid (System N/A) transporters of the SLC38 gene family. *Pflugers Arch*, 447(5), 784-95 (2004)
DOI: 10.1007/s00424-003-1117-9
PMid:12845534
18. H. S. Hundal and P. M. Taylor: Amino acid transceptors: gate keepers of nutrient exchange and regulators of nutrient signaling. *Am J Physiol Endocrinol Metab*, 296(4), E603-13 (2009)
DOI: 10.1152/ajpendo.91002.2008
PMid:19158318 PMCID:PMC2670634
19. H. N. Christensen: Role of amino acid transport and countertransport in nutrition and metabolism. *Physiol Rev*, 70(1), 43-77 (1990)
DOI: 10.1152/physrev.1990.70.1.43
PMid:2404290
20. A. P. Halestrap and D. Meredith: The SLC16 gene family-from monocarboxylate transporters (MCTs) to aromatic amino acid transporters and beyond. *Pflugers Arch*, 447(5), 619-28 (2004)
DOI: 10.1007/s00424-003-1067-2
PMid:12739169
21. J. T. Brosnan: Interorgan amino acid transport and its regulation. *J Nutr*, 133(6 Suppl 1), 2068S-2072S (2003)
22. D. C. Goberdhan, C. Wilson and A. L. Harris: Amino Acid Sensing by mTORC1: Intracellular Transporters Mark the Spot. *Cell Metab*, 23(4), 580-9 (2016)
DOI: 10.1016/j.cmet.2016.03.013
PMid:27076075 PMCID:PMC5067300
23. A. Yeramian, L. Martin, N. Serrat, L. Arpa, C. Soler, J. Bertran, C. McLeod, M. Palacin, M. Modolell, J. Lloberas and A. Celada: Arginine transport via cationic amino acid transporter 2 plays a critical regulatory role in classical or alternative activation of macrophages. *J Immunol*, 176(10), 5918-24 (2006)
DOI: 10.4049/jimmunol.176.10.5918
PMid:16670299
24. C. C. Dibble, W. Elis, S. Menon, W. Qin, J. Klekota, J. M. Asara, P. M. Finan, D. J. Kwiatkowski, L. O. Murphy and B. D. Manning: TBC1D7 is a third subunit of the TSC1-TSC2 complex upstream of mTORC1. *Mol Cell*, 47(4), 535-46 (2012)
DOI: 10.1016/j.molcel.2012.06.009
PMid:22795129 PMCID:PMC3693578
25. D. H. Kim, D. D. Sarbassov, S. M. Ali, J. E. King, R. R. Latek, H. Erdjument-Bromage, P. Tempst and D. M. Sabatini: mTOR interacts with raptor to form a nutrient-sensitive complex that signals to the cell growth machinery. *Cell*, 110(2), 163-75 (2002)
DOI: 10.1016/S0092-8674(02)00808-5
26. K. Yonezawa, C. Tokunaga, N. Oshiro and K. Yoshino: Raptor, a binding partner of target of rapamycin. *Biochem Biophys Res Commun*, 313(2), 437-41 (2004)
DOI: 10.1016/j.bbrc.2003.07.018
PMid:14684181

27. Y. Sancak, C. C. Thoreen, T. R. Peterson, R. A. Lindquist, S. A. Kang, E. Spooner, S. A. Carr and D. M. Sabatini: PRAS40 is an insulin-regulated inhibitor of the mTORC1 protein kinase. *Mol Cell*, 25(6), 903-15 (2007)
DOI: 10.1016/j.molcel.2007.03.003
PMid:17386266
28. M. Laplante and D. M. Sabatini: mTOR signaling at a glance. *J Cell Sci*, 122(Pt 20), 3589-94 (2009)
29. M. Laplante and D. M. Sabatini: An emerging role of mTOR in lipid biosynthesis. *Curr Biol*, 19(22), R1046-52 (2009)
30. V. P. Krymskaya and E. A. Goncharova: PI3K/mTORC1 activation in hamartoma syndromes: therapeutic prospects. *Cell Cycle*, 8(3), 403-13 (2009)
DOI: 10.4161/cc.8.3.7555
PMid:19177005 PMCID:PMC3718392
