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The role of leucine in the activation of cellular metabolism: a large integrative review

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Abstract

This review addressed the signaling of cellular activation by leucine, discussed the risks of excessive signaling by proteins in the Western diet, and explored the potential of leucine stimulation in tissue regeneration. As result, amino acids are, in addition to building blocks of macromolecules, cellular activation signals. Essential amino acids are not produced by animals and leucine appears to be the main signaling amino acid. Mammals adjusted the cell activation and growth rate of their young by the leucine concentration of the milk produced. Several studies demonstrate the benefits of leucine supplementation in preventing sarcopenia, improving muscle and liver performance, as well as a possible neuroprotective role in head trauma and dementia. However, its excess, so common in the Western diet, is related to obesity, type II diabetes, neurodegenerative diseases, and cancer. The mTORC1 kinase integrates cellular activation stimuli from macro protein synthesis to epigenetic regulation. Controlling mTORC1 activity by consuming leucine can prevent, treat, or cause disease. A greater understanding of the regulatory effects of leucine and mTOR in unstable tissues such as tumors or fragile tissues such as the CNS are areas of great relevance and with extensive fields still to be explored.

Keywords: Leucine. Cell metabolism. Signaling. Tissue regeneration.

Introduction

Amino acids are essential elements used as "building blocks", energy substrates in certain metabolic situations, cell activation signals, and buffering agents (glutamate in the CNS, for example) **[1-6]**. Insulin and growth factors are incapable of cell activation in the absence of amino acids such as leucine **[7-13]**.

Plants and bacteria synthesize their amino acids, but animals are unable to synthesize half of the twenty existing amino acids, thus making their ingestion necessary, hence called essential amino acids, the main ones being branched chain (leucine, isoleucine, and valine), known as BCAAs (Branched-Chain Amino Acids) **[13]**.

Therefore, this review addressed the signaling of cellular activation by leucine, discussed the risks of excessive signaling by proteins in the Western diet, and explored the potential of leucine stimulation in tissue regeneration.

Milk, leucine and mTOR complex

Milk and its derivatives are the main natural source of leucine. According to Melnik (2012) **[14]**, the action of milk on the growth rate of the calf has a direct relationship between growth and leucine concentration in the species' milk. Rat milk has 7.9 mg of leucine/mL and their pups double in weight every 4 days; calves double in weight after 40 days (cow's milk has 3.3 mg leucine/mL) and human milk has the lowest concentration of all mammals: 1.0 mg/mL of leucine, which slows growth for greater learning acquisition. The human baby doubles in weight only after six months of life.

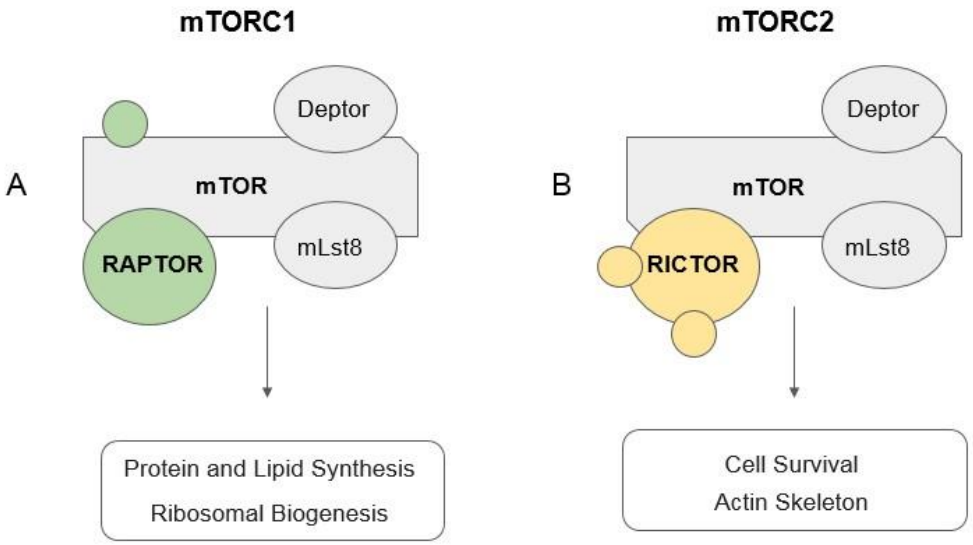
Furthermore, Melnik describes breastfeeding not as a simple source of nutrition, but as an evolution of cell activation signaling **[1,14-16]**. The leucine-activated mTOR (mammalian/mechanistic Target Of Rapamycin) complex integrates nutritional, hormonal, and environmental stimuli in the control of cellular metabolism **[17-19]**.

In the 1970s Sabatini et al. **[18]** investigating the lack of fungi in the soil of Easter Island discovered a

bacterial strain that produced a potent antifungal, named rapamycin (named after the island Rapa Nui, in the local language). Rapamycin is a potent cellular inhibitor by blocking the mTOR protein **[20-22]** and is being used in clinical practice even today as an immunosuppressant, antistenotic, and in the treatment of cancer **[23-25]**.

The discovery of the mTOR complex began with the discovery of its inhibitor, rapamycin in 1975, and with the cloning of its genes in 1993. It was discovered that mTOR forms two distinct complexes when associating with other proteins: mTORC1 when binding to RAPTOR (Regulatory-Associated Protein of mTOR) and mTORC2 when associated with RIcTOR (Rapamicyn-Insensitive Companion of mTOR) (**Figure 1**) **[26-28]**.

Figure 1. Structure mTORC1 (A) and mTORC2 (B) and their main functions in cell activation.



The mTORC1 complex consists of the union of mTOR, Raptor, mLST8 (mammalian Lethal with Sec13 protein T8), Deptor, and DAS40 protein. Activated initiates cellular anabolism with lipid and protein synthesis. Deactivated, it causes autophagy by activating the kinase glycogen synthetase GSK3 β **[29,30]**. The mTORC2 complex organizes the actin cytoskeleton, cell migration, and survival.

Also, mTORC1 integrates cellular activation stimuli from fungi to mammals **[31-35]**. Several studies indicate mTORC1 as a central regulator of gene transcription, ribosomal translation, mRNA transcription, suppressor of autophagy, and activator of ribosomal and mitochondrial neogenesis **[36-41]**. The human mTORC1 framework is a dimer of mTOR, Raptor, and mLST8 **[30]**. The mTORC1 complex is extremely sensitive to amino acid exposure and leucine appears to be one of its main activators **[42-45]**. The absence of leucine prevents mTORC1 activation even in the presence of all other amino acids, growth factors, glucose, and insulin **[46-48]**. The mTORC2 complex appears to be insensitive to amino acids, responding primarily to trophic factors **[48-50]**.

Actions of leucine on muscle, liver, and CNS

Tissue changes from trauma, disease or aging disrupt cell physiology and regenerative responses are necessary for homeostasis. Mammals have little regenerative capacity in vital organs such as the heart and central nervous system (CNS) but the liver, skin, intestine, and muscles have the great regenerative capacity in adult mammals **[51-53]**.

Understanding the mechanisms of tissue regeneration is essential for therapeutic interventions and the mTORC1 system seems to be its main pathway. In the CNS (minimum regenerative capacity), the mTORC1 pathway is stimulated in the inactivation of PTEN (phosphatase and tensin homologous) and TSC1 (tuberous sclerosis complex 1) kinases, allowing axonal regenerative expansion **[54-57]**.

