mTOR-Mediated Regulation of Cancer Metabolism

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Abstract
Altered cellular metabolism is one of the hallmarks of cancer development and progression since rapidly proliferating cells have elevated requirements for energy and biosynthesis. The mechanistic target of rapamycin (mTOR) signaling pathway has attracted attention due to its regulatory influence on metabolism and cell growth. Cancer cells exploit the signalling activity of mTOR to stimulate anabolic processes while inhibiting catabolism in order to create biomass and support uncontrolled growth. The present thesis explores the effects of mTOR-mediated signalling in the metabolism of cancer cells, while focusing in the most fundamental processes that include glycolysis, nucleotide, fatty acid and protein synthesis as well as protein degradation and autophagy.

Introduction
Cancer cells, driven by exponential growth, are known to strategically adapt their metabolic functions to support their characteristic aberrant proliferation despite demanding conditions. A century after Otto Warburg first described the phenomenon of aerobic glycolysis, scientists have extensively studied metabolic reprogramming and the ways with which proliferating cells coordinate both their catabolic pathways to create energy and anabolism for the formation of precursor molecules and biogenesis. In fact, cancer cells are partial to transforming glucose to lactate in the presence of oxygen, omitting the respiratory pathway, in order to gain adenosine triphosphate (ATP) and also maintain the pool of precursors through the tricarboxylic acid (TCA) cycle for the synthesis of essential biomolecules such as nucleotides, proteins and lipids (Vander Heiden & DeBerardinis, 2017). Nonetheless, while normal cells require separate molecular signals to regulate growth and cell cycle progression, malignant cells acquire mutations that hyperactivate the signalling network of mechanistic target of rapamycin (mTOR) which plays a role in the integration of these mechanisms (Saxton & Sabatini, 2017).

The mTOR signalling pathway is fundamentally important for physiological and clinical reasons. Named after being the target of rapamycin, researchers attempted to elucidate the molecular mechanism of action of a compound that shows antifungal, immunosuppressive, anti-cancer and cardioprotective properties by inhibiting the activation of mTOR signals (Saxton & Sabatini, 2017). As it was hypothesised, mTOR holds a pivotal position in cell mass assimilation by regulating metabolic synthesis and degradation, hence suppressing catabolic processes such as autophagy and protein turnover while stimulating biosynthesis (Figure 1) (Mossmann et al., 2018). Evolutionary evidence provides an explanation for the development of such a network so that eukaryotes are able to control the two competing functions in response to the nutrients that are available (Loewith & Hall, 2011). Moreover, mTOR contributes to cancer development and progression either via inducing increased expression or activity of enzymes that catalyse key metabolic reactions (Mossmann et al., 2018). With this thesis, I aim to analyse the influence of mTOR-mediated signalling in the metabolism of cancer cells, while focusing in the most fundamental processes that include glycolysis, nucleotide, fatty acid and protein synthesis as well as protein degradation and autophagy.

