The PI3K–AKT network at the interface of oncogenic signalling and cancer metabolism

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Abstract | The altered metabolic programme of cancer cells facilitates their cell-autonomous proliferation and survival. In normal cells, signal transduction pathways control core cellular functions, including metabolism, to couple the signals from exogenous growth factors, cytokines or hormones to adaptive changes in cell physiology. The ubiquitous, growth factor-regulated phosphoinositide 3-kinase (PI3K)–AKT signalling network has diverse downstream effects on cellular metabolism, through either direct regulation of nutrient transporters and metabolic enzymes or the control of transcription factors that regulate the expression of key components of metabolic pathways. Aberrant activation of this signalling network is one of the most frequent events in human cancer and serves to disconnect the control of cell growth, survival and metabolism from exogenous growth stimuli. Here we discuss our current understanding of the molecular events controlling cellular metabolism downstream of PI3K and AKT and of how these events couple two major hallmarks of cancer: growth factor independence through oncogenic signalling and metabolic reprogramming to support cell survival and proliferation.

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The phosphoinositide 3-kinase (PI3K)–AKT pathway is the most commonly activated pathway in human cancers[1]. Under physiological conditions, this pathway is activated in response to insulin, growth factors and cytokines and regulates key metabolic processes, including glucose metabolism, biosynthesis of macromolecules and maintenance of redox balance, to support both systemic metabolic homeostasis and the growth and metabolism of individual cells. Oncogenic activation of the PI3K–AKT pathway in cancer cells reprogrammes cellular metabolism by augmenting the activity of nutrient transporters and metabolic enzymes, thereby supporting the anabolic demands of aberrantly growing cells. Understanding how the PI3K–AKT pathway governs metabolic networks in normal cells and how this control is altered in cancer cells could reveal metabolic vulnerabilities and thus inform new therapeutic strategies, which is underscored by the 'druggable' nature of metabolic enzymes. Here we review the physiological functions of the PI3K–AKT network in controlling metabolic networks and the potential consequences from oncogenic PI3K–AKT signalling, leading to dysregulation of these key metabolic control points in cancer cells and tumours.

Signal transduction networks are the cellular lines of communication, allowing cells to perceive and relay signals, including those from the extracellular environment, to downstream targets that suitably adapt cellular functions to maintain cell, tissue and organismal homeostasis. The PI3K–AKT signalling network is activated downstream of receptor tyrosine kinases (RTKs), cytokine receptors, integrins and G protein-coupled receptors (GPCRs) and plays a central role in promoting cell survival and growth[2]. Class Ia PI3K exists as heterodimers of a catalytic subunit (p110α, p110β or p110δ) associated with a regulatory subunit (p85α or p85β, or shorter variants thereof), while class Ib is composed of the catalytic subunit p110γ, associated with the regulatory subunit p101 (REF.[3]). Class Ia PI3K is activated upon engagement of SH2 domains within the regulatory subunits with phospho-tyrosine residues on activated receptors (for example, RTKs or cytokine receptors) or adaptor proteins, whereas class Ib is activated by GPCRs. Activation of PI3K at the plasma membrane stimulates phosphorylation of its phospholipid substrate phosphatidylinositol 4,5-bisphosphate ($PtdIns(4,5)P_2$) to produce the second messenger, phosphatidylinositol 3,4,5-trisphosphate ($PtdIns(3,4,5)P_3$) (FIG. 1a). PI3K signalling is attenuated by phosphatase and tensin homologue (PTEN), which dephosphorylates $PtdIns(3,4,5)P_3$ so as to regenerate $PtdIns(4,5)P_2$. $PtdIns(3,4,5)P_3$ accumulation at the plasma membrane, and perhaps at other intracellular membranes, creates docking sites to recruit downstream effector proteins that contain a subclass

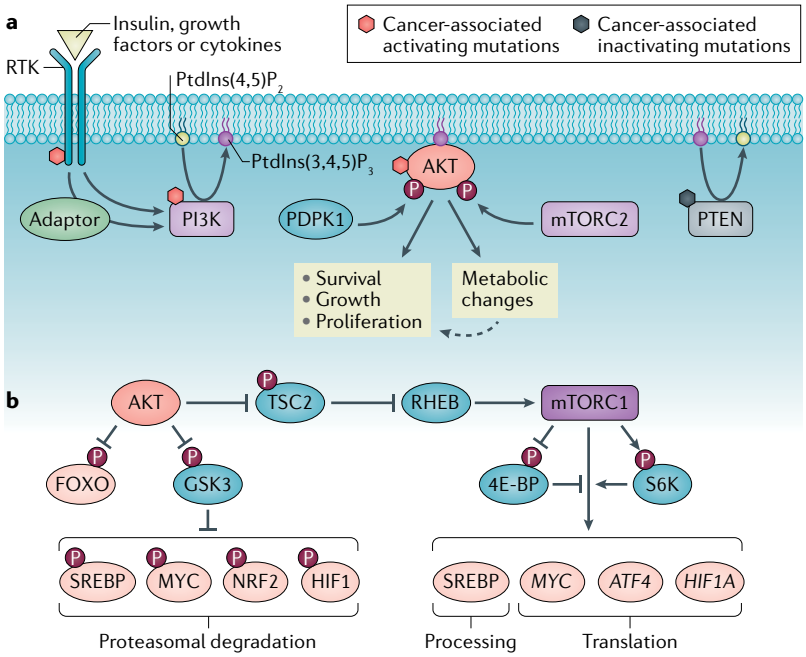


Fig. 1 | **The PI3K–AKT pathway and its major downstream effectors. a** | Mechanisms of AKT activation. Receptor tyrosine kinase (RTK) activation and tyrosine phosphorylation of its cytosolic domain or of scaffolding adaptors creates binding sites that recruit the lipid kinase phosphoinositide 3-kinase (PI3K) to the plasma membrane. PI3K phosphorylates phosphatidylinositol 4,5-bisphosphate (PtdIns(4,5)P_2) to produce phosphatidylinositol 3,4,5-trisphosphate (PtdIns(3,4,5)P_3), which can be dephosphorylated back to PtdIns(4,5)P_2 by phosphatase and tensin homologue (PTEN), a lipid phosphatase. PtdIns(3,4,5)P_3 acts as a second messenger to recruit the serine/threonine protein kinase AKT to the plasma membrane, where it is fully activated through phosphorylation at T308 and S473 by the phosphoinositide-dependent protein kinase 1 (PDPK1) and mechanistic target of rapamycin complex 2 (mTORC2) protein kinases, respectively. AKT signalling serves to promote cell survival, growth and proliferation, in part by inducing various changes to cellular metabolism. Coloured hexagons denote common points of activation and inactivation by cancer-associated mutations, and 'P' indicates protein phosphorylation events. **b** | AKT controls cellular metabolism, in part, through three key downstream substrates: tuberous sclerosis complex 2 (TSC2), glycogen synthase kinase 3 (GSK3) and the forkhead box O (FOXO) transcription factors. AKT phosphorylates and inhibits TSC2, a component of the TSC complex, thus activating mTORC1 by relieving TSC complex-mediated inhibition of Ras homologue enriched in brain (RHEB). The ribosomal protein S6 kinase 1 (S6K) and eukaryotic translation initiation factor 4E-binding protein (4E-BP) are canonical downstream targets of mTORC1, which together with other targets serve to stimulate the processing and activation of the sterol regulatory element-binding protein (SREBP) family of transcription factors, as well as mRNA translation of the *MYC*, *HIF1A* and *ATF4* transcription factors. GSK3-mediated phosphorylation of the transcription factors SREBP, MYC, nuclear factor erythroid 2-related factor 2 (NRF2) and HIF1α targets them for ubiquitylation and proteasomal degradation.