Leucine is well known for its action on muscle hypertrophy, obesity, metabolic disorders, liver disease, immune activation, and cancer **[14]**. The correlation between obesity and an excessive supply of amino acids is observed in obese individuals due to mTOR hyperactivation, which may justify greater viral replication in these people and a worse prognosis in cases of COVID-19 **[58]**. Interestingly, the coronavirus

has a 5'-end mRNA and uses the same cellular protein translation machinery, which is hyperactivated in the obese **[59,60]**.

Amino acid signaling has been extensively studied in recent decades for therapeutic use in multiple trauma, severe burns, and senile sarcopenia, where the clinical benefit has been demonstrated in increasing the supply of BCAAs **[61-65]**.

Muscle

Leucine increases muscle performance during exercise and its intake reduces fat mass and prevents both senile and inadequate diet obesity, as well as type 2 diabetes **[66-70]**. Leucine is the most important amino acid for protein synthesis **[71]** and can be administered as a nutraceutical agent in the prevention of sarcopenia.

Leucine has been known to induce muscle anabolism since the 1970s. In skeletal muscle, 20% of leucine is metabolized for energy production (reduction of glutamate and keto acids). The remaining leucine (80%) activates protein synthesis (via mTORC1) and satellite cell expansion **[72-75]**. Maltais et al. (2016) **[75]** randomized 26 overweight sarcopenic men into resistance training for 4 months, offering post-exercise dairy or rice milk as a control group. Resistance training increased lean body mass (DEXA) in both groups, but the dairy group decreased their body fat rate more and gained more muscle mass.

Another similar study randomized 26 sarcopenic obese women to receive hydrolyzed whey protein (whey protein) or placebo for 3 months under resistance training, resulting in a greater increase in lean mass in the group receiving the milk protein **[76]**. HMB (hydroxy-methyl butyrate) is a leucine metabolite used in an attempt to prevent muscle breakdown or lean mass gain, but it has controversial results in human and animal studies **[77-79]** performed a meta-analysis of 11 randomized trials of HMB in training. of resistance and concluded that there was no significant effect on lean mass gain, fat mass loss, or strength increase with HMB, even advising its use as a nutraceutical supplementation.

Gran and Cameron-Smith (2011) **[80]** studying human muscle cultures demonstrated the activation of mTORC1 by leucine at physiological doses. Chronic stimulation resulted in increased eIF4G activity (ribosomal transcription) at two peaks: 3h and 24h after leucine/insulin introduction. Continuous stimulation by leucine and hormones can generate a persistent cellular anabolic state **[81]**.

Deldique et al (2008) **[82]** studying muscle cultures observed a 50% increase in mTORC1 activation soon after the addition of 5mM leucine, falling at 30 minutes. Atherton et al (2010) **[83]** reported lower doses (2 Mm) also activated mTORC1. They demonstrated that 5 mM leucine increases 70-S6K activation by 10-fold and 2 mM increases p70-SK6 activity by 5.9-fold in muscle cultures.

In vivo tissue perfusion models are also used in studies of anabolic stimulation, protein synthesis, and/or cellular edema studies. Some studies have found that increasing the concentration of amino acids by up to ten times its plasma value does not result in tissue edema **[84,85]**.

Bolster et al (2004) **[86]** cannulated and perfused the hind legs of rats with 1x or 10x concentrations of serum leucine and monitored mTOR, p70-SK6, eIF4E, and 4E-BP1 activation. They observed a 66% increase in protein synthesis in the gastrocnemius muscle and a 70% increase in the soleus muscle of the paws perfused with a 10x leucine solution. The effects of tissue infusion supplementation with 10x leucine did not cause muscle edema in the rats.

Several studies of muscle culture use leucine in concentration five or ten times the physiological one, being able to increase protein synthesis. Omitting leucine from the solution, even increasing the concentration of the other amino acids tenfold, does not increase protein synthesis in muscle **[87-89]**. Peyrollier et al (2000) **[90]** adding 2 mM leucine (normal concentration) to amino acid-free muscle cultures obtained rapid anabolic activation, doubling the protein synthesis marker p70-S6K and increasing five-fold activation of the PI3K pathway. The addition of leucine also increased the cellular uptake of amino acids by 50%.

MAP4K3 (Mitogen-Activating Protein Kinase-Kinase-Kinase-Kinase-3) activity is also regulated by amino acids, but not by insulin. MAP4K3 kinase activates satellite cell myogenesis in rat muscle, however complete mTORC1 activation occurs only in the presence of leucine **[91]**.

Supplementation with BCAAs improves oxidative respiration and prevents mitochondrial dysfunction. Studies show mitochondrial biogenesis in the cardiac and skeletal muscles of patients with Barth myopathy **[92]** and skeletal muscle of elderly rodents **[93]**. Supplementation with BCAAs increased mitochondrial survival in cardiomyocytes from animals intoxicated by doxorubicin **[94]**.

Leucine signaling increases the number and size of mitochondria in the muscle fiber. It is an energy substrate, potentiates the oxidation of fatty acids, and increases glucose absorption **[95-97]**. Leucine

supplementation prevents mitochondrial dysfunction in nervous tissue, muscle, and liver, and is indicated in aging, neurodegenerative and cardiovascular diseases, obesity, and diabetes **[98-104]**.

Amino acid supplementation increases cellular respiration by inducing mitochondrial biogenesis **[105-108]**. Mitochondria undergo cycles of fusion and fission that either unite with each other (respirosome) or attach to lysosomes and the endoplasmic reticulum **[109-111]**. Mitochondria show ancestral symbiosis with the host cell, as they have their own (circular) DNA, but depend on proteins transcribed from the host cell's DNA **[112,113]**.

There is evidence that leucine enhances mitochondrial biogenesis via PGC-1α and SIRT1 factors **[114-118]**. In animals, supplementation with BCAAs resulted in mitochondrial biogenesis with increased SIRT1 factor in skeletal muscle **[93,107]**.

Liver

The literature is rich in evidence of the benefits of BCAA supplementation in hepatic failure encephalopathies **[119]**. Pavlov (1893) made the first description of hepatic encephalopathy with ataxia and convulsions after portocaval anastomosis in meatfed dogs and the reversal of encephalopathy by switching to a milk-only diet in these same dogs **[120]**.

Muting and Wortmann in 1956 described a decrease in the concentration of BCAAS in cirrhotic patients and an increase in aromatic amino acids **[120]**. This condition became known as Fischer's ratio: the lower the concentration of BCAAs, the greater the brain intoxication **[121]**. Supplementation with leucine/BCAAs is indicated in liver disease in patients with cirrhosis **[122-124]**.

Supplementation with BCAAs is a nutracenic factor in chronic liver disease **[123]**. Decreased serum BCAA levels are credited with muscle uptake and glutamine synthesis by the cirrhotic patient's muscle. In vitro experiments have shown that high levels of ammonia cause leucine oxidation in muscle, consuming nitrate. This sequestration of ammonia in situations of azotemia produces glutamine in muscle tissue **[125]**.