31. A. Kalender, A. Selvaraj, S. Y. Kim, P. Gulati, S. Brule, B. Viollet, B. E. Kemp, N. Bardeesy, P. Dennis, J. J. Schlager, A. Marette, S. C. Kozma and G. Thomas: Metformin, independent of AMPK, inhibits mTORC1 in a rag GTPase-dependent manner. *Cell Metab*, 11(5), 390-401 (2010)
DOI: 10.1016/j.cmet.2010.03.014
PMid:20444419 PMCID:PMC3081779
32. Y. Duan, F. Li, K. Tan, H. Liu, Y. Li, Y. Liu, X. Kong, Y. Tang, G. Wu and Y. Yin: Key mediators of intracellular amino acids signaling to mTORC1 activation. *Amino Acids*, 47(5), 857-67 (2015s)
33. Y. Sancak, L. Bar-Peled, R. Zoncu, A. L. Markhard, S. Nada and D. M. Sabatini: Regulator-Rag complex targets mTORC1 to the lysosomal surface and is necessary for its activation by amino acids. *Cell*, 141(2), 290-303 (2010)
DOI: 10.1016/j.cell.2010.02.024
PMid:20381137 PMCID:PMC3024592
34. A. Roczniak-Ferguson, C. S. Petit, F. Froehlich, S. Qian, J. Ky, B. Angarola, T. C. Walther and S. M. Ferguson: The transcription factor TFEB links mTORC1 signaling to transcriptional control of lysosome homeostasis. *Sci Signal*, 5(228), ra42 (2012)
35. C. Pous and P. Codogno: Lysosome positioning coordinates mTORC1 activity and autophagy. *Nat Cell Biol*, 13(4), 342-4 (2011)
DOI: 10.1038/ncb0411-342
PMid:21460804
36. R. T. Abraham: Cell biology. Making sense of amino acid sensing. *Science*, 347(6218), 128-9 (2015)
DOI: 10.1126/science.aaa4570
PMid:25574008
37. E. Kim, P. Goraksha-Hicks, L. Li, T. P. Neufeld and K. L. Guan: Regulation of TORC1 by Rag GTPases in nutrient response. *Nat Cell Biol*, 10(8), 935-45 (2008)
DOI: 10.1038/ncb1753
PMid:18604198 PMCID:PMC2711503
38. T. P. Nguyen, A. R. Frank and J. L. Jewell: Amino acid and small GTPase regulation of mTORC1. *Cell Logist*, 7(4), e1378794 (2017)
DOI: 10.1080/21592799.2017.1378794
PMid:29296509 PMCID:PMC5739091
39. J. L. Jewell, R. C. Russell and K. L. Guan: Amino acid signalling upstream of mTOR. *Nat Rev Mol Cell Biol*, 14(3), 133-9 (2013)
DOI: 10.1038/nrm3522
PMid:23361334 PMCID:PMC3988467
40. E. Hirose, N. Nakashima, T. Sekiguchi and T. Nishimoto: RagA is a functional homologue of *S. cerevisiae* Gtr1p involved in the Ran/Gsp1-GTPase pathway. *J Cell Sci*, 111 (Pt 1), 11-21 (1998)
41. M. P. Peli-Gulli, A. Sardu, N. Panchaud, S. Raucci and C. De Virgilio: Amino Acids Stimulate TORC1 through Lst4-Lst7, a GTPase-Activating Protein Complex for the Rag Family GTPase Gtr2. *Cell Rep*, 13(1), 1-7 (2015)
DOI: 10.1016/j.celrep.2015.08.059
PMid:26387955
42. J. L. Bos, H. Rehmann and A. Wittinghofer: GEFs and GAPs: critical elements in the control of small G proteins. *Cell*, 129(5), 865-77 (2007)
DOI: 10.1016/j.cell.2007.05.018
PMid:17540168
43. J. L. Jewell and K. L. Guan: Nutrient signaling to mTOR and cell growth. *Trends Biochem Sci*, 38(5), 233-42 (2013)
DOI: 10.1016/j.tibs.2013.01.004
PMid:23465396 PMCID:PMC3634910

44. Y. Sancak, T. R. Peterson, Y. D. Shaul, R. A. Lindquist, C. C. Thoreen, L. Bar-Peled and D. M. Sabatini: The Rag GTPases bind raptor and mediate amino acid signaling to mTORC1. *Science*, 320(5882), 1496-501 (2008)