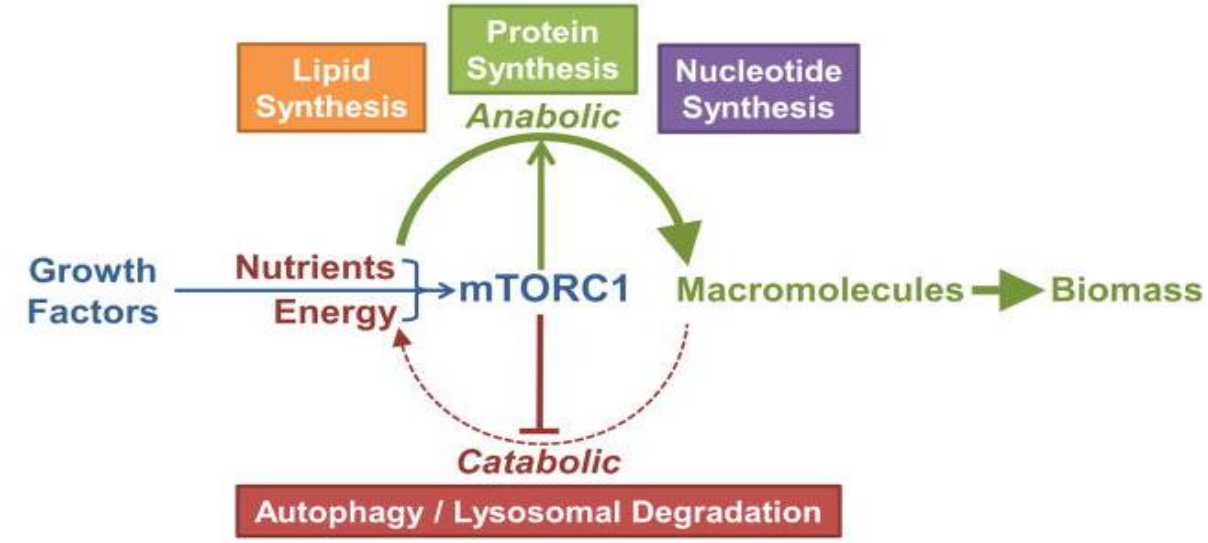

Figure 1 | *mTORC1 Signalling Controls Cellular Growth. Stimuli such as growth factors, nutrients and energy activate the mTORC1 pathway which in turn stimulates anabolic processes while inhibiting catabolism. It enhances the synthetic pathways of essential macromolecules (proteins, nucleotides, lipids) to generate biomass and promote growth. (Source: Ben-Sahra & Manning, 2017)*

The mTOR Complexes

The mTOR protein is a serine/threonine kinase part of the PI3K-related kinase family of protein kinases (Saxton & Sabatini, 2017). As part of two distinct complexes, mTOR complex I (mTORC1) and mTORC2, it is shown to have different functions according to the complex that it is involved with. mTORC1 consists of two core components other than the catalytic subunit mTOR (Figure 2A). The protein Raptor assists with recruiting substrates to mTOR and is responsible for the lysosomal translocation of the complex via recombination activating genes (RAGs) in order to be activated by RHEB as well as mLST8 which is required for the stabilization of the kinase subunit (Kim et al., 2002; Yang et al., 2017). Furthermore, it contains the inhibitory components PRAS40 and DEPTOR (Yang et al., 2013; Yang et al., 2017). The activation of the signalling depends on extracellular stimuli that include nutrients, energy, stress, oxygen, growth factors and mitogens while treatment with rapamycin suppresses signal transduction after association with the peptidyl-prolyl-isomerase FKBP12 (Saxton & Sabatini, 2017). On the other hand, mTORC2 is insensitive to the rapamycin-FKBP12 complex despite containing the mTOR subunit (Saxton & Sabatini, 2017). It also contains the proteins mLST8 and DEPTOR and as an alternative to Raptor the protein Rictor (Figure 2B) (Peterson et al., 2009). In addition, it comprises two regulatory elements mSin1 and Protor1/2 (Saxton & Sabatini, 2017). The mTORC2 complex acts as an effector to growth factors, predominantly insulin, to control cell survival and proliferation.

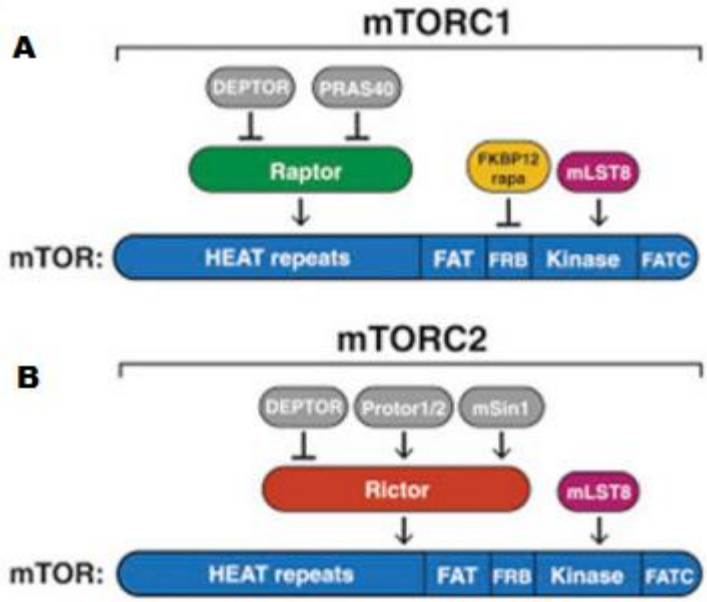

Figure 2 | *The mTORC1 & mTORC2 Complexes. (A) The structural elements of mTORC1 include the subunits mTOR, Raptor, mLST8 as well as the inhibitory molecules DEPTOR, PRAS40. In addition, the target of the FKBP12-rapamycin resides in the FRB domain of mTOR. The protein domains of mTOR are present and binding sites for each subunit are also depicted. (B) mTORC2 consists of the subunits mTOR, Rictor, mLST8 as well as the regulatory molecules DEPTOR, Protor1/2, mSin1. The protein domains of mTOR are present and binding sites for each subunit are also depicted. (Source: Saxton & Sabatini, 2017)*

mTOR Signalling in Cancer

Dysregulation of mTOR signalling is strongly involved in malignant cell growth and proliferation due to mutations that affect both oncogenic and tumour suppressor pathways. To date, several oncogenic pathways have been identified to drive mutations that enhance the signalling activity of the mTOR complex including mitogen-activated protein kinases/extracellular signal-regulated kinase (MAPK/ERK) pathway and the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) pathway (Saxton & Sabatini, 2017). Furthermore, the second pathway has been one of the most studied ones in relation to mTOR as it plays an important role in regulating metabolism. Mutations in its components and effectors can interfere with the activity of both mTORC1 and mTORC2 (Saxton & Sabatini, 2017).