Supplementation with BCAAs stimulates mitochondrial biogenesis in the liver, preventing alcohol steatosis in animal models **[126]**. Increased post-hemihepatectomy regeneration has also been demonstrated with leucine supplementation **[127]**. Jefferson & Korner (1967) **[128]** perfusing the liver of rats with amino acids at a physiological dose of growth hormone (GH) did not obtain an increase in protein production, but with three times the dose of amino acids (the same dose of GH), they obtained increased protein synthesis by the liver.

Krause et al (2002) **[129]** studying the effects of leucine, glutamine, and insulin on rat liver cells found that isolated insulin does not increase anabolism in the liver, but isolated leucine can activate p70-S6K and ACC (synthesis markers). protein and lipid, respectively), concluding that the action of insulin on the hepatocyte depends on the joint presence of leucine. Dennis et al (2011) **[130]** perfused the liver of rats with amino acids with and without insulin and found that at normal or doubled insulin concentrations they obtained maximal PI3K/Akt stimulation, but no increase in protein synthesis. Perfusion without insulin and at four times the concentration of amino acids produced moderate protein synthesis but a combination of insulin and four times more amino acids caused maximum protein synthesis, suggesting that stimulation by amino acids in conjunction with insulin is necessary for mTORC1 activation.

CNS

The central nervous system (CNS) depends on oxygen and glucose, but adaptive responses allow the use of ketone bodies in metabolic crises, where amino acids are an energy source that does not require mitochondrial respiration **[131-134]**. Under CNS stress conditions, BCAAs (leucine, isoleucine, and valine) are metabolized to glutamate and keto-acids. Glutamate can yield glutamine or alanine and, in a second reduction, acetyl-CoA to the Krebs cycle **[135,136]**.

BCAAs are reduced to glutamate and ketone bodies in the CNS by glial mitochondrial aminotransferases (astrocytes) and by cytoplasmic aminotransferases in neurons. The presence of leucine stimulates the reduction of glutamate in glutamine and acetyl-CoA, an energy source for the Krebs cycle **[137,138]**.

The action of BCAAs in Neuronal Metabolic Crisis

After traumatic brain injury (TBI) there is a halt in mitochondrial glucose metabolism in the CNS, a situation known as a "metabolic crisis". Some studies suggest that supplementation with BCAAs promotes neuroprotection, minimizing neural damage and improving clinical recovery **[139-141]**. Jeter et al (2013) **[142]** studied the metabolic alterations of human TBI, measuring the serum level of BCAAs in the first 24h in moderate TBI (EG: Glasgow scale > 12), severe TBI (EG <8), orthopedic traumatic injuries and in healthy individuals. They observed little reduction in BCAAs after moderate TBI and in orthopedic injuries, but very low values in severe TBI. Low serum BCAA levels in TBI are also a prognostic factor for intracranial

hypertension (ICP≥25 mm Hg).

Mitochondria are the cellular energy machinery par excellence and use glucose and oxygen as their primary substrate. But in the absence of glucose or oxygen - or the presence of any other mitochondrial dysfunction - ketone bodies and acetyl-CoA are the energy source of the CNS. Differentiating between ischemia and metabolic crisis is fundamental in the management after TBI. Studies suggest that supplementation with intravenous BCAAs minimizes neurological damage to the CNS after the reversal of ischemia **[143,144]**.

Ketone bodies can reach 70% of the energy matrix in the CNS of mammals during fasting, trauma, or prolonged exercise. Blood-brain barrier (BBB) permeability for ketone bodies also increases during lactation and fasting. Recall that mammalian infant neuronal development is dictated by milk, which is rich in BCAAs, glucose, and fats **[145-150]**.

Leucine, glutamate, and glutamine metabolism in the CNS

Astrocytes are responsible for brain energy stability through the production of ketone bodies from amino acids and fatty acids in metabolic crises by mitochondrial aminotransferases (BCTAm) **[151,152]**. Leucine (typical BCAA) is the amino acid that crosses the BBB the fastest **[151-154]**, being metabolized in astrocytes as soon as they enter the BBB. It is estimated that 30% to 50% of CNS glutamate and glutamine derive from leucine absorbed in the BBB **[155-158]**.

Nissin et al (1987) **[159]** were the first to suggest buffering in the CNS by glutamate and ketoacids in leucine transamination. These keto acids (KICs) are taken up by neurons and re-aminated into leucine, with the consumption of glutamate in the synaptic cleft (**Figure 1**). Excess glutamate in the synaptic cleft is responsible for secondary injury to the TBI/SCI, tissue ischemia, and sequential neuronal death after CNS trauma **[160-163]**. Glutamate needs to be quickly removed from the synaptic cleft, being taken up by astrocytes and reduced to keto acids (mitochondrial aminotransferases: BCTAm) - glutamate-glutamine cycle - or reduced to keto acids by neurons (cytosolic aminotransferases: BCTAc) - leucine-glutamate cycle (**Figure 2a**). Glutamate can be transformed into glutamine (glutamine synthetase - GS) in astrocytes and exchanged for leucine in the BBB (**Figure 2b**) or taken up by the neuron, returning to glutamate via glutaminase (GlnAse) **[164-166]**.

Figure 2. **(A)** Glutamate is removed from the synaptic cleft by the neuron itself and reduced to keto acid + leucine by cytosolic aminotransferases (leucine-glutamate cycle) or taken up by astrocytes and reduced to glutamine + keto acid by mitochondrial aminotransferases (leucine-glutamate cycle). **(B)** Glutamine is exchanged in the BBB for leucine in counterflow pumps or taken up by the neuron (returning to glutamate via glutaminase). The astrocyte can also take up glutamate and convert it to glutamine by the enzyme glutamine synthetase.