of pleckstrin homology (PH) domain that specifically engage this lipid species[2]. One such protein is the serine–threonine kinase AKT (also known as protein kinase B or PKB), which upon PtdIns(3,4,5)P_3 binding is subsequently phosphorylated by phosphoinositide-dependent protein kinase 1 (PDPK1, also known as PDK1) at T308, an event essential for kinase activation, and by mechanistic target of rapamycin (mTOR) complex 2 (mTORC2) at S473, which further increases the activity of AKT[4–6] (FIG. 1a). There are three isoforms of AKT (AKT1, AKT2 and AKT3), which are all activated in this manner. AKT1 and AKT2 are broadly expressed, with AKT2 being particularly important in insulin-responsive metabolic tissues, while AKT3 is more restricted in its tissue distribution, being highest in the brain[7,8]. Active AKT phosphorylates a large and diverse array of downstream substrates, the majority of which appear to be redundantly regulated by the three AKT isoforms (hereon referred to as AKT unless an isoform-specific function is noted). AKT-mediated phosphorylation of these protein targets serves to influence a variety of cell biological functions, including cell growth, proliferation, survival and, as we detail here, metabolism[8].

Genetic events leading to growth factor-independent activation of the PI3K–AKT pathway are among the most frequently occurring drivers of human cancer. Common alterations in cancer include (1) activating mutations in *PIK3CA*, which encodes the p110α catalytic subunit of PI3K and which is the most frequently mutated single oncogene found in analyses across cancer lineages[1]; (2) loss-of-function mutations and deletions in *PTEN*, the second most mutated tumour suppressor gene (following *TP53*); (3) amplification and activation of specific PI3K-activating RTKs, including EGFR and HER2; and (4) amplification and gain-of-function missense mutations in genes encoding one of the three isoforms of AKT[1,9–11] (FIG. 1a).

Key effectors in control of cell metabolism

While there are many downstream effectors of both PI3K and AKT that alter the function of both normal and cancer cells, we focus here on those that influence cellular metabolism. In a cell-intrinsic manner, the metabolic functions of AKT serve to support its canonical functions in promoting cell survival, growth and proliferation (FIG. 1a). AKT signalling alters metabolism either directly, through phosphorylation-mediated regulation of metabolic enzymes, or indirectly, through control of various transcription factors. Phosphorylation of metabolic enzymes allows for acute changes in the activity of metabolic pathways and the directionality of metabolic flux, whereas longer-term changes in cellular metabolism are often achieved through the control of gene expression programmes. While AKT directly phosphorylates several metabolic enzymes or regulators of nutrient transport, it also activates a few key downstream effectors that play a major role in cellular metabolic reprogramming, including mTORC1, glycogen synthase kinase 3 (GSK3) and members of the forkhead box O (FOXO) family of transcription factors[8] (FIG. 1b).

The serine/threonine kinase mTOR functions as the catalytic subunit of two multi-protein complexes, mTORC1 and mTORC2, with distinct subunit compositions, substrate specificities and functions[12]. Both mTORC1 and mTORC2 can be activated by PI3K signalling, with mTORC2 being an upstream regulator of AKT and mTORC1 being a downstream effector. The primary mechanism through which AKT activates mTORC1 is through phosphorylation of the tuberous sclerosis complex 2 (TSC2) protein, which as a component of the TSC protein complex acts as a GTPase-activating protein (GAP) to inhibit the Ras-related small G protein Ras homologue enriched in brain (RHEB)[13]. The AKT-mediated phosphorylation of TSC2 disrupts colocalization of the TSC complex with RHEB, thereby allowing accumulation of RHEB–GTP,

which binds to and activates mTORC1 (REF.[14]) (FIG. 1b). The AKT-mediated stimulation of mTORC1 acts in parallel to nutrient- and energy-sensing mechanisms that also control the activation state of mTORC1 and, as we discuss below, serves as a key point of regulation for anabolic metabolism and cell growth[13].

GSK3 was the first identified AKT substrate and is a key regulator of cellular metabolism, established originally for its role in blocking glycogen synthesis via phosphorylation and inhibition of its namesake substrate, glycogen synthase[15,16]. GSK3 is active under basal conditions and is inhibited in response to growth factors and insulin via AKT-mediated phosphorylation[15,17] (FIG. 1b). GSK3 has many downstream substrates, the phosphorylation of which often exerts inhibitory control over these targets[18]. Among these are several transcription factors that regulate the metabolism of both normal and cancer cells downstream of PI3K–AKT signalling. GSK3-mediated phosphorylation of these factors marks them for ubiquitylation and proteasomal degradation (FIG. 1b).

Another canonical substrate of AKT is the FOXO family of transcription factors (FOXO1, FOXO3A, FOXO4), which upon phosphorylation are sequestered from the nucleus, thus preventing expression of their target genes[19,20] (FIG. 1b). Given the established FOXO gene expression programme, which includes numerous suppressors of growth, proliferation and survival, together with specific metabolic enzymes, the AKT-mediated inhibition of FOXO has been implicated in various aspects of cancer development and progression[21].

Control of glucose metabolism

Altered glucose metabolism is perhaps the most common metabolic change distinguishing cancer cells from their cell of origin. This metabolic feature, characterized by an increased rate of glucose uptake and its glycolytic conversion to lactate even under oxygen-rich conditions, was originally described nearly 100 years ago, by Otto Warburg[22], and is referred to as aerobic glycolysis or the Warburg effect[23]. Glycolysis, in addition to producing ATP, provides metabolic intermediates as substrates for metabolic pathways that branch off of glycolysis and support biosynthetic processes for the production of proteins, lipids and nucleotides that are required for cell growth and proliferation. Under aerobic glycolysis, the predominant diversion of pyruvate to lactate, rather than its entry into the mitochondria for oxidation, also serves a key role in redox homeostasis by regenerating NAD^+. How the genetic events leading to cellular transformation and cancer promote the Warburg effect is still being elucidated. However, the PI3K–AKT pathway can control several aspects of this metabolic programme (FIG. 2).