Mutations occurring in the genes responsible for encoding the various subunits of the PI3K protein have been suggested to cause alterations that bypass the requirement for external signal transduction. As a consequence, the downstream pathway initiates in an independent manner which over-activates mTOR signalling. Among these genetic alterations, the most frequently observed ones are associated with phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) gene which is responsible for encoding the catalytic subunit of PI3K (Mayer & Arteaga, 2016). These mutations predominantly affect either the helical subunit, leading to an increase in catalytic activity, or the kinase domain, causing the catalytic subunit to remain bound to the plasma membrane which leads to increased phosphorylation of Akt and subsequent activation of mTORC1 (Huang et al., 2007; Burke et al., 2012).

Mutations that lead to the functional inactivation of the tumour suppressor gene PTEN are also found to affect the interaction between the PI3K-Akt and mTOR pathways in cancer. Lack of PTEN increases the activity of the mTORC2 complex and blocks its negative feedback regulation, allowing cancer cells to use mTORC2 to elevate the phosphorylation of Akt and that targets various proteins for further phosphorylation (Guertin et al., 2009). Consequently, the lack of

activity of PTEN triggers aberrant PI3K-Akt signalling and hyperactivation of mTORC1 enhances cellular growth and upregulates metabolism, which in turn facilitates diverse oncogenic cellular processes (Song et al., 2012).

Mutations that render tumour suppressors inactive are also found to increase the activity of mTORC1 since their negative feedback contribution loses its influence on the signalling pathway. Genetic variations on either tuberous sclerosis complex I (TSC1) or TSC2 genes reduce the efficiency of their tumour suppressive function which results in an abnormal state of hyperactivation of the mTORC1 complex (Menon & Manning, 2008). Likewise, mutations that alter the activity of tumour suppressors, such as liver kinase B1 (LKB1) and tumor protein p53 (TP53), increase mTORC1 signalling by losing their regulatory effects upstream of the TSC1/TSC2 complex (Zhou et al., 2013; Cui et al., 2021). Nonetheless, more than 30 mutations have been described to directly impact distinct regions of the MTOR gene and induce hyperfunction in different subtypes of cancers (Grabiner et al., 2014)

Glucose metabolism

As discussed earlier, cancer cells are avid glucose consumers. They can effectively utilize the glycolytic process aerobically, so that not only the required net production of energy is reached but also carbon building blocks and nicotinamide adenine dinucleotide phosphate (NADPH) are generated to meet their malignant proliferative needs. The involvement of the mTOR pathway begins early in tumour progression and regulates glucose uptake and metabolism by means of multiple mechanisms (Figure 3) (Tian et al., 2019). First and foremost, a correlation between increased expression of the glucose transporter 1 (GLUT1) and increased mTOR pathway activity has been described as common in many types of cancers (Carvalho et al., 2011). This phenomenon that allows cells to upregulate the influx of glucose into the cell was indicated to be the consequence of abnormal TSC2 function that results in the loss of their suppressive influence on mTOR signalling (Buller et al., 2008). In addition, mTOR activation in cancer has been proposed to enhance the production of GLUT1 via the regulation of two transcription factors, hypoxia inducible factor 1 subunit alpha (HIF1a) and MYC (Tran et al., 2016). These specific transcription factors are known to impact several aspects of glycolysis by controlling the expression of not only glucose transporters but also multiple glycolytic enzymes including hexokinase, phosphofructokinase and pyruvate kinase among others as will be described later in more detail.

The initial step of glucose metabolism relies on the phosphorylation of glucose by the enzyme hexokinase (HK) to produce glucose-6-phosphate. In cancer cells, the HK2 isoform is present and upregulated, and it is highly involved in the influx of glycolytic patterns (Wolf et al., 2011). The contribution of mTORC1 signalling to the increased activity of the enzyme is induced either via increased transcription by HIF1a and Myc factors, or elevated HK2 synthesis (Wang et al., 2014; Tran et al., 2016). Furthermore, the mTORC2 complex promotes glycolysis by Akt-induced phosphorylation of HK2 to improve its affinity to the outer mitochondrial membrane and by inhibition of the transcription factors FOXO1 and FOXO3 (Mossmann et al., 2018). The second irreversible step of glycolysis that is affected by mTOR dysregulation is the phosphorylation of fructose 6-phosphate to form fructose 1,6-bisphosphate at the expense of ATP, a reaction that is catalyzed by the enzyme phosphofructokinase (PFK) and sets the pace of the entire metabolic