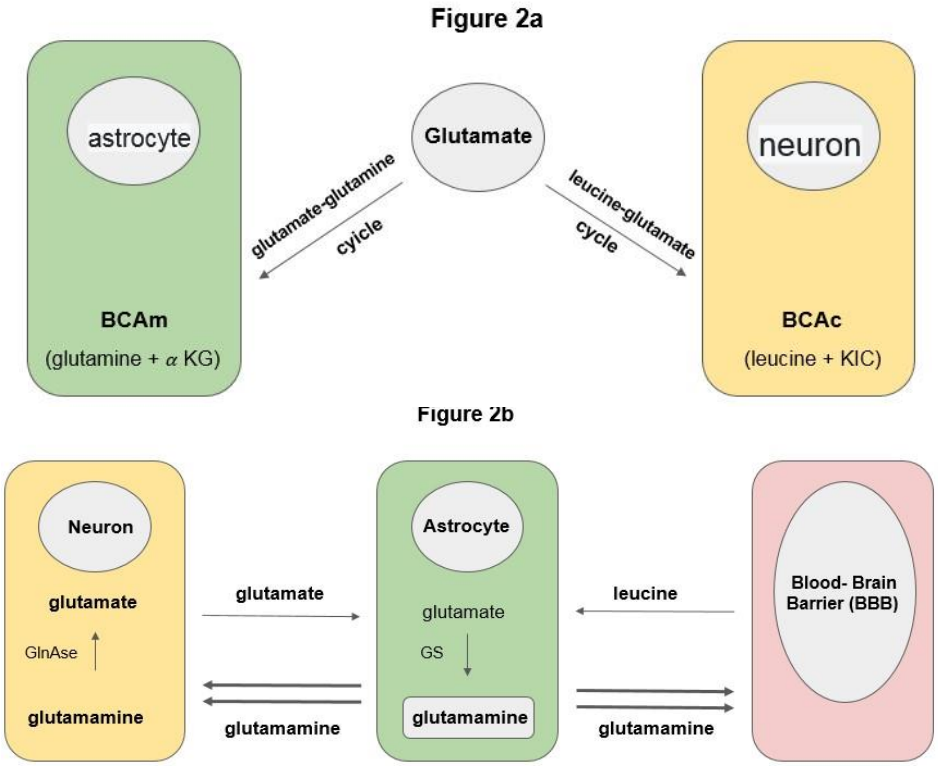
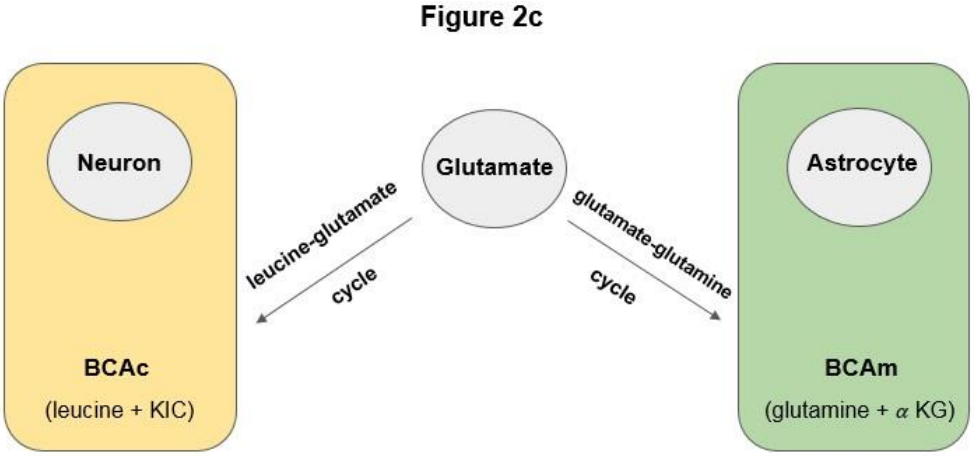


Figure 2. **(C)** Equilibrium of reanimation of keto acids generating glutamate (in the neuron) or leucine (in the astrocyte).

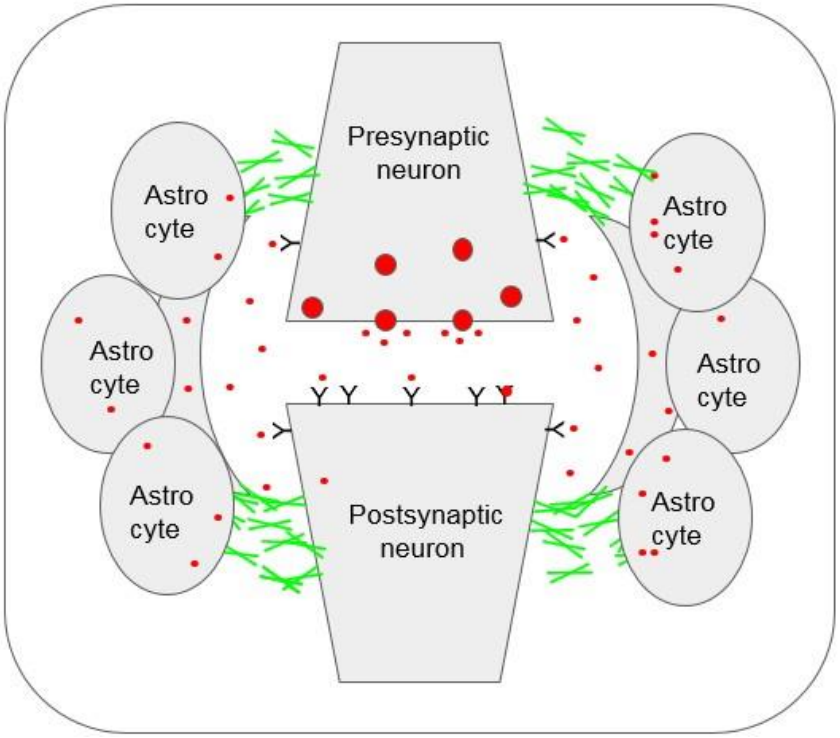


Source: Own authorship.

Leucine is the amino acid that most easily crosses the BBB, via transporters' counter-exchange for glutamine. This leucine is taken up by the astrocyte and mBCAT metabolizes leucine into glutamate and keto isocaproic acid (KIC). This is reanimated in the neuron into leucine and the ketoacid α-ketoglutarate (αKG), with the consumption of glutamate (**Figure 2c**).

The CNS is the only tissue that has both aminotransferases and BCAAs are fundamental to biochemical regulation in the CNS, because, in addition to being a raw material in the synthesis of glutamate, they buffer its excess in the CNS, avoiding toxic levels. /leucine and ketoacid/glutamate and observed three times more leucine formation than glutamate **[165,166]**. The participation of astrocytes in the synapse resulted in the concept of the tripartite synapse **[167]** and the presence of a dense extracellular matrix, "sealing off" some synapses and preventing the extravasation of glutamate from the cleft resulted in the concept of the quadripartite synapse **[168,169]**. Schafer et al (2013) **[170]** also describe the participation of microglia in the regulation of some synapses (**Figure 3**).

Figure 3. Neurons and astrocytes modulate the presence of glutamate in the synaptic cleft in the tripartite synapse model. A dense extracellular matrix "seals" some synapses preventing the diffusion of neurotransmitters in the quadripartite model.



Metabolic alterations of BCAAs and their effects on the CNS

Aminoacidopathies are errors in amino acid metabolism. Maple syrup urine disease (MSUD), or human leucosis, is a congenital deficiency of the ketoacid dehydrogenase that metabolizes BCAAs resulting in their progressive accumulation. It is a rare and serious genetic disease with encephalopathy crises, lethargy, lowering of consciousness, convulsions, and death due to an excessive increase in serum leucine (normal: 100 +-60 μml/L; MSUD up to 60,000 μmol/L). Complete elimination of BCAAs from the diet or urgent dialysis during decompensations reverses the neurological picture **[171-178]**.

Studying the intelligence coefficient (IQ) of children with MSUD under 6 years, Hoffman et al (2006) observed IQ 1.2 times higher in children with a serum leucine level below 200 μmol/L (189 ± 82 μmol/L) compared to children with higher plasma leucine levels (572 ± 217 μmol/L). Leukemias of up to 1000 μmol/L may even be asymptomatic, but negatively affect intelligence scores **[174]**.

Several studies indicate alterations in BCAA metabolism in neurodegenerative diseases such as Alzheimer's, Parkinson's, and Hungtinton **[179,180]**. Low levels of valine are linked to accelerated cognitive decline. On the other hand, high levels of valine reduce the risk of Alzheimer's. BCAA-related "metabolic signatures" have been identified in other diseases such as senile obesity, type II diabetes, and atherosclerosis **[181,182]**.