AKT activation has been shown to be sufficient to promote aerobic glycolysis[24,25]. The expression of constitutively active AKT results in a growth factor-independent increase in glucose uptake and glycolytic rate[24–29]. This AKT-mediated induction of aerobic glycolysis can render cancer cells dependent on glucose for survival[25,29]. Multiple control points in glycolysis have been found to be regulated by PI3K–AKT signalling, which include both acute, post-translational modifications and more prolonged transcriptional effects on glucose transporters and glycolytic enzymes (FIGS 2,3).

Direct regulation of glucose uptake and glycolysis. Glucose is a primary carbon and energy source in all organisms. The controlled uptake of glucose into cells is mediated by the glucose transporter family (GLUTs)[30]. Among these, GLUT1 is ubiquitously expressed and is most frequently elevated in cancer[31], while GLUT4 is expressed mainly in insulin-responsive muscle and adipose tissue to function in plasma glucose clearance after food intake[32]. AKT promotes glucose uptake through both GLUT1 and GLUT4. Studies of insulin-stimulated glucose uptake found that AKT2 associates with vesicles containing GLUT4, where it induces trafficking of GLUT4 from these vesicles to the plasma membrane[32,33]. A major mechanism underlying this regulation is the AKT-mediated phosphorylation and inhibition of TBC1D4 (also known as AS160), a GAP for Rab GTPases that promote GLUT4 trafficking[34,35]. However, this mechanism appears to be specific to GLUT4 and thus is unlikely to play a major role in glucose uptake into cancer cells, which predominantly use GLUT1. Studies in both normal and transformed haematopoietic cells have demonstrated that the cytokine-stimulated translocation of GLUT1 to the plasma membrane is mediated through AKT activation[24,36,37]. Recent studies have implicated thioredoxin-interacting protein (TXNIP) as a direct AKT substrate in the regulation of both GLUT1 and GLUT4 trafficking[38] (FIG. 2). TXNIP promotes endocytosis of GLUT1 and inhibits glucose uptake[39,40]. AKT phosphorylates and inhibits TXNIP, resulting in a rapid increase in GLUT1 and GLUT4 at the plasma membrane and enhanced glucose uptake in various cell types (mouse embryonic fibroblasts and 3T3-L1 adipocytes) and in mouse tissues (skeletal muscle, white adipose tissue and liver)[38]. Regulation of TXNIP by oncogenic PI3K–AKT signalling has also been suggested to enhance aerobic glycolysis in non-small-cell lung cancer cell lines[41], but the significance of the AKT–TXNIP–GLUT1 axis in the widely observed increase in tumour glucose uptake in vivo remains to be determined[42].

In addition to glucose uptake, AKT controls key steps in glycolysis through the phosphorylation and activation of specific glycolytic enzymes (FIG. 2). Following its transport into cells, glucose becomes activated to enter metabolic pathways through the action of hexokinases that phosphorylate glucose to form glucose-6-phosphate, which cannot be transported out of the cell. AKT activation has been found to promote hexokinase 2 (HK2) activity, at least in part, by increasing its association with a voltage-dependent anion channel at the outer mitochondrial membrane[27,43]. This mechanism has been proposed to provide a rich source of mitochondria-derived ATP for rapid and sustained HK2-mediated glucose phosphorylation, and has also been found to promote cell survival by preserving mitochondrial integrity[44–46]. HK2 expression is elevated in many human cancers, including ovarian, colorectal, pancreatic and liver cancer, as well as glioblastoma, and its activity has been found to be critical for tumorigenesis and metastasis in various mouse models[47–50].

Redox homeostasis
Maintaining proper levels of cellular NAD(P)H and $NAD(P)^+$ for metabolic reduction and oxidation reactions, respectively.

HK2 has also been exploited as a metabolic liability in mouse tumour models displaying hyperactive AKT signalling, such as in PTEN-deficient prostate cancer, where HK2 deletion attenuates tumour growth[50–53]. HK2 and other hexokinases can be competitively inhibited by 2-deoxy-D-glucose, and HK2 has attracted much interest as a potential target for cancer treatment[54], although more specific and potent inhibitors will likely be needed.