DOI: 10.1126/science.1157535
PMid:18497260 PMCID:PMC2475333
45. L. Bar-Peled, L. D. Schweitzer, R. Zoncu and D. M. Sabatini: Ragulator is a GEF for the rag GTPases that signal amino acid levels to mTORC1. *Cell*, 150(6), 1196-208 (2012)
DOI: 10.1016/j.cell.2012.07.032
PMid:22980980 PMCID:PMC3517996
46. R. V. Duran, W. Oppliger, A. M. Robitaille, L. Heiserich, R. Skendaj, E. Gottlieb and M. N. Hall: Glutaminolysis activates Rag-mTORC1 signaling. *Mol Cell*, 47(3), 349-58 (2012)
DOI: 10.1016/j.molcel.2012.05.043
PMid:22749528
47. R. Zoncu, L. Bar-Peled, A. Efeyan, S. Y. Wang, Y. Sancak and D. M. Sabatini: mTORC1 Senses Lysosomal Amino Acids Through an Inside-Out Mechanism That Requires the Vacuolar H⁺-ATPase. *Science*, 334(6056), 678-683 (2011)
DOI: 10.1126/science.1207056
PMid:22053050 PMCID:PMC3211112
48. C. S. Zhang, B. Jiang, M. Li, M. Zhu, Y. Peng, Y. L. Zhang, Y. Q. Wu, T. Y. Li, Y. Liang, Z. Lu, G. Lian, Q. Liu, H. Guo, Z. Yin, Z. Ye, J. Han, J. W. Wu, H. Yin, S. Y. Lin and S. C. Lin: The lysosomal v-ATPase-Ragulator complex is a common activator for AMPK and mTORC1, acting as a switch between catabolism and anabolism. *Cell Metab*, 20(3), 526-40 (2014)
DOI: 10.1016/j.cmet.2014.06.014
PMid:25002183
49. L. Bar-Peled, L. Chantranupong, A. D. Cherniack, W. W. Chen, K. A. Ottina, B. C. Grabiner, E. D. Spear, S. L. Carter, M. Meyerson and D. M. Sabatini: A Tumor suppressor complex with GAP activity for the Rag GTPases that signal amino acid sufficiency to mTORC1. *Science*, 340(6136), 1100-6 (2013)
DOI: 10.1126/science.1232044
PMid:23723238 PMCID:PMC3728654
50. A. Parmigiani, A. Nourbakhsh, B. Ding, W. Wang, Y. C. Kim, K. Akopiants, K. L. Guan, M. Karin and A. V. Budanov: Sestrins inhibit mTORC1 kinase activation through the GATOR complex. *Cell Rep*, 9(4), 1281-91 (2014)
DOI: 10.1016/j.celrep.2014.10.019
PMid:25457612 PMCID:PMC4303546
51. R. L. Wolfson, L. Chantranupong, G. A. Wyant, X. Gu, J. M. Orozco, K. Shen, K. J. Condon, S. Petri, J. Kadir, S. M. Scaria, M. Abu-Remaileh, W. N. Frankel and D. M. Sabatini: KICSTOR recruits GATOR1 to the lysosome and is necessary for nutrients to regulate mTORC1. *Nature*, 543(7645), 438-442 (2017)
DOI: 10.1038/nature21423
PMid:28199306 PMCID:PMC5360989
52. Z. Y. Tsun, L. Bar-Peled, L. Chantranupong, R. Zoncu, T. Wang, C. Kim, E. Spooner and D. M. Sabatini: The folliculin tumor suppressor is a GAP for the RagC/D GTPases that signal amino acid levels to mTORC1. *Mol Cell*, 52(4), 495-505 (2013)
DOI: 10.1016/j.molcel.2013.09.016
PMid:24095279 PMCID:PMC3867817
53. C. S. Petit, A. Roczniak-Ferguson and S. M. Ferguson: Recruitment of folliculin to lysosomes supports the amino acid-dependent activation of Rag GTPases. *J Cell Biol*, 202(7), 1107-22 (2013)
DOI: 10.1083/jcb.201307084
PMid:24081491 PMCID:PMC3787382
54. M. Ishida, E. O. M and M. Fukuda: Multiple Types of Guanine Nucleotide Exchange Factors (GEFs) for Rab Small GTPases. *Cell Struct Funct*, 41(2), 61-79 (2016)
DOI: 10.1247/csf.16008