Recent studies in epidemiology have shown that protein intake is vital for brain function in the elderly population. Shang et al (2021) **[182]** in a 9-year cohort study linking protein consumption and dementia found that higher protein intake was associated with less cognitive decline in the elderly. Sato et al (2021) **[183]** observed lower neuroinflammation in protein-deficient mice after supplementation with essential amino acids.

Besides, mTOR activation in brain tissue optimizes memory and learning **[184,185]**. During aging, there is a decrease in neuronal mTOR activity **[186-188]**. It has been shown that in retinal and cerebral cortex neurons, mTOR signaling decreases with age and alters the capacity for axonal regeneration and dendritic remodeling, underscoring the importance of the consumption of essential amino acids **[189,190]**. In this context, Suzuki et al (2020) **[191]** conducted a randomized double-blind study of cognitive assessment in adults aged 55 years and over with supplemental essential amino acid intake. Daily intake of 3 g or 6 g of amino acids for 12 weeks resulted in better attention, cognition, and psychosocial functioning compared to the pre-supplementation state and the placebo group.

Elderly people with dementia have a lower protein intake than healthy elderly people. Tynkkynen et al (2018) **[192]**, in a cohort study, demonstrated low serum levels of BCAAs associated with the development of Alzheimer's disease. Fernando et al (2018) **[193]**, in another cohort study, observed that the more protein was consumed, the lower the presence of β-amyloid in the brain of the population studied. These results highlight the protective impact of protein intake on the brains of older adults. Leucine is a BCAA known to activate the mTOR pathway. Glycogen synthetase 3β kinase (GSK-3β) is a counter-regulatory and potent inhibitor of mTORC1. GSK-3β is hyperactivated in neurodegenerative diseases **[194-198]** and the accumulation of β-amyloid is responsible for neurotoxicity in tauopathies **[198-201]**.

Cellular uptake of leucine

Despite the recognition of the importance of amino acids in cell activation since 1955 (Hosios et al, 2016) **[202]**, only in the last decades has there been a better understanding of the mechanisms of cell activation by amino acids, their transporters, metabolizing enzymes and correlation with diagnosis and treatment of tissue disease and dysfunction **[203-206]**. The uptake of amino acids depends on specific channels, but also non-selective endocytosis processes. There are at least 17 amino acid transport channels, the main ones being the L (leucine-preferred), A (alanine-preferred), and ASCT2 (alanine-serine-cysteine 2) transporter **[207-209]**.

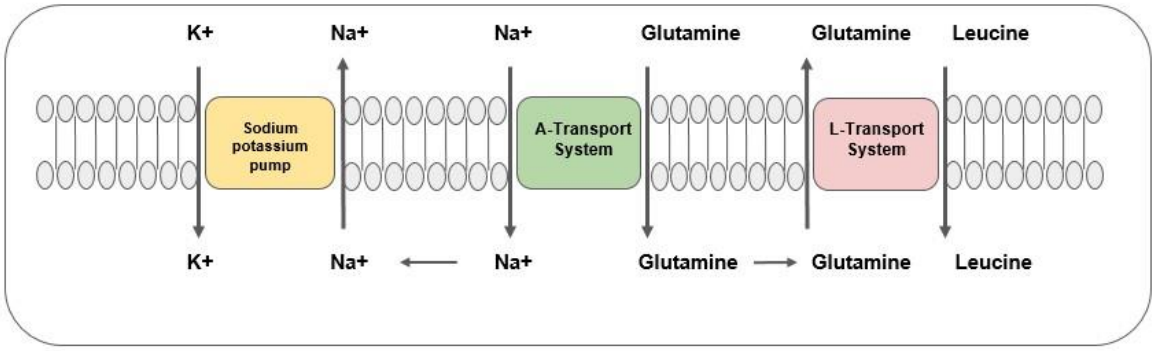
Free amino acids are rapidly taken up by cells via membrane channels and activate mTORC1 within minutes (Nicklin et al, 2009) **[210]** whereas albumin or larger proteins activate mTOR only after 2 hours, peaking at 4 hours. Therefore proteins taken up by endocytosis activate mTORC1 much more slowly than free amino acids **[211]**.

Selective uptake of amino acids

Amino acids such as leucine and glutamine are as essential to cellular metabolism as oxygen and glucose **[212-215]**. The L channel is the main transporter of essential amino acids and is highly expressed in the brain, gonads, pancreatic islets, and placenta, but also tumors such as lung, prostate, and breast. Blockade of L channels, in particular LAT1, results in apoptosis and is a therapeutic target in the treatment of acute lymphoblastic leukemia, osteosarcoma, and cholangiocarcinoma **[216-220]**.

The LAT1 channel is the main transporter of essential amino acids to the CNS, T lymphocytes, and skeletal muscle, with LAT1 increasing in skeletal muscle 1 and 3 hours after ingestion of essential amino acids. The LAT1 transporter is of great importance in amino acid uptake and cell signaling **[221-223]**. Leucine transport by L channels (SLC1A5, SLC7A5, and SLC3A2) exchanges intracellular glutamine for extracellular leucine. Glutamate, metabolized to glutamine, also enhances leucine absorption in Lexchange channels **[224,225]** (**Figure 4**).

Figure 4. System A (SNAT2) absorbs glutamine and sodium. The sodium-potassium pump expels sodium and the leucine L transporter system (LAT1) absorbs leucine expelling glutamine.



Source: Own authorship.

The LAT1 transporter is the main controller of free amino acid entry and subsequent mTORC1 activation in the brain, muscle, and immune system. In the brain, the LAT1 channel is essential for the development of the nervous system and its exclusion in KO (Knock Out) mice is lethal. In humans, LAT1 mutations are related to autism spectrum disorders and disorders such as microcephaly and seizures **[226]**. Inhibiting the uptake of BCAAs may be beneficial in neurological tumors with high LAT1 expression such as in gliomas **[227]**.

LAT1-dependent amino acids influence the bone skeleton, a tissue that undergoes constant remodeling dependent on the activation of osteoclasts and osteoblasts **[225]**. Ozaki et al (2019) **[226]** identified the LAT1 transporter in osteoclasts and its reduction in post-ovariectomy mice. Decreased leucine uptake inhibits mTORC1 activation in osteoclasts resulting in osteoporosis. mTOR activation promoted bone loss recovery in LAT1 knock-out mice. There is a strong dependence of leucine levels on the growth of bone sarcomas. Biopsies show an increase in BCAA enzymes in these tumors and the use of a leucine analog, N-Acetyl-Leucine Amide (NALA) blocks leucine uptake, dramatically decreasing the activity of bone sarcomas **[228]**.