pathway. Studies have shown that mTOR-mediated activation of the PI3K-Akt pathway as well as HIF1a and Myc transcription intervention can effectively overexpress PFK and thus, secure the fate of glucose solely into a glycolytic intermediate that feeds the pathway (Fan et al., 2021). In a similar fashion, mTOR signalling stimulates glucose breakdown by regulating the allosteric modulation of PFK (Bartrons et al., 2018). Both mTORC1 and mTORC2 have been implicated in the upregulation of the enzyme 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3) which is responsible for the intercellular levels of fructose-2,6-bisphosphate, a potent allosteric activator of PFK (Fan et al., 2021). The outflow of the pathway is also controlled by mTOR and it involves the last glycolytic step of the formation of pyruvate via pyruvate kinase catalysis. The mammalian isomer 2 of pyruvate kinase (PKM2) is overexpressed in the majority of cancer cells and research has shown that mTOR regulates this process by HIF-1a activation and c- Myc/heterogeneous nuclear ribonucleoproteins (hnRNPs) alternative splicing, which in turn increases the yield of pyruvate that serves as fundamental metabolic intermediate (Zahra et al., 2020).

The reaction that completes the process of aerobic glycolysis is the reduction of pyruvate to lactate and this conversion is catalyzed by lactate dehydrogenase (LDH). This is an important step for cancer cells because it allows them to sustain glycolysis in the presence of oxygen by maintaining the NAD+ supply and inhibiting the oxidation of pyruvate in the mitochondria via the electron transport chain (Vander et al., 2009). Furthermore, cancer cells are able to shift between the utilization of glucose and lactate as metabolites to ensure maximal mutual benefit in a process called metabolic symbiosis, therefore they depend on the molecular mechanisms that allow the uptake and secretion of the substrates (Fan et al., 2021). Regarding lactate, glycolytic cancer cells depend on the monocarboxylate transporter 4 (MCT4) to discard excessive intracellular lactate, while normoxic cancer cells import lactate via MCT1 for it to be converted back into pyruvate and enter the TCA cycle to meet their energy requirements and generate amino acids, however, it has been demonstrated that the balance of this synergy can be obstructed by inhibition of the mTOR pathway (Mossmann et al., 2018).