PMid:27246931
55. J. Goldberg: Structural and functional analysis of the ARF1-ARFGAP complex reveals a role for coatamer in GTP hydrolysis. *Cell*, 96(6), 893-902 (1999)
DOI: 10.1016/S0092-8674(00)80598-X
56. M. R. Reynolds, A. N. Lane, B. Robertson, S. Kemp, Y. Liu, B. G. Hill, D. C. Dean and B. F. Clem: Control of glutamine metabolism by the tumor suppressor Rb. *Oncogene*, 33(5), 556-66 (2014)
DOI: 10.1038/onc.2012.635
PMid:23353822 PMCID:PMC3918885
57. Y. C. Kim, H. W. Park, S. Sciarretta, J. S. Mo, J. L. Jewell, R. C. Russell, X. Wu, J. Sadoshima and K. L. Guan: Rag GTPases are cardioprotective by regulating lysosomal function. *Nat Commun*, 5, 4241 (2014)

58. L. Li, E. Kim, H. Yuan, K. Inoki, P. Goraksha-Hicks, R. L. Schiesher, T. P. Neufeld and K. L. Guan: Regulation of mTORC1 by the Rab and Arf GTPases. *J Biol Chem*, 285(26), 19705-9 (2010)
DOI: 10.1074/jbc.C110.102483
PMid:20457610 PMCID:PMC2888380
59. M. H. Lee, Y. J. Yoo, D. H. Kim, N. H. Hanh, Y. Kwon and I. Hwang: The Prenylated Rab GTPase Receptor PRA1.F4 Contributes to Protein Exit from the Golgi Apparatus. *Plant Physiol*, 174(3), 1576-1594 (2017)
DOI: 10.1104/pp.17.00466
PMid:28487479 PMCID:PMC5490915
60. S. Naramoto, M. S. Otegui, N. Kutsuna, R. de Rycke, T. Dainobu, M. Karampelias, M. Fujimoto, E. Feraru, D. Miki, H. Fukuda, A. Nakano and J. Friml: Insights into the localization and function of the membrane trafficking regulator GNOM ARF-GEF at the Golgi apparatus in Arabidopsis. *Plant Cell*, 26(7), 3062-76 (2014)
DOI: 10.1105/tpc.114.125880
PMid:25012191 PMCID:PMC4145132
61. J. D. Thomas, Y. J. Zhang, Y. H. Wei, J. H. Cho, L. E. Morris, H. Y. Wang and X. F. S. Zheng: Rab1A Is an mTORC1 Activator and a Colorectal Oncogene. *Cancer Cell*, 30(1), 181-182 (2016)
DOI: 10.1016/j.ccell.2016.06.014
PMid:27479033
62. F. A. Barr: Rab GTPase function in Golgi trafficking. *Semin Cell Dev Biol*, 20(7), 780-3 (2009)
DOI: 10.1016/j.semcdb.2009.03.007
PMid:19508857
63. B. H. Xu, X. X. Li, Y. Yang, M. Y. Zhang, H. L. Rao, H. Y. Wang and X. F. Zheng: Aberrant amino acid signaling promotes growth and metastasis of hepatocellular carcinomas through Rab1A-dependent activation of mTORC1 by Rab1A. *Oncotarget*, 6(25), 20813-28 (2015)
DOI: 10.18632/oncotarget.5175
PMid:26308575 PMCID:PMC4673231
64. J. H. Lee, A. V. Budanov, S. Talukdar, E. J. Park, H. L. Park, H. W. Park, G. Bandyopadhyay, N. Li, M. Aghajan, I. Jang, A. M. Wolfe, G. A. Perkins, M. H. Ellisman, E. Bier, M. Scadeng, M. Foretz, B. Viollet, J. Olefsky and M. Karin: Maintenance of metabolic homeostasis by Sestrin2 and Sestrin3. *Cell Metab*, 16(3), 311-21 (2012)
DOI: 10.1016/j.cmet.2012.08.004
PMid:22958918 PMCID:PMC3687365
65. J. H. Lee, A. V. Budanov and M. Karin: Sestrins orchestrate cellular metabolism to attenuate aging. *Cell Metab*, 18(6), 792-801 (2013)
DOI: 10.1016/j.cmet.2013.08.018
PMid:24055102 PMCID:PMC3858445
66. J. S. Kim, S. H. Ro, M. Kim, H. W. Park, I. A. Semple, H. Park, U. S. Cho, W. Wang, K. L. Guan, M. Karin and J. H. Lee: Sestrin2 inhibits mTORC1 through modulation of GATOR complexes. *Sci Rep*, 5, 9502 (2015)