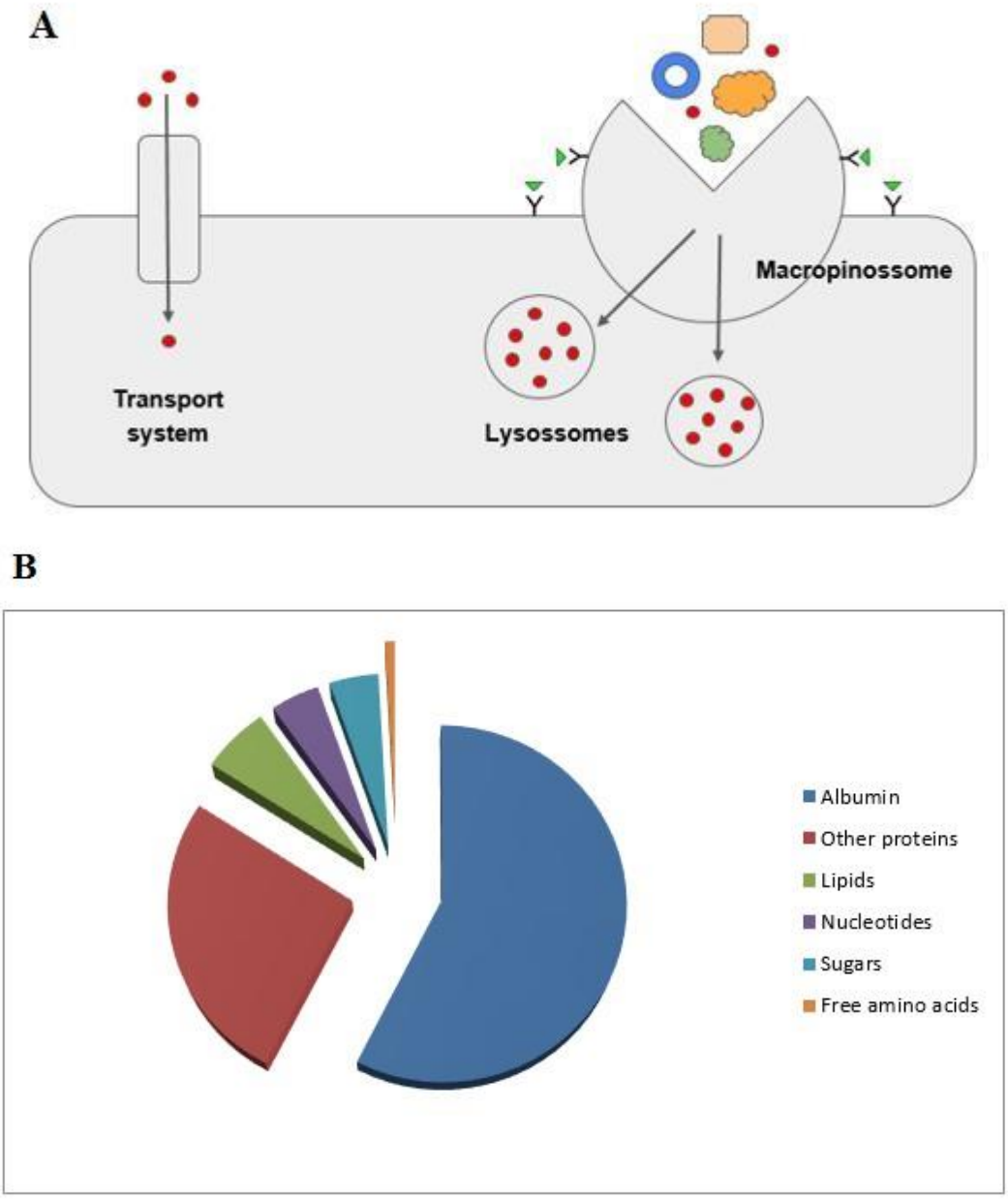
Leucine is an amino acid transported by LAT1 channels and its blockade is a target in cancer control, a channel overexpressed in malignant tumors **[227-231]**. High LAT1 expression in cancer biopsies is even a poor prognostic factor. The activated mTORC1 system increases the expression of amino acid transporters **[232-233]**. Lymphocyte activation in the immune response depends on metabolic reprogramming, with increased expression of glucose and amino acid channels for rapid proliferative expansion **[234]**. Leucine is a potent mTORC1 stimulator and depleting leucine or blocking its transporter prevents T lymphocyte activation to the same extent as total amino acid deprivation. Inhibition of leucine entry into T cells prevents their proliferation, allowing control over allergies and lymphomas for example **[235-244]**.

Non-selective uptake of amino acids

Mammalian cells utilize glucose and free amino acids as an energy source, even in protein- or albumin-rich environments such as plasma **[245-247]**. In addition to specific transporters, cells have developed alternative uptake of amino acids in the presence of growth factors or ischemic and deficient conditions. Although mTORC1 is activated only by free amino acids such as leucine, these are the smallest fraction in circulating plasma. Even with an increase in selective transporters, the macropinocytosis system is the main uptake mechanism during cell activation **[248]**.

The first cellular change that occurs after activation of the membrane receptor by growth factor is surface cytoskeleton remodeling **[246-248]**, which forms pseudopods that "embrace" large amounts of extracellular solute. Even in tumor cells, which are independent of growth factors, mTORC1 activation depends on the uptake of free amino acids **[249-255]** (**Figure 5**).

Figure 5. A) Entry of amino acids and glucose into the cell occurs through selective channels (left) or, more intensely and nonspecifically, via macropinocytosis activated by growth factors (right) - adapted from Yoshida et al, 2009. **B)** Graph showing a large amount of albumin, other proteins, etc. and the minimum fraction of free amino acids in the blood plasma (smallest slice) highlighted - adapted from Palm et al, 2015.



Also, macropinosomes are growth factor signal transducers **[256]**. Macrophages exhibit immediate macropinocytosis after exposure to the growth factor MCSF **[257-259]**. The protein synthesis marker S6K increases 5 minutes after the addition of MCSF to the culture medium, as well as the anabolic activation markers MAPK, ERK, PI3K, and mTORC2. Cultures in amino acid-rich media have greater mTORC1 activity than amino acid-poor media with the same MCSF concentration **[260]**.

Growth factors activate mTORC1 by macropinocytosis with the rapid uptake of free amino acids. mTORC1 activation appears to be proportional to leucine uptake **[261]**. With the same PDGF trophic factor concentration, but different leucine concentrations (0.4 mM and 4 mM), there was an increase in mTORC1 activity in cultures with higher leucine concentrations.Macropinocytosis was first demonstrated by Lewis in 1931, calling his description "pinocytosis" ("cell engulfing") **[255]**. Macropinosomes form macro protein vesicles that bind to the Golgi Complex and lysosomes hydrolyze macro proteins into the free amino acids required for mTORC1 activation **[262-264]**.

Electron microscopy studies have demonstrated macropinocytosis in the CNS and its decrease appears

to be related to amyloid accumulation and neurodegenerative diseases such as Alzheimer's **[265,266]**. Macropinocytosis also occurs at the regenerating ends of axons; the growth cones. In vitro and in vivo analyses demonstrated that these terminations form membrane extensions with high molecular weight (10 KDa) vesicles, suggesting macropinocytosis in the axon and synaptic connections **[267-270]**.

By verifying the amount of leucine captured by transporters and by macropinocytosis, the PDGF-dependent mTORC1 activation was measured by the presence of the dipeptide Ala-Leu (does not pass through the transporters) in culture media. There was an increase in S6KF only 30 minutes after the introduction of the AlaLeu dipeptide, indicating that mTORC1 activation occurs only after the hydrolysis of AlaLeu into free leucine. The presence of free leucine activates mTORC1 between 2 and 3 minutes **[261]**.