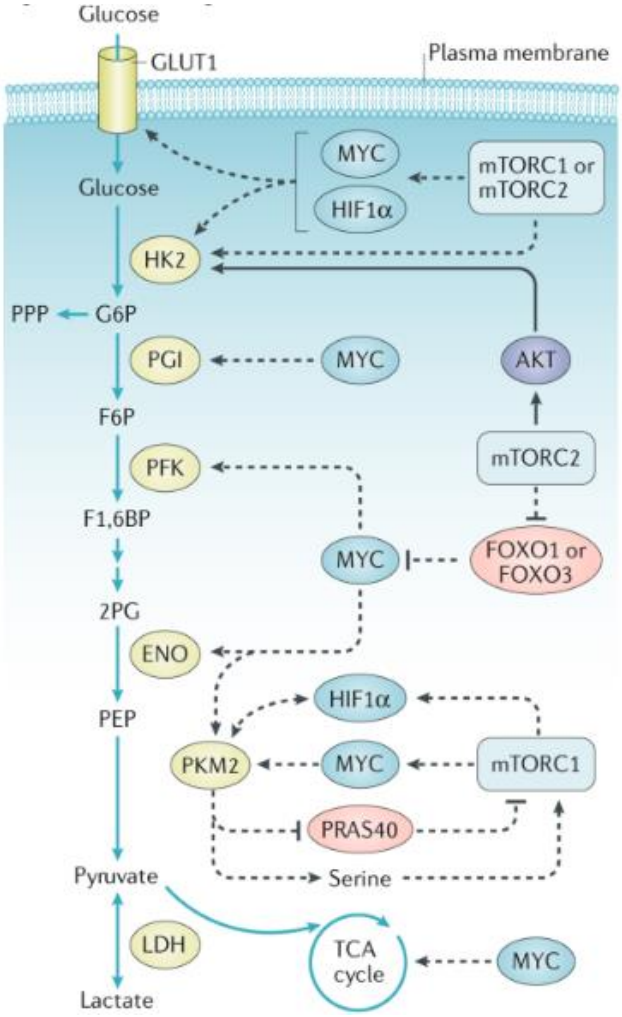

Figure 3 | *The Role of mTOR in Glucose Metabolism. Cancer cells exhibit increased glucose uptake via glucose transporter 1 (GLUT1) which feeds the glycolytic pathway and yields the production of pyruvate. Further enzymatic processing by lactate dehydrogenase (LDH) leads to the interconversion of pyruvate to lactate which is linked with the tricarboxylic (TCA) cycle. The activity of mTORC1/mTORC2 influences both the function of the enzymes hexokinase 2 (HEK2), phospho-glucoisomerase (PGI), phosphofructo-kinase (PFK), enolase (ENO), pyruvate kinase muscle isoform 2 (PKM2) and it stimulates the transcription factors MYC and hypoxia-inducible factor 1α (HIF1α). The light blue arrows show the metabolic pathway while black arrows and dotted lines indicate signalling pathways. PPP, pentose phosphate pathway. G6P, glucose-6-phosphate. F6P, fructose-6-phosphate. F1,6BP, fructose-1,6-bisphosphate. 2PG, 2-phosphoglycerate. PEP, phosphoenolpyruvate. (Source: Mossmann et al., 2018)*

Nucleotide synthesis

The increased glucose uptake and metabolism that rapidly dividing cells exhibit result in the formation of substrates ready to be loaded into other metabolic pathways and be utilised to the fullest extent possible. Besides the increased energy demand, a typical requirement for cellular growth in malignancies is the constant supply of nucleotides, so they heavily rely on these biosynthetic pathways to sustain a pool of molecules that will be used to generate building blocks to fuel nucleic acid production and support rapid proliferation (Mullen & Singh, 2023). The metabolic alterations that cancer cells undergo allow them to exploit carbon precursor molecules towards nucleotide synthesis for increased DNA replication, RNA synthesis as well as their repair and maintenance mechanisms, all of which are required for prolific cell division (Ma et al., 2021).

The intersection of glucose and nucleotide metabolism begins when cells use glycolytic intermediates to synthesise ribose-5-phosphate (R5P), a major component of DNA and RNA, through the pentose phosphate pathway (PPP) (Ma et al., 2021). The PPP employs the excess glucose 6-phosphate (G6P) that forms in the early stages of glycolysis and converts it to biomolecule precursors and reducing power in the form of NADPH molecules, both of which

promote biosynthesis. In detail, the oxidative branch of the PPP begins with the irreversible reaction of G6P dehydrogenation and is followed by hydrolysis and an oxidative decarboxylation step that yields a molecule of R5P and 2 NADPH cofactors (Berg et al., 2002). The influence of mTORC1 signalling in the PPP reflects on both the oxidative and the non-oxidative branches by manipulating the expression of key enzymes, while mTORC2 is thought to exclusively promote glycolysis through activation of HK2 and drive the flux of G6P (Mossmann et al., 2018). More specifically, mTORC1 targets the expression of G6P dehydrogenase, the enzyme responsible for the catalysis of the rate-determining step of PPP, as well as the expression of R5P isomerase A which converts ribulose-5-phosphate to R5P (Evert et al., 2012). Research has led scientists to consider that this mechanism is induced when the mTORC1 effector protein S6K stimulated the transcription factors HIF1a and (sterol regulatory element binding transcription factor 1 (SREBP1) (Duvel et al., 2010).

The following step in the pathway of nucleotide biogenesis includes the conversion of R5P to 5-phosphoribosyl-1-pyrophosphate (PRPP) by the enzymes phosphoribosyl pyrophosphate synthase 1 (PRPS1). PRPP is an essential precursor of both purine and pyrimidine synthesis along with amino acids, ATP, CO2, and other substrates (Berg et al., 2002). In cancer cells, de novo synthesis of nucleotides is preferred over the salvage pathway which is achieved by adapting their metabolic signalling (Figure 4) (Howell et al., 2013). Although the assembly of purines take place gradually but directly onto the PRPP molecule to form inosine monophosphate (IMP), the pyrimidine ring gets constructed and then added to the ribose phosphate in distinct steps that involve the enzyme carbamoyl phosphate synthetase 2, aspartate transcarbamylase and dihydroorotase (CAD) which produces dihydroorotate (DHO) which in turn gets converted to orotate for it to be incorporated with the PRPP and form orotate monophosphate (OMP) (Lane & Fan, 2015). It has been established that the mTOR pathway impacts nucleotide biogenesis not only via transcriptional mechanisms but also through post-translational modifications that involve both purine and pyrimidine synthetic pathways (Howell et al., 2013). Regarding purine synthesis, mTOR signalling does not show to have a direct impact on the pathway itself, but rather it stimulates it by upregulating enzymes that provide precursors via activation of transcription factors (Mossmann et al., 2018). On the contrary, de novo pyrimidine synthesis is promoted by mTOR through induced activation of CAD by either MYC transcription regulation or S6K phosphorylation of the enzyme (Howell et al., 2013; Ben-Sahra et al., 2014).