67. J. S. Kim, S. H. Ro, M. Kim, H. W. Park, I. A. Semple, H. Park, U. S. Cho, W. Wang, K. L. Guan, M. Karin and J. Hee Lee: Corrigendum: Sestrin2 inhibits mTORC1 through modulation of GATOR complexes. *Sci Rep*, 5, 14029 (2015)
68. X. Shi, L. Xu, D. M. Doycheva, J. Tang, M. Yan and J. H. Zhang: Sestrin2, as a negative feedback regulator of mTOR, provides neuroprotection by activation AMPK phosphorylation in neonatal hypoxic-ischemic encephalopathy in rat pups. *J Cereb Blood Flow Metab*, 37(4), 1447-1460 (2017)
DOI: 10.1177/0271678X16656201
PMid:27381825 PMCID:PMC5453464
69. J. K. Byun, Y. K. Choi, J. H. Kim, J. Y. Jeong, H. J. Jeon, M. K. Kim, I. Hwang, S. Y. Lee, Y. M. Lee, I. K. Lee and K. G. Park: A Positive Feedback Loop between Sestrin2 and mTORC2 Is Required for the Survival of Glutamine-Depleted Lung Cancer Cells. *Cell Rep*, 20(3), 586-599 (2017)
DOI: 10.1016/j.celrep.2017.06.066
PMid:28723563
70. M. Peng, N. Yin and M. O. Li: Sestrins function as guanine nucleotide dissociation inhibitors for Rag GTPases to control mTORC1 signaling. *Cell*, 159(1), 122-133 (2014)
DOI: 10.1016/j.cell.2014.08.038
PMid:25259925 PMCID:PMC4181352
71. R. A. Saxton, K. E. Knockenhauer, R. L. Wolfson, L. Chantranupong, M. E. Pacold, T. Wang, T. U. Schwartz and D. M. Sabatini: Structural basis for leucine sensing by the Sestrin2-mTORC1 pathway. *Science*, 351(6268), 53-8 (2016)
DOI: 10.1126/science.aad2087
PMid:26586190 PMCID:PMC4698039

72. L. Chantranupong, R. L. Wolfson, J. M. Orozco, R. A. Saxton, S. M. Scaria, L. Bar-Peled, E. Spooner, M. Isasa, S. P. Gygi and D. M. Sabatini: The Sestrins interact with GATOR2 to negatively regulate the amino-acid-sensing pathway upstream of mTORC1. *Cell Rep*, 9(1), 1-8 (2014)
DOI: 10.1016/j.celrep.2014.09.014
PMid:25263562 PMCID:PMC4223866
73. A. V. Budanov: SESTRINs regulate mTORC1 via RAGs: The riddle of GATOR. *Mol Cell Oncol*, 2(3), e997113 (2015)
DOI: 10.1080/23723556.2014.997113
PMid:27308486 PMCID:PMC4905323
74. R. L. Wolfson, L. Chantranupong, R. A. Saxton, K. Shen, S. M. Scaria, J. R. Cantor and D. M. Sabatini: Sestrin2 is a leucine sensor for the mTORC1 pathway. *Science*, 351(6268), 43-8 (2016)
DOI: 10.1126/science.aab2674
PMid:26449471 PMCID:PMC4698017
75. R. A. Saxton, L. Chantranupong, K. E. Knockenhauer, T. U. Schwartz and D. M. Sabatini: Mechanism of arginine sensing by CASTOR1 upstream of mTORC1. *Nature*, 536(7615), 229-33 (2016)
DOI: 10.1038/nature19079
PMid:27487210 PMCID:PMC4988899
76. J. Xia, R. Wang, T. Zhang and J. Ding: Structural insight into the arginine-binding specificity of CASTOR1 in amino acid-dependent mTORC1 signaling. *Cell Discov*, 2, 16035 (2016)
77. J. E. H. Hallett and B. D. Manning: CASTORing New Light on Amino Acid Sensing. *Cell*, 165(1), 15-17 (2016)
DOI: 10.1016/j.cell.2016.03.002
PMid:27015302