In tumor cells, macropinocytosis occurs without the need for growth factors (RAS-mutant cells). These have enormous energy demand that is met by glutamine. Glutaminolysis generates the NADPHs and fatty acids needed for growth without the need for mitochondrial respiration. This is known as the Warburg Effect and allows cell growth even under ischemic conditions **[271-276]**. The Warburg effect is the dissociation of mitochondrial metabolism generating a cellular growth phenotype even in hypoxia, highlighting the importance of amino acids in situations of metabolic stress **[277,278]**. BCAAs are reduced to keto acids, glutamate, and glutamine, substrates for the Krebs cycle during the Warburg effect. Glutamine is the fuel used by most cancer cells through macropinocytosis (Ras-mutant cells) **[279-283]**.

The presence of amino acids allows cellular anabolism without the need for mitochondrial respiration (even in the presence of oxygen and glucose) in tumor and nontumor cells, as in ischemic wound healing **[284-286]**. Activated T cells use macropinocytosis for rapid amino acid uptake and immediate lymphoproliferative response, both immune and tumor, without the need for mitochondrial respiration **[287-288]**. There is a strong dependence between the levels of BCAAs and the growth of osteo and chondrosarcomas. Tumor biopsies in patients reveal overexpression of BCAAmetabolizing cytosolic aminotransferases **[288]**. These are prognostic markers as they are increased in more aggressive tumors **[284-287]**. BCAT1 (cytosolic aminotransferase for BCAAs) is overactive in chronic myeloid leukemia (CML) and overexpressed in chronic myeloid leukemia **[282-284]**.

Physiological and pathological signaling mTORC1

mTORC1 controls cell activation in the presence of nutrients and trophic factors. Several studies indicate mTORC1 as the center of convergence of the various anabolic activation signals **[289-298]**. mTORC1 regulates gene transcription, and ribosomal translation suppresses autophagy and activates the mitochondrial machinery and the protein and lipid synthesis machinery **[299-304]**. mTORC1 is activated by the Rag (Ras adenosine guanidine) and Rheb (Ras homolog enriched in the brain) GTPases, each controlled by a pathway. Rag fixes mTORC1 on the lysosome surface in the presence of some amino acids (Raptor binding) **[305-309]** and Rheb, present in the lysosome, activates mTORC1 through trophic factors and glucose **[310]**.

Initial activation: the RAG pathway

Sancak et al (2010) **[305]** demonstrated that, in the presence of amino acids, free mTORC1 binds to the lysosome surface (via RAG) and is only later activated (via Rheb) by trophic factors. Mammals have four Rags (A, B, C, and D) that form A/B and C/D dimers. Raptor binding (from mTORC1) to RagD (present in lysosome) is activated by leucine and arginine **[311-315]**. Leucine mTOR activation is a consensus and the mechanisms are detailed in several reviews **[316-320]**. Recently Meng et al (2020) **[316]** reassessed the mTORC1 activation capacity of each amino acid and found that 10 amino acids (alanine, arginine, asparagine, glutamine, histidine, leucine, methionine, serine, threonine, and valine) are capable of binding to mTORC1 to the lysosome, but leucine, arginine, and methionine are the most potent, increasing S6K1 (a marker of ribosomal activity) in just 15 minutes, while glutamine, asparagine, and methionine take, for example, over an hour **[317,318]**. Activation of mTORC1 by glutamine is slower because it is RAG-independent **[319]**. There is also an exchange of glutamine for leucine by antitransport channels **[320,321]**. The discovery of Rags improved the understanding of mTORC1 regulation by amino acids **[319,322]**.

In this sense, Han et al identified the LRS (leucyl-tRNA synthetase) sensor, which binds leucine to RAG-D, binding free cytosolic mTORC1 to the lysosome. LRS/RagD – mTORC1 associations are observed only in the presence of leucine. LRS-deficient mice are unable to attach mTORC1 to the lysosomal surface, even in the presence of leucine **[323]**. Other studies have also confirmed the role of the LRS sensor in mTORC1 preactivation **[324-329]**.

In addition to LRS, Sestrin 2 is another leucine

sensor, which inhibits the mTORC1 inhibitor kinase GATOR1 **[329]**. The presence of leucine disrupts the Sestrin 2 - Gator2 bond, releasing the GATOR 2 kinase that blocks GATOR1 and activates mTORC1. Wolfson et al tested the effect of amino acids on Sestrin 2 and found that only leucine (and not arginine) produces Sestrin 2-GATOR 2 dissociation with GATOR 1 blockade and mTORC1 activation **[330-332]**. Further to leucine, arginine and methionine are mTORC1 activators. Arginine uses the CASTOR1 pathway and methionine inhibits SAMTOR and GATOR 1/2 kinases. Both activate mTORC1 by inhibiting GATOR1 **[333-338]**. These sensors are present in lysosomes, mitochondria, rough endoplasmic reticulum, and Golgi complex, attaching mTORC1 to their surfaces in the presence of these amino acids **[339-341]**.

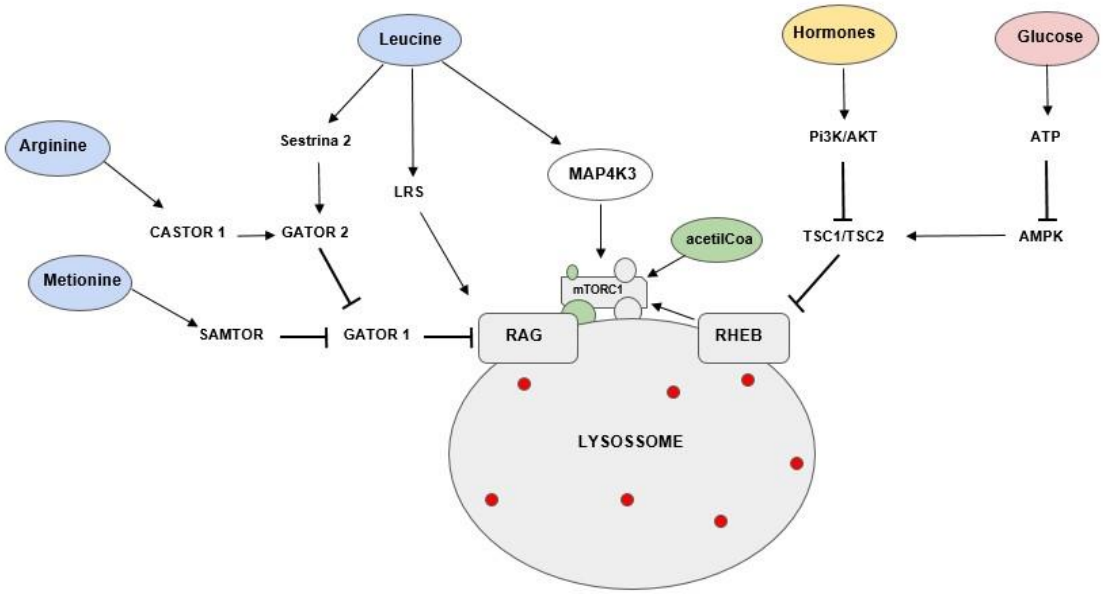
In cell cultures, the removal of leucine or arginine prevents S6K activation, suggesting that both, in addition to methionine, are the main regulatory amino acids of mTORC1 activity. Wolfson et al (2016) **[332]** examined Sestrin-2/GATOR2 binding and observed that a lack of leucine, but not arginine, blocks mTORC1 activation. Thus, GATOR 2 acts more as an amino acid sensor than a mTORC1 activator **[334]**. There are other indirect mechanisms of mTORC1 activation by amino acids, such as the increase of intracellular calcium, by the mobilization of stores of the endoplasmic reticulum by SHP-2, activated by amino acids **[342,343]**. The acetyl-Coa metabolite enhances the RagD-Raptor interaction, binding mTORC1 to the lysosome **[340]**. Very recent studies have identified dysfunction of GATOR kinases 1 and 2 in the origin of some epilepsy, diseases called GATORpathies **[344-350]**. GATOR dysfunction alters mTORC1 activation, being part of the group of mTORC1 hyperactivity disorders (mTORpathies) **[351-354]**. mTORpathies occur in obesity, cancer, neurodegenerative diseases, and type II diabetes **[355-363]**, which will be discussed below.