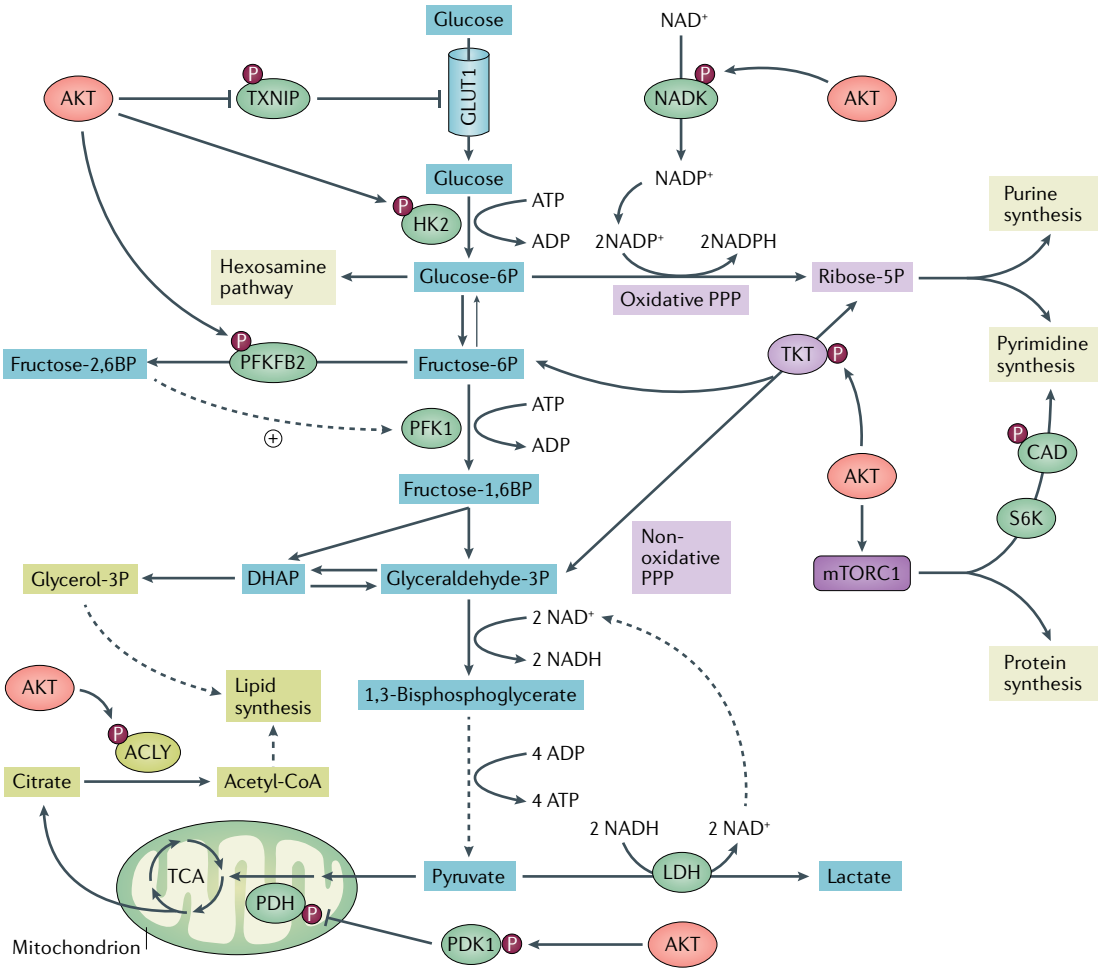


Fig. 2 | **Direct post-translational regulation of metabolic enzymes and processes downstream of the PI3K–AKT pathway.** AKT stimulates metabolic changes that contribute to anabolic metabolism by directly phosphorylating key metabolic enzymes. AKT promotes plasma membrane localization of glucose transporter 1 (GLUT1) and increased glucose uptake by directly phosphorylating and inhibiting thioredoxin-interacting protein (TXNIP), a protein that promotes the endocytosis of GLUT1. AKT signalling also promotes retention and metabolic activation of the newly acquired glucose by activating hexokinase 2 (HK2), which phosphorylates glucose in order to generate glucose-6-phosphate (glucose-6P), which cannot be transported out of the cell by GLUT1 and is the entry metabolite for the hexosamine pathway, the oxidative pentose phosphate pathway (PPP) and glycolysis. AKT enhances flux into glycolysis through the phosphorylation and activation of 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase (PFKFB2), which produces fructose-2,6-bisphosphate (fructose-2,6BP), an allosteric activator of the rate-limiting glycolytic enzyme phosphofructokinase 1 (PFK1), which commits the glucose-derived carbon to glycolysis. Both the oxidative and non-oxidative PPP, which branch off of glycolytic intermediates, generate ribose-5-phosphate (ribose-5P), which serves as the sugar moiety for purine and pyrimidine nucleotides. AKT phosphorylates and activates the non-oxidative PPP enzyme transketolase (TKT), thereby contributing to ribose-5-phosphate production for nucleotides. AKT also phosphorylates and increases the activity of nicotinamide adenine dinucleotide (NAD) kinase (NADK), which catalyses the phosphorylation of NAD^+ to generate $NADP^+$, a limiting substrate for the oxidative PPP, which generates two molecules of the reducing cofactor NADPH through its oxidation of glucose-6P. Downstream of AKT, mechanistic target of rapamycin complex 1 (mTORC1) activation acutely stimulates de novo pyrimidine synthesis through S6 kinase 1 (S6K)-dependent phosphorylation of the pyrimidine synthesis enzyme carbamoyl-phosphate synthetase 2, aspartate transcarbamylase and dihydroorotase (CAD). Pyruvate, the end product of glycolysis, is either converted to lactate by lactate dehydrogenase (LDH), which regenerates the NAD^+ needed for sustained glycolysis, or can enter the mitochondria and the tricarboxylic acid (TCA) cycle for oxidation initiated by the pyruvate dehydrogenase (PDH) complex, the activity of which can be inhibited by pyruvate dehydrogenase kinase (PDK1). AKT phosphorylates PDK1 and promotes its inhibition of PDH, thus favouring the LDH reaction (this phosphorylation is believed to occur within the mitochondria). AKT directly regulates lipid synthesis through the phosphorylation of ATP citrate lyase (ACLY), which generates acetyl-CoA in the cytosol from the TCA cycle-derived citrate. DHAP, dihydroxyacetone phosphate.

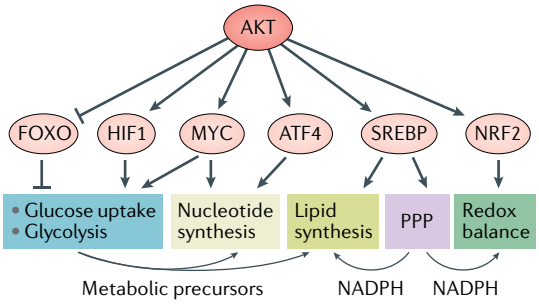


Fig. 3 | **Transcriptional control of metabolic processes downstream of AKT signalling.** AKT regulates metabolism through a number of downstream transcription factors that control the expression of genes encoding metabolic enzymes. Forkhead box O (FOXO), hypoxia-inducible factor 1 (HIF1) and MYC regulate the expression of glucose transporters and glycolytic enzymes, and intermediates of glycolysis contribute to both nucleotide and lipid synthesis. MYC and activating transcription factor 4 (ATF4) induce the expression of enzymes that contribute to nucleotide synthesis. Sterol regulatory element-binding protein (SREBP) isoforms globally induce the expression of lipogenic enzymes as well as enzymes in the oxidative pentose phosphate pathway (PPP), which can provide reduced nicotinamide adenine dinucleotide phosphate (NADPH) as a reducing equivalent for lipid synthesis and redox balance. Nuclear factor erythroid 2-related factor 2 (NRF2) regulates redox homeostasis.

The HK2 product, glucose-6-phosphate, can then enter one of three metabolic pathways: the hexosamine pathway, the pentose phosphate pathway or glycolysis.

AKT signalling indirectly stimulates the activity of phosphofructokinase 1 (PFK1), the first committed step of glycolysis. AKT phosphorylates and activates 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase (PFKFB2)[55], a key enzyme that catalyses the interconversion of fructose-6-phosphate and fructose-2,6-bisphosphate, with the latter metabolite serving as a potent allosteric activator of PFK1 (REF.[56]). The AKT-mediated phosphorylation of PFKFB2 increases its synthesis of fructose 2,6-bisphosphate, leading to enhanced PFK1-driven glycolytic flux (FIG. 2). AKT has also been found to activate the related isoform PFKFB3 through phosphorylation of a conserved residue that it also phosphorylates in PFKFB2 (REF.[57]), but it is worth noting that the AKT site on PFKFB3 lacks a critical sequence feature found in other established AKT substrates[58]. Fructose-2,6-bisphosphate levels have been reported to be markedly increased, compared to non-malignant cells, in mouse models of lung and mammary carcinomas, perhaps promoting high glycolytic flux[59,60]. However, the role of oncogenic AKT-mediated phosphorylation of PFKFB2 or PFKFB3 in the induction of aerobic glycolysis in various cancers remains to be elucidated.