78. X. Gu, J. M. Orozco, R. A. Saxton, K. J. Condon, G. Y. Liu, P. A. Krawczyk, S. M. Scaria, J. W. Harper, S. P. Gygi and D. M. Sabatini: SAMTOR is an S-adenosylmethionine sensor for the mTORC1 pathway. *Science*, 358(6364), 813-818 (2017)
DOI: 10.1126/science.aao3265
PMid:29123071 PMCID:PMC5747364
79. M. Rebsamen, L. Pochini, T. Stasyk, M. E. de Araujo, M. Galluccio, R. K. Kandasamy, B. Snijder, A. Fauster, E. L. Rudashevskaya, M. Bruckner, S. Scorzoni, P. A. Filipek, K. V. Huber, J. W. Bigenzahn, L. X. Heinz, C. Kraft, K. L. Bennett, C. Indiveri, L. A. Huber and G. Superti-Furga: SLC38A9 is a component of the lysosomal amino acid sensing machinery that controls mTORC1. *Nature*, 519(7544), 477-81 (2015)
DOI: 10.1038/nature14107
PMid:25561175 PMCID:PMC4376665
80. G. A. Wyant, M. Abu-Remaileh, R. L. Wolfson, W. W. Chen, E. Freinkman, L. V. Danai, M. G. Vander Heiden and D. M. Sabatini: mTORC1 Activator SLC38A9 Is Required to Efflux Essential Amino Acids from Lysosomes and Use Protein as a Nutrient. *Cell*, 171(3), 642-654 e12 (2017)
81. J. Jung, H. M. Genau and C. Behrends: Amino Acid-Dependent mTORC1 Regulation by the Lysosomal Membrane Protein SLC38A9. *Mol Cell Biol*, 35(14), 2479-94 (2015)
DOI: 10.1128/MCB.00125-15
PMid:25963655 PMCID:PMC4475919
82. M. Rebsamen and G. Superti-Furga: SLC38A9: A lysosomal amino acid transporter at the core of the amino acid-sensing machinery that controls mTORC1. *Autophagy*, 12(6), 1061-2 (2016)
DOI: 10.1080/15548627.2015.1091143
PMid:26431368 PMCID:PMC4922434
83. D. W. Lamming, L. Ye, P. Katajisto, M. D. Goncalves, M. Saitoh, D. M. Stevens, J. G. Davis, A. B. Salmon, A. Richardson, R. S. Ahima, D. A. Guertin, D. M. Sabatini and J. A. Baur: Rapamycin-induced insulin resistance is mediated by mTORC2 loss and uncoupled from longevity. *Science*, 335(6076), 1638-43 (2012)
DOI: 10.1126/science.1215135
PMid:22461615 PMCID:PMC3324089
84. K. F. Petersen, D. Befroy, S. Dufour, J. Dziura, C. Ariyan, D. L. Rothman, L. DiPietro, G. W. Cline and G. I. Shulman: Mitochondrial dysfunction in the elderly: possible role in insulin resistance. *Science*, 300(5622), 1140-2 (2003)
DOI: 10.1126/science.1082889
PMid:12750520 PMCID:PMC3004429
85. M. S. Yoon and C. S. Choi: The role of amino acid-induced mammalian target of rapamycin complex 1(mTORC1) signaling in insulin resistance. *Experimental and Molecular Medicine*, 48 (2016)
86. R. Zoncu, A. Efeyan and D. M. Sabatini: mTOR: from growth signal integration to

cancer, diabetes and ageing. *Nat Rev Mol Cell Biol*, 12(1), 21-35 (2011)
DOI: 10.1038/nrm3025
PMid:21157483 PMCID:PMC3390257

87. D. A. Guertin and D. M. Sabatini: Defining the role of mTOR in cancer. *Cancer Cell*, 12(1), 9-22 (2007)
DOI: 10.1016/j.ccr.2007.05.008
PMid:17613433

88. D. M. Sabatini: mTOR and cancer: insights into a complex relationship. *Nat Rev Cancer*, 6(9), 729-34 (2006)
DOI: 10.1038/nrc1974
PMid:16915295

89. H. A. Lane and M. Breuleux: Optimal targeting of the mTORC1 kinase in human cancer. *Curr Opin Cell Biol*, 21(2), 219-29 (2009)
DOI: 10.1016/j.ceb.2009.01.016
PMid:19233631

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