Final activation: the Rheb pathway

With mTORC1 attached to the lysosome surface in the presence of amino acids, it binds to Rheb, activated by trophic factors and glucose **[364]**. Lysosomes are the ideal site of mTORC1 activation due to the high concentration of amino acids **[365-366]**. Other organelles, such as mitochondria and the Golgi complex, also attach mTORC1 to their surfaces in the presence of amino acids **[360]**. Recently, a fusion of the Golgi complex to lysosomes in the presence of amino acids has been described to transfer Rheb from the Golgi complex to lysosomes, increasing Rheb on the lysosomal surface to maximize mTORC1 activation in lysosomes **[362-365]**.

Rheb is the final pathway of mTORC1 activation that occurs in the presence of trophic factors and glucose. Trophic factors dissociate TSC-1 from TSC-2 (Tuberous Sclero Complex 1 and 2) **[319,320]**. During fasting, cytosolic TSC-2 is shifted to the lysosome, inactivating Rheb and turning off mTORC1 activity **[321-324]**. Tuberous sclerosis is the prototypical disease of TSC1/2 dysfunction, with consequent mTORC1 hyperactivation (**Figure 6**). It is a rare autosomal dominant with tumor formation in kidneys, heart, lungs, eyes, skin, and brain. About 80 to 90% of these people have epilepsy, developmental delay or mental retardation, behavioral disorders, and autism **[325-329]**.

Figure 6. Growth factors and amino acids activate mTORC1 via different pathways: amino acids (right) bind mTORC1 to the lysosome via RAG and via RHEB (left) it is the ultimate activator of mTORC1 by growth factors and glucose.



Source: Own authorship.

Therapeutic Interventions on mTORC1

Congenital mTOR hyperactivity disorders are often associated with difficult-tocontrol epilepsies **[367-370]** and mTOR inhibitors such as rapamycin, everolimus, and other rapanalogues are studied in the treatment of these epilepsies. As in tuberous sclerosis, autism, dementia, traumatic brain injury and stroke, and cancer **[371-379]**. The tuberous sclerotic complex TSC1/2 is inhibited in most tumors, with mTORC1 hyperactivity and rapid tumor growth **[379,380]**. Kaposi's sarcoma, for example, is a highly vascularized tumor and angiogenesis and growth are blocked with the use of rapamycin **[381-386]**.

Mantle cell lymphomas (MCL) respond to rapamycin **[387-390]**. Rapanalogues are used in the treatment of leukemias to block the PI3K/AKT/TSC1/2/mTORC1 pathway, which is overactivated **[387-392]**. mTORC1 inhibitors are also used as immunosuppressants in certain kidney transplants **[393]**, in the treatment of gliomas **[394-399]**, and other cancers **[400-405]**. Recent data suggest imbalances of mTOR activity in diseases such as Parkinson's, Huntington's, Alzheimer's, frontotemporal dementia, and amyotrophic lateral sclerosis **[406-409]**. Rapanalogues and newer mTOR inhibitors can slow these neurodegenerative changes **[410-413]**.

Alzheimer's disease (AD) is the most common form of dementia **[414]**, characterized by the accumulation of proteins (β amyloid and tau) in brain tissue resulting in cognitive decline. Post-mortem studies of human AD brains indicate mTOR hyperactivation and overproduction of β amyloid and tau proteins **[415-421]**. Down syndrome is the most frequent chromosomal abnormality and it is associated with a congenital intellectual deficit. There is also an accumulation of tau and β amyloid proteins in brain tissue by mTOR hyperactivation **[422-426]**. Several studies of mTORC inhibition with rapamycin and rapanalogues suggest strong clinical potential in slowing the progression of cognitive impairment in Alzheimer's disease and Down syndrome **[427-430]**.

Not only mTOR blockade has therapeutic action, but its activation is also a clinical target, as discussed in topic 3. mTORC1 activation is necessary for tissue regeneration such as muscle, liver, bone, intestine, etc. and its non-activation is a crucial factor. from the lack of CNS regeneration **[431-438]**. Neurons are particularly distinct, highly polarized cells with unique morphology and axon processes that can be thousands of times in length relative to the size of their cell bodies. The accumulation of cytoplasmic organelles along the axon forms small regional centers of synthesis, with some independence from the distant nucleus, which allows the synthesis of proteins necessary for reparative axonal budding or creation of new synapses in the CNS **[438-441]**.

Also, mTOR activation results in axonal regeneration of optic nerve injury in animal models stimulated by growth factors **[442,443]**. mTORC1 activation occurs at the axon tip, on the surface of lysosomes present there, producing the macromolecules necessary for the formation of the growth cone and neoaxon expansion **[443,444]**.

Besides, mTORC1 activation may, however, be contrary to the recovery of the injured spinal cord, as activated astrocytes form extensive glial scars and block local axonal attempts at regeneration **[444]**. TRM models of hemisection and mTORC1 hyperactivation provoked by injection of interleukin 6 (PIP3/AKT/mTOR pathway activator) or by PTEN kinase blockade (PIP3/AKT/mTOR pathway inhibitor) provoked regenerative growth of the corticospinal tract in mice **[445-447]**.

Therefore, the current understanding of the molecular mechanisms of cell activation indicates that axonal organelles are fundamental organizational centers for growth cone progress and mTORC1 stimulation of axonal lysosomes may be one of the missing keys to CNS repair.

Conclusion

Amino acids are, in addition to building blocks of macromolecules, cellular activation signals. Essential amino acids are not produced by animals and leucine appears to be the main signaling amino acid. Mammals adjusted the cell activation and growth rate of their young by the leucine concentration of the milk produced. Several studies demonstrate the benefits of leucine supplementation in preventing sarcopenia, improving muscle and liver performance, as well as a possible neuroprotective role in head trauma and dementia. However, its excess, so common in the Western diet, is related to obesity, type II diabetes, neurodegenerative diseases, and cancer. The mTORC1 kinase integrates cellular activation stimuli from macro protein synthesis to epigenetic regulation. Controlling mTORC1 activity by consuming leucine can prevent, treat, or cause disease. A greater understanding of the regulatory effects of leucine and mTOR in unstable tissues such as tumors or fragile tissues such as the CNS are areas of great relevance and with extensive fields still to be explored.

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