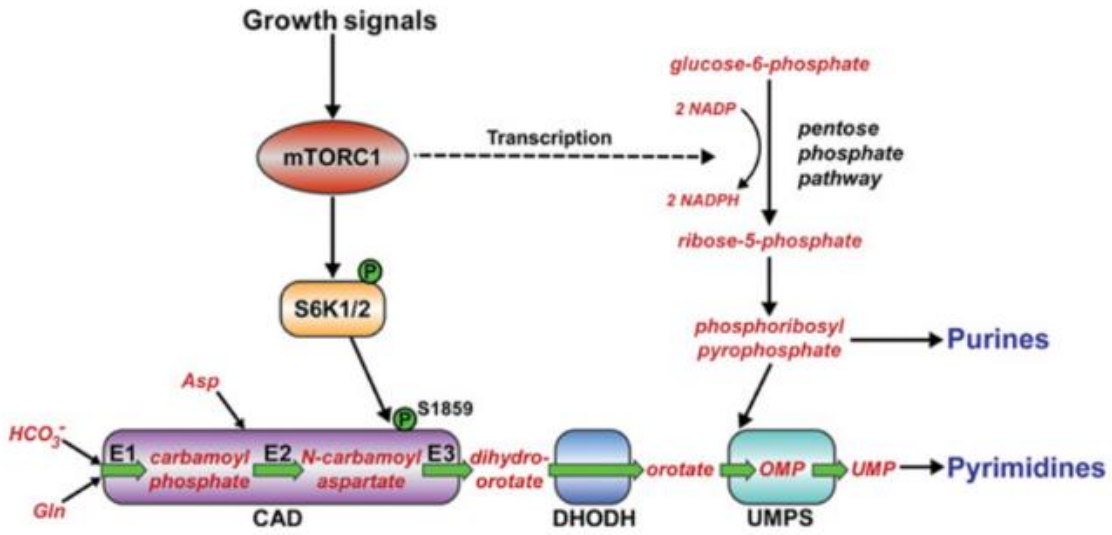

Figure 4| *mTORC1 Induces de novo Purine and Pyrimidine Synthesis. By upregulating the expression of key enzymes, mTORC1 increases the metabolic influx of the pentose phosphate pathway and consequently the production of NADPH and phosphoribosyl pyrophosphate, both of which promote nucleotide biosynthesis. Moreover, mTORC1 stimulates the ribosomal protein S6 kinase 1/2 (S6K1/2) which directly acts on the trifunctional enzyme carbamoyl-phosphate synthetase 2, aspartate transcarbamylase, and dihydroorotase (CAD), responsible for the initial reactions of pyrimidine synthesis. DHODH, dihydroorotate dehydrogenase. OMP, orotidine monophosphate. UMPS, uridine monophosphate synthase. (Source: Howell et al., 2013)*

Fatty Acid & Sphingolipid Synthesis

We have discussed so far, the unique metabolic demands of cancer cells that are characterized by altered energy production and elevated metabolic precursor requirements to fuel other crucial metabolic processes. Since mitotic cells require to double their membrane during each cell cycle, the imperative of acquiring fatty acids for lipid synthesis and membrane biogenesis inevitably results in the upregulation of these processes in tumours. Indeed, it is unique to cancer cells to rely heavily on the pathway of de novo fatty acid synthesis to provide building blocks for the structural components of membranes and also for signalling molecule production (Röhrig & Schulze, 2016). Conventionally, the citric acid cycle, the PPP and the glycolytic pathway integrate to coordinate fatty acid synthesis by supplying citrate as a precursor molecule, NADPH as a reductant and ATP respectively in order to generate palmitate, the precursor of all other fatty acids (Berg et al., 2002).

The mTOR pathway is heavily involved in the processes that enable the de novo synthesis of fatty acids to meet the rapid proliferation and growth-related needs of cancer cells (Mossmann et al., 2018). Foremost, the expression and maturation of the transcription factor SREBP1 is determined by the activity of both mTORC1 and mTORC2 and it is crucial for the elevated expression of the following enzymes that drive fatty acid synthesis (Yecies et al.,2011; Hagiwara et al., 2012). The enzyme ATP citrate lyase converts the excess citrate yielded from the TCA cycle to acetyl-CoA and employs products of carbohydrate metabolism to produce fatty acids

(Currie et al., 2013). In addition, acetyl coenzyme A (acetyl-CoA) carboxylase acts as a catalyst in the production of malonyl-CoA from acetyl-CoA while fatty acid synthase generates palmitate using acetyl-CoA and malonyl-CoA (Currie et al., 2013). Following those steps, the saturated palmitate gains a double bond by the enzyme stearoyl-CoA desaturase and forms monosaturated fatty acids that can undergo further elongation and yield a wide array of lipid species for cells to use (Koundouros & Poulogiannis, 2020).