PI3K signalling has also been found to potentiate glycolytic flux in an AKT-independent manner. Growth factor stimulation of PI3K induces a Rac-dependent release of the glycolytic enzyme aldolase A from an actin-bound, low-activity state to increase glycolytic flux[61]. High aldolase A expression in cancer is correlated with poor patient prognosis[62,63]. While the role of PI3K-stimulated aldolase A release from the actin cytoskeleton in tumorigenesis has yet to be established, studies have reported that targeting aldolase A in tumour xenograft models can attenuate tumour growth[64,65].

Transcriptional regulation of glucose uptake and glycolysis. In addition to acute regulation of glycolytic enzymes, the PI3K–AKT pathway also promotes sustained aerobic glycolysis through an increase in protein levels of glucose transporters and glycolytic enzymes mediated by the control of downstream transcription factors (FIG. 3). Hypoxia-inducible factor 1α (HIF1α), which is degraded in an oxygen-dependent manner and stabilized under conditions of hypoxia, induces the expression of GLUT1 and of nearly all the enzymes of glycolysis[66]. As part of the adaption to hypoxia, HIF1α also activates the expression of lactate dehydrogenase 1 (LDH1) and pyruvate dehydrogenase kinase 1 (PDK1), which together function to channel pyruvate to lactate and away from its oxidation into acetyl-CoA for entry into the mitochondrial tricarboxylic acid (TCA) cycle.

AKT has also been proposed to phosphorylate and increase the activity of PDK1 during hypoxia, thus further facilitating a switch towards glycolysis to support cancer cell proliferation under these conditions[67] (FIG. 2). However, it is unknown how activated AKT in the cytosol gains access to PDK1 in the mitochondria and whether AKT exerts this direct regulation of PDK1 in response to oncogenic PI3K signalling. Importantly, several studies have shown that the activation of mTORC1 downstream of AKT signalling in cell and tumour models, including prostate cancer, leads to an increase in HIF1α protein levels, expression of gene targets, and increased glucose uptake and glycolytic conversion to lactate, even under normal oxygen concentrations (that is, normoxia)[68–71]. HIF1α remains unstable under such conditions, but its protein levels increase due to enhanced mTORC1-regulated translation of the *HIF1A* mRNA[68,72,73]. It is worth noting that hypoxia is a much stronger inducer of HIF1α, and the PI3K–mTOR pathway is not involved in this oxygen-mediated regulation of HIF1α protein stability. The importance of HIF1α as a downstream effector of AKT signalling in cancer development and progression is unclear, and one study showed this transcription factor to be dispensable for AKT-driven tumour growth in a hepatoma xenograft model[74]. However, the normoxic upregulation of the HIF1α programme downstream of PI3K–mTOR signalling is likely to contribute to the induction of aerobic glycolysis in cancer cells and may provide metabolic flexibility in growing tumours that facilitates regional adaptation to nutrient and oxygen fluctuations.

The transcription factor MYC induces expression of numerous genes that promote cell growth and proliferation, and is one of the most frequently altered oncogenes in human cancers[75]. MYC induces expression of the major glucose transporters and most glycolytic enzymes and can drive aerobic glycolysis[75]. In contrast to HIF1α, MYC activation does not appear to lead to preferential directing of glycolysis-derived pyruvate towards lactate and away from mitochondrial respiration. Instead, many MYC gene targets function to enhance mitochondrial

Metabolic flexibility
The ability of a cell to adapt its metabolism in response to changing environmental conditions, such as nutrient and energy availability.

metabolism[75]. MYC activity is generally dictated by its abundance, and it is increased downstream of PI3K–AKT signalling through a combination of transcriptional, translational, and post-translational mechanisms[75]. For example, mTORC1 signalling enhances the translation of MYC[76,77], while AKT promotes MYC stabilization by inhibiting GSK3, which phosphorylates MYC and targets it for proteasomal degradation[78–80]. The FOXO transcription factors have been found to suppress the expression of glycolytic genes in some settings through an antagonistic effect on MYC function[81–84]. Activation of AKT relieves the inhibitory effects of FOXO transcription factors on glycolytic enzymes and MYC, thereby further enhancing glycolysis[83]. However, it is important to note that MYC activation downstream of the PI3K–AKT pathway is likely to be context-dependent in cancer. For instance, PI3K inhibitors have failed to reduce MYC levels in various cancer models, including colorectal cancer, acute myeloid leukaemia, and multiple myeloma, likely due to dominant regulatory inputs from the RAS–ERK pathway to MYC that are active in many cancer settings[85–87]. Thus, the vast metabolic programme downstream of MYC should not be universally equated to PI3K–AKT signalling.

This collective work demonstrates the central role that the PI3K–AKT pathway plays in promoting glucose uptake and glycolysis, both under physiological conditions and in cancer. In the setting of oncogenic PI3K–AKT signalling, these combined regulatory mechanisms are likely to drive the constitutive induction of aerobic glycolysis. This common feature of cancer cells facilitates metabolic flux into pathways that branch off of glycolysis and contribute to the synthesis of cellular macromolecules[23], and these biosynthetic processes are also further controlled downstream of AKT. While mitochondrial metabolism through the TCA cycle has also emerged as a process supporting the energetic and biosynthetic demands of proliferating cancer cells[88,89], defined functions of the PI3K–AKT pathway in direct control of the TCA cycle have not been established. It is possible that under conditions of aerobic glycolysis, the PI3K–AKT pathway might promote anaplerotic metabolism to sustain TCA cycle flux — for instance, by promoting glutaminolysis via MYC activation[77,90].

Anaplerotic metabolism
Metabolic reactions that replenish tricarboxylic acid (TCA) cycle intermediates used for biosynthetic processes.

Glutaminolysis
The two-step removal of the amide and amine nitrogens from glutamine to produce the TCA cycle intermediate α-ketoglutarate; these reactions can serve as one form of anaplerosis.

Anabolic processes
Metabolic processes and pathways that utilize nutrients and ATP to generate macromolecules such as proteins, lipids and nucleotides.

Control of anabolic metabolism

Proliferating cells need to double their protein, lipid and nucleotide content with each cell division. To meet this biosynthetic demand, cells stimulate anabolic processes to drive the production of these macromolecules. Here we discuss the roles of AKT, mTORC1 and MYC in inducing a PI3K-driven anabolic programme in cancer.

De novo lipid synthesis. Aberrant activation of lipid biosynthesis is a common feature of cancer cells[91]. While the majority of the cells in our body rely on the uptake of fatty acids and lipoproteins from the bloodstream to fulfil their lipid requirements, cancer cells activate de novo lipid biosynthesis to facilitate the generation of cellular membranes and support their increased growth and proliferation[92]. Both sterols and fatty acids are synthesized from cytosolic acetyl-CoA, which is produced from the TCA cycle intermediate citrate via ATP citrate lyase (ACLY) or from acetate via acetyl-CoA synthetase. The PI3K–AKT pathway induces de novo lipid synthesis through both post-translational and transcriptional mechanisms.

AKT can initiate de novo lipid synthesis by directly phosphorylating ACLY[93], thereby increasing its activity[94] and boosting the production of cytosolic acetyl-CoA to be used for sterol and fatty acid synthesis, as well as protein acetylation reactions (FIG. 2). The AKT–ACLY axis has been reported to promote tumour growth and to globally influence histone acetylation[95,96]. In addition to its oncogenic regulation through the PI3K–AKT pathway, ACLY is frequently overexpressed in various human cancers, and inhibition of ACLY diminishes cancer cell proliferation both in vitro and in vivo, making this enzyme a potentially attractive target for cancer therapy[97–99]. Owing to its key role in lipid biogenesis, inhibitors of ACLY, originally developed for metabolic disorders such as hypercholesterolaemia and type 2 diabetes[100,101], are being considered as potential anticancer drugs[102,103].

AKT signalling also promotes de novo lipid synthesis through activation of the sterol regulatory element-binding protein (SREBP) family of transcription factors (SREBP1a, SREBP1c and SREBP2), which induce the expression of nearly all enzymes of fatty acid and sterol synthesis, including ACLY[104,105]. The SREBPs exist as inactive endoplasmic reticulum (ER) transmembrane proteins that must traffic to the Golgi for proteolytic processing to be activated. SREBP processing releases the N-terminal portion of the protein that serves as the mature active form, which then translocates to the nucleus to initiate transcription at sterol response elements contained in the promoters of lipogenic genes and those involved in the NADPH production required to support lipid synthesis. AKT activates SREBP through at least two downstream branches. mTORC1 has been shown to stimulate the processing and nuclear translocation of SREBPs through several different proposed mechanisms, leading to the induction of lipogenic gene expression and an increase in de novo lipid synthesis in the liver in response to insulin or in cancer cells downstream of oncogenic PI3K or Ras[68,105–108]. Once processed, the mature active form of SREBP is targeted for ubiquitin-dependent degradation by GSK3-mediated phosphorylation[109,110]. Thus, AKT signalling can stimulate the processing of SREBP through mTORC1 activation and promote stability of the processed active SREBP by inhibiting GSK3. Recently, MYC was also reported to cooperate with SREBP to induce lipogenesis and promote cancer growth[111]. Interestingly, many of the mRNAs induced by SREBP are regulated by the serine/arginine-rich (SR) protein family of splicing factors. The splicing of these mRNAs encoding lipogenic enzymes has been found to be stimulated by mTORC1 signalling through its downstream target S6 kinase 1 (S6K), which phosphorylates and activates SR protein kinase 2 (SRPK2), leading to subsequent phosphorylation and activation of the SR proteins and enhanced splicing[112]. Many factors and enzymes involved in de novo lipid synthesis, including the SREBPs, SRPK2 and the lipogenic enzymes induced by the SREBPs, have been found to

be elevated in diverse cancer lineages, and these remain potential targets of interest for cancer therapy[91,108,113].

Nucleotide synthesis. Nucleotides, composed of purines and pyrimidines, are essential building blocks for the synthesis of nucleic acids (RNA and DNA), among other cellular functions[114]. In contrast to normal, quiescent cells, cancer cells stimulate robust de novo synthesis of nucleotides to accommodate the nucleic acid synthesis required for cell growth and proliferation[115,116]. The de novo nucleotide synthesis pathways require coordinated input from multiple metabolic pathways, including the pentose phosphate pathway (PPP) and the serine and glycine synthesis pathway (both of which branch off of glycolysis), aspartate synthesis from the TCA cycle intermediate oxaloacetate, one-carbon metabolism and glutamine uptake, to supply the ribose sugar and necessary atoms to form the corresponding pyrimidine and purine bases (FIG. 4a). Thus, it is not surprising that AKT signalling appears to regulate nucleotide synthesis through multiple parallel mechanisms that affect these metabolic inputs.

The PI3K–AKT–mTORC1 network promotes glucose carbon flux into both the oxidative and non-oxidative branches of the PPP, thus producing ribose for nucleotide synthesis. As an alternative to entering glycolysis, glucose-6-phosphate can enter the oxidative PPP through the action of glucose-6-phosphate dehydrogenase (G6PD) to be irreversibly oxidized to produce ribose-5-phosphate. Downstream of AKT signalling, mTORC1 activation enhances oxidative PPP flux, at least in part, via activation of SREBP and its transcriptional induction of G6PD expression[68]. AKT has also been found to directly activate transketolase (TKT), a key enzyme in the non-oxidative PPP[117] (FIGS 2,4b).

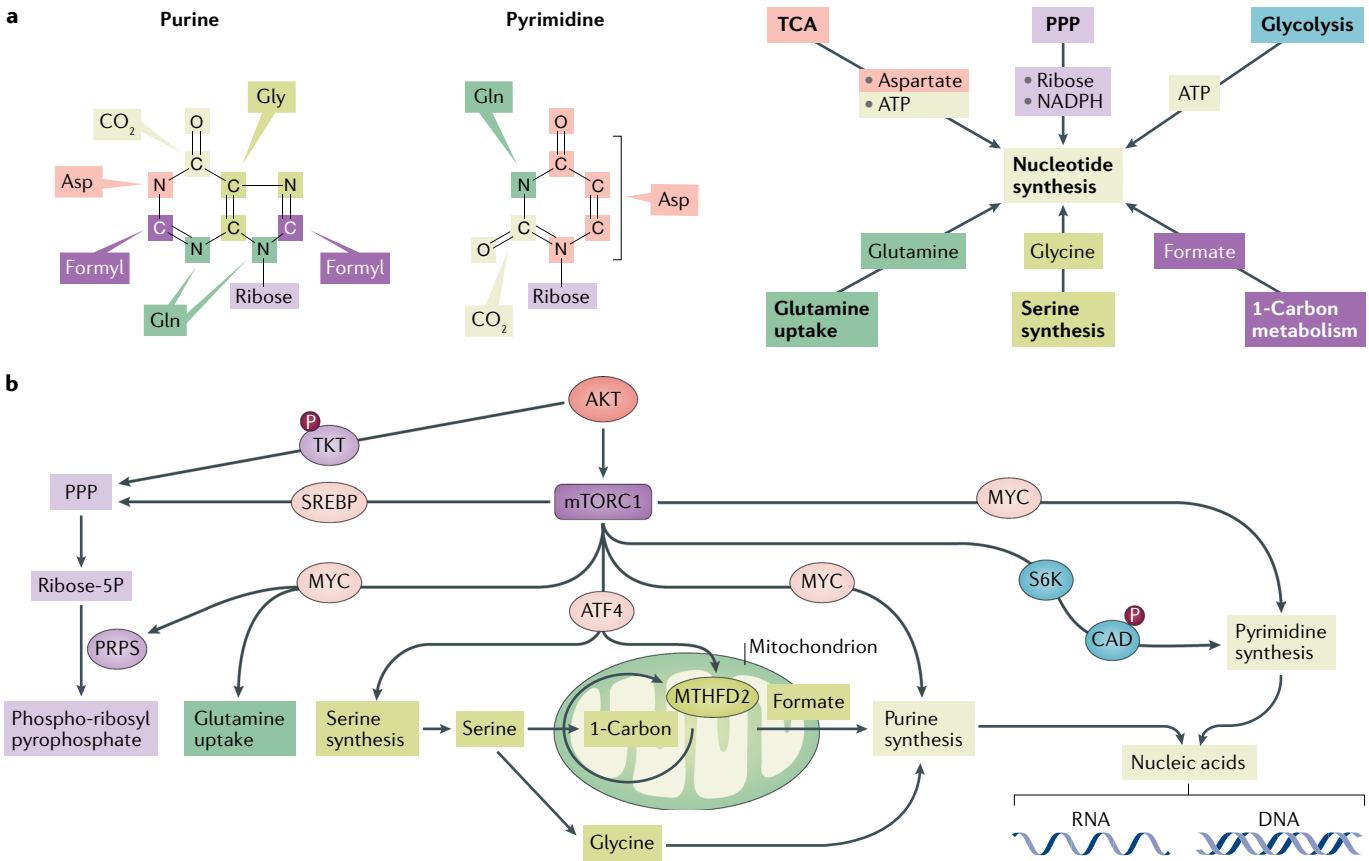


Fig. 4 | **Regulation of nucleotide metabolism downstream of the AKT–mTORC1 pathway. a** | Left to right: Schematic of purine and pyrimidine nucleotides, indicating the donors of the carbon and nitrogen atoms that form the nucleotides. The small molecules are colour coded according to the contributing metabolic pathways from which they are commonly derived, shown schematically on the right. **b** | Transcriptional and post-translational mechanisms contributing to de novo nucleotide synthesis downstream of the AKT–mTORC1 pathway. Left to right: AKT-mediated phosphorylation of the non-oxidative pentose phosphate pathway (PPP) enzyme transketolase (TKT) and sterol regulatory element binding protein (SREBP)-mediated regulation of the oxidative PPP enhance the production of ribose-5-phosphate (ribose-5P), which can then be used for nucleotide synthesis by conversion to phospho-ribosyl pyrophosphate through the enzyme phospho-ribosyl pyrophosphate synthase (PRPS), the levels of which are elevated upon MYC activation. MYC promotes glutamine uptake and stimulates the expression of several genes that encode enzymes of both the purine and pyrimidine synthesis pathways. In addition to being downstream of mechanistic target of rapamycin complex 1 (mTORC1), SREBP and MYC can also be stabilized via AKT-mediated inhibition of glycogen synthase kinase 3 (GSK3). Activating transcription factor 4 (ATF4) activation downstream of mTORC1 contributes to enhanced purine synthesis through the induction of serine biosynthesis enzymes and the mitochondrial tetrahydrofolate cycle enzyme methylenetetrahydrofolate dehydrogenase 2 (MTHFD2), thus supplying both glycine and one-carbon formyl units. mTORC1 acutely stimulates pyrimidine synthesis through S6 kinase 1 (S6K)-mediated phosphorylation of the pyrimidine synthesis enzyme carbamoyl-phosphate synthetase 2, aspartate transcarbamylase and dihydroorotase (CAD). The newly synthesized purines and pyrimidines are used for the synthesis of RNA, predominantly rRNA for ribosome biogenesis, and DNA in proliferating cells. NADPH, nicotinamide adenine dinucleotide phosphate (reduced).

Treatment of breast cancer cells with PI3K inhibitors was found to disproportionally reduce glucose flux through the non-oxidative PPP and result in nucleotide depletion and DNA damage[118], suggesting a higher dependence on the non-oxidative PPP in this setting. Enzymes in both branches of the PPP, including G6PD and TKT, are overexpressed in cancer, and their inhibition attenuates cell proliferation in various settings, including colorectal, breast, lung and liver cancer cells[119–121]. More research will be required in order to develop potent and selective inhibitors of key PPP enzymes and to identify the cancer contexts in which PPP inhibition is a vulnerability[122].

AKT exerts transcriptional control of nucleotide synthesis, in part, through its regulation of MYC. MYC drives the expression of an array of metabolic genes involved in supplying metabolite precursors for nucleotide synthesis, including glutamine, and directly induces the expression of many of the enzymes of the pyrimidine and purine synthesis pathways[123,124] (FIG. 4b). MYC controls both the transcription and translation of phosphoribosyl pyrophosphate (PRPP) synthase 2 (PRPS2), which catalyses the reaction that commits ribose-5-phosphate to nucleotide synthesis by producing PRPP, and PRPS2 has been found to be a critical effector of MYC-mediated tumorigenesis[125,126]. Glutamine serves as the major nitrogen source for the synthesis of both pyrimidine and purine bases, and MYC promotes glutamine uptake by inducing expression of the glutamine transporters SLC1A5 and large amino acid transporter 1 (LAT1), which is a heterodimer composed of SLC7A5 and SLC3A2 (REFS[90,127]) (FIG. 4b).

As a downstream effector of PI3K–AKT signalling, mTORC1 has also emerged as a major driver of de novo nucleotide synthesis, which it regulates through both post-translational and transcriptional mechanisms (FIGS 2,4b). Growth factor signalling to mTORC1 acutely stimulates pyrimidine synthesis through the S6K-mediated phosphorylation and activation of the first, and rate-limiting, enzyme in this pathway, carbamoyl-phosphate synthetase 2, aspartate transcarbamylase and dihydroorotase (CAD), which catalyses the first three steps of pyrimidine biosynthesis[128,129] (FIG. 4b). While this phosphorylation is not required for basal CAD activity, it is required for PI3K–AKT signalling to increase metabolic flux through this pathway and increase pyrimidine synthesis. With more delayed kinetics, mTORC1 signalling also induces de novo purine synthesis through transcriptional mechanisms involving MYC, SREBP and ATF4, which stimulate the expression of specific metabolic enzymes in the purine synthesis pathway or in pathways that feed metabolites into purine synthesis[130]. For instance, mTORC1 was found to activate ATF4, in a manner distinct from ATF4's canonical activation as part of the integrated stress response, resulting in transcriptional induction of the enzymes catalysing serine synthesis and its conversion through the mitochondrial tetrahydrofolate (mTHF) cycle to formate, which provides one-carbon units essential for building the purine ring[130] (FIG. 4a,b).

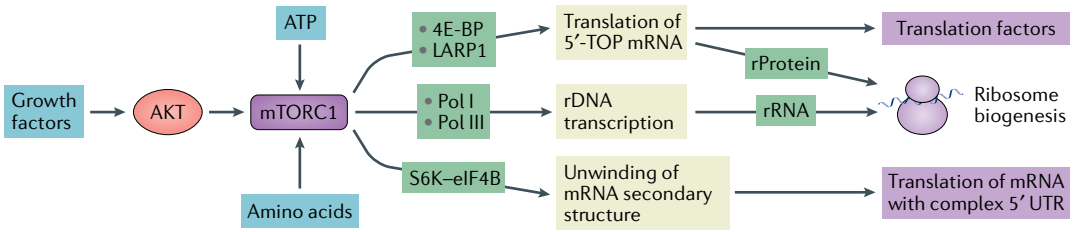
It is interesting to note that in growing cells, including cancer cells, there is a robust increase in ribosome biogenesis. Over half of the mass of the ribosome is rRNA, which constitutes more than 80% of total cellular RNA. Thus, ribosome biogenesis underlying cell growth places a substantial increased demand on the cell for more nucleotides to support rRNA synthesis. It is well established that mTORC1 and MYC serve as key drivers of ribosome biogenesis in both normal and cancer cells[131,132], thereby providing the logic for their parallel induction of nucleotide synthesis. Indeed, the newly synthesized pyrimidine and purine nucleotides produced in response to mTORC1 activation can be traced into rRNA[128,130].

Although inhibitors of the enzymes involved in nucleotide synthesis were the first chemotherapeutics introduced in the 1940s[133] and have become part of established cancer therapy regiments, the factors that dictate vulnerability to such inhibitors remain poorly understood. Because immune cells, like cancer cells, upregulate de novo nucleotide synthesis to support cell proliferation upon activation, several immunosuppressants that target nucleotide synthesis pathways have been developed for clinical use. The growth of cancer cells in vitro and tumour models in vivo with uncontrolled mTORC1 or MYC activation has been found to be very sensitive to inhibitors of the enzyme inosine monophosphate dehydrogenase (IMPDH), such as mizoribine, which is a widely used immunosuppressant in Asia[134,135]. Interestingly, IMPDH is required for the synthesis of guanylates, which are disproportionately represented in pre-rRNA (37%). Therefore, the process of rRNA synthesis more rapidly depletes guanylates in cells with active ribosome biogenesis, thereby depriving cells of nucleotides for DNA synthesis, resulting in replication stress and apoptosis in response to IMPDH inhibitors[134]. Thus, it is possible that such agents, despite their immunosuppressive effects, might be effective and selective antitumour agents in settings with strong increases in ribosome biogenesis, such as those with active mTORC1 or MYC. Interestingly, widely used chemotherapeutic agents that target nucleotide synthesis, including methotrexate and 6-mercatopurine, have been found to inhibit mTORC1 signalling through a mechanism involving the depletion of purine, but not pyrimidine, nucleotides[136,137]. Whether some of the anticancer effects of these agents are due to the inhibition of mTORC1 remains to be determined.

Protein synthesis. The growth programme of PI3K–AKT signalling involves a robust increase in protein synthesis, with much of this driven by mTORC1 activation. Such activation leads to an increase in the protein synthesis capacity of cells through multiple mechanisms[13] (BOX 1). As a complement to the control of translation by mTORC1, MYC transcriptionally induces the expression of multiple components of the protein synthesis machinery, including ribosomal proteins and translation initiation factors[132]. MYC can directly stimulate RNA polymerase I and III (Pol I and Pol III) to transcribe rDNA, and also promotes expression of the rRNA processing enzymes required to produce the mature forms that are assembled into ribosomes[132]. Interestingly, cancers with high MYC are characterized by elevated rates of protein synthesis and ribosome biogenesis, and the inhibition of protein synthesis has been

Box 1 | **Protein synthesis downstream of mTORC1**

Protein synthesis is a highly nutrient- and energy-costly process that is induced downstream of AKT signalling through mechanistic target of rapamycin complex 1 (mTORC1)[13]. Much of this regulation occurs through phosphorylation of its two best-established substrates, S6 kinase 1 (S6K) and eukaryotic translation initiation factor 4E (eIF4E)-binding protein (4E-BP). The mTORC1-mediated phosphorylation of 4E-BP triggers its release from eIF4E at the 5′ cap of mRNAs, allowing assembly of the translation initiation complex[189]. This regulation has been found to be particularly important for the translation of mRNAs that have 5′-terminal oligopyrimidine (5′-TOP) or 5′-TOP-like sequences at the 5′ end of their 5′ untranslated regions (UTRs), which encompass transcripts encoding the translation machinery, including ribosome proteins (rProteins) and translation factors[190,191] (see the figure). Oncogenic activation of mTORC1 is believed to enhance the rate of protein synthesis largely through the 4E-BP–eIF4E axis, to support cancer cell growth[138]. Phosphorylation of another mTORC1 substrate, La-related protein 1 (LARP1), has also been implicated in the selective induction of translation of 5′-TOP mRNAs downstream of mTORC1 (REFS[192–194]). In addition to mTORC1, both AKT and S6K have been reported to phosphorylate LARP1 and relieve its inhibitory effect on translation by dissociating it from 5′ UTRs[192]. A key target of S6K in the induction of translation is eIF4B, which upon phosphorylation forms an active heterodimer with the RNA helicase eIF4A, thereby enhancing the unwinding of 5′ UTRs with complex secondary structures[77,195,196]. Interestingly, translation of the *MYC* mRNA is particularly sensitive to the S6K-mediated phosphorylation of eIF4B[77]. Finally, mTORC1 signalling enhances rDNA transcription through both RNA polymerase I (Pol I) and RNA polymerase III (Pol III), thus producing the rRNA needed for assembly with newly translated ribosomal proteins (rProteins) into ribosomes[131].



shown to confer synthetic lethality in these cancers[138,139]. Future studies will be needed to increase our understanding of whether cancer cells with oncogenic PI3K signalling share this vulnerability.

PI3K–AKT and redox homeostasis

One consequence of the metabolic changes underlying cancer cell proliferation is an increase in the production of reactive oxygen species (ROS). Accumulating evidence suggests that moderate levels of ROS support cancer cell growth, proliferation and survival, whereas too much ROS is detrimental to the macromolecular constituents of the cell[140]. In addition to promoting anabolic metabolism and cell growth, the PI3K–AKT pathway also regulates multiple metabolic processes that modulate ROS levels.

Production of cellular reducing power