Fatty acids can be used as substrates for sphingolipid production, a class of plasma membrane lipids that are found abundant in lipid rafts which are essential for signal transduction (Berg et al., 2002). Two particular sphingolipid derivatives, ceramide and sphingosine-1-phosphate (S1P), act as signalling molecules that respectively hinder or induce cell growth and proliferation in cancers (Ogretmen & Hannun, 2004). With regard to ceramide, it had been observed that it serves a protective role against malignancies by inhibiting the Akt signalling pathway and inducing programmed cell death (Kim et al., 2010). However, cancer cells employ the enzyme glucosylceramide synthase, which is part of the glycolipid biosynthetic pathway, to prevent intracellular accumulation by mTOR-mediated increase of the expression of the enzyme as suggested by the research of Guri et al. (Guri et al., 2017). On the contrary, there are indications that the mTOR activation may be involved in cancer development and progression as a result of abnormal S1P signalling in hypoxic cancer cells (Bouquerel et al., 2016).

Protein Synthesis

The regulatory role of mTOR has arguably been the most established in regard to of protein synthesis, and since the process requires substantial amounts of energy compared to other anabolic pathways it needs to be tightly regulated to maintain the balance between the altered metabolic needs of highly proliferative cancer cells. Namely, mTOR is responsible for the phosphorylation of key downstream effectors that initiate mRNA translation as well as stimulate the production of structural components of the translational apparatus, thus generating both acute and prolonged effects on protein synthesis (Howell et al., 2013).

One of the direct phosphorylation targets of mTORC1 that influences protein synthesis is the eukaryotic translation initiation factor 4E (eIF4E)-binding protein (4EBP) which normally controls the initiation of translation by remaining bound to eIF4E to inhibit the formation of the translation initiation complex eIF4F unless mTORC1 phosphorylates the substrate at multiple sites, so it detaches from the eIF4F complex and allows 5’ cap-dependent mRNA translation (Merrick, 2015). Interestingly, studies conducted by Hsieh et al. hinted at the outcome of 4EBP phosphorylation by mTORC1 and the effects of translation initiation in cells as a decisive part of oncogenesis for certain cancers highlighting its importance (Hsieh et al., 2012). In addition, mTORC1 phosphorylates the ribosomal S6 kinase 1 (S6K1) to activate it and stimulate a series of phosphorylation events that involve the translation initiation factor 4B (eIF4B) which, similarly to eIF4E, enables the translation initiation complex and encourages cap-dependent translation (Holz et al., 2005).

As mentioned earlier, mTORC1 plays a role in the increase of the protein biosynthetic capacity of cells by stimulating the biogenesis of the ribosomal apparatus to meet the demands of elevated translation. This event occurs when mTORC1 phosphorylates 4EBP which contributes to the

translation of mRNA with 5'-terminal oligopyrimidine tracts (5'-TOPs) known for encoding the majority of ribosomal proteins. (Thoreen et al., 2012). Moreover, mTORC1 signal transduction stimulates the transcription of ribosomal RNA as well as other genes that regulate ribosomal biogenesis (Howell et al., 2013). Lastly, it is worth mentioning that there is a strong dependence between protein and nucleotide synthesis since rRNA takes up more than 80% of the total content of cellular RNA and increased ribosome biogenesis escalates nucleotide demands, risking depleting the pool of nucleotides and hinders cellular growth provided that mTOR signalling fails to regulate the synergistic mechanisms (Valvezan et al., (2017).

mTOR Signalling & Catabolism

Thus far, anabolic and biogenic processes have been prioritised when reviewing mTOR-specific metabolic alterations in tumour cells overlooking the importance of cellular degradation mechanisms and their target therapeutic potential. Emerging as a dynamic interplay between cellular homeostasis and malignant transformation, the mTOR pathway and autophagy have been the focus of research in an attempt to elucidate the role of catabolic regulation in cancer cell survival and growth. mTOR activity has been proven to hinder the initiation of autophagy by inhibiting autophagosome formation, cargo selection and lysosomal degradation (Paquette et al., 2018). More specifically, the Unc-51-like kinase 1 (ULK1), which is a molecule that initiates autophagy and drives the formation of autophagosomes, gets phosphorylated by the sustained mTORC1 signalling which in turn inhibits AMPK-induced activation and blocks autophagy altogether (Kim et al., 2011). In addition, mTOR phosphorylation of ATG13 prohibits complex formation with ULK1, and other proteins, which further impairs the formation of autophagosomes (Puente et al., 2016). Lastly, mTOR phosphorylation of the transcription factor EB (TFEB) prevents its translocation to the nucleus and reduces the expression of genes involved in lysosomal biogenesis to produce the organelles responsible for the degradative step of autophagy (Settembre et al., 2011).

Understanding the mechanisms by which the mTOR pathway manages to balance protein synthesis and degradation, and thereby coordinate molecular signalling to fulfilling the energy and growth requirements of cancer cells, has been challenging. Other than the autophagy pathway, cells normally use their protein quality control mechanism to spot damaged or misfolded proteins, tag them with ubiquitin markers and proceed to proteasomal degradation via the ubiquitin–proteasome system (Li et al., 2022). While attempting to provide an explanation for the inconclusive findings concerning the influence of mTOR on proteasomal degradation, it is theorised that mTORC1 increases proteolysis under both inhibition and activation of the complex since constant overstimulation elevates the synthesis of proteins and the phenomenon needs to be counterbalanced (Saxton & Sabatini, 2017). It appears critical to study further the effects of mTOR signalling on protein turnover in cancer cells not only to shed light on the underlying mechanisms of tumorigenesis but also to decode unknown dynamics that facilitate rapid tumour growth and foster resilience.

Discussion

There is now a good deal of evidence that supports the notion of the mTOR pathway being a central player in the regulation of cancer cell metabolism and contributing to the development and progression of the disease. In summary, numerous genetic alterations regarding oncogenes, tumour suppressor genes as well as mutations that occur directly on the MTOR gene, induce the ability to reinforce the activity of mTOR signalling and result in increased transduction of signalling cascades that upregulate metabolism and facilitate cancer cell processes. Aerobic glycolysis is essential for energy production and mTOR mediates its function by enhancing not only the import of glucose by the cells but also the activation of enzymes that drive the entire pathway. The products of glycolysis are then utilised by other anabolic pathways such as the synthesis of nucleotides to support the increase in DNA replication and RNA synthesis, mRNA translation and ribosomal biogenesis for protein synthesis and last but not least, the synthesis of fatty acids and consequently lipids to provide building blocks for the structural components of membranes and for signalling molecule production. In brief, mTOR signalling mainly acts by either directly reacting with effector molecules that transduce the signal further or by regulating the activity of transcription factors and thus, the expression of key metabolic enzymes. Additionally, mTOR signalling impacts catabolic pathways including the inhibition of the mechanism of autophagy and regulation of proteasomal degradation. Therefore, the mTOR pathway acts as a skilled orchestra conductor that coordinates metabolic uptake and utilization to create a dynamic harmony that ensures an adequate energy supply for the demanding needs of cancer cells. Nonetheless, the aim of this paper was to give an overview of mTOR-mediated regulation of the most fundamental metabolic pathways, and I ought to mention that the products of such pathways connect with more complex molecular processes that can be of vital importance for proliferative cells and might give rise to the potential of new therapeutic strategies against cancer.

Several of the mechanisms that involve upregulated mTOR signalling have been studied to determine whether targeted interference can be used as an effective anti-cancer treatment. Currently, clinical trials are evaluating the effectiveness of mTOR inhibitors with different modes of action either alone or in combination with other drugs and in a wide range of cancer types with varying results (Ali et al., 2022). The main categories of the evolution of mTOR inhibitors include rapamycin and rapalogs, ATP-competitive mTOR kinase inhibitors, dual PI3K/mTOR inhibitors and rapalink-1, which is a hybrid molecule of rapamycin bound to an ATP-competitive mTOR kinase inhibitor (Ali et al., 2022). However, only a fraction of the active compounds has gotten FDA approval since there is still little understanding of the underlying mechanisms that are involved, including the effects on healthy cells that can cause severe side effects and feedback responses that counteract the desired therapeutic target. Recently, the combination of mTOR inhibitors and metformin has emerged as a potential cancer treatment that targets both the glycolytic pathway and the fatty acid synthesis and is shown to reduce cancer growth (Libby et al., 2009; Mossmann, 2018). Overall, the mTOR pathway demonstrates immense potential for the development of pioneering targeted cancer therapies since it is heavily involved in the anabolic pathways that enable cancer cells to proliferate and compete with the neighboring cells causing pathogenesis. Further research is suggested to elucidate in detail the molecular mechanisms that drive cancer metabolism, as well as to determine unique metabolic alterations in different subtypes to achieve treatment that exploits the most vulnerable targetable processes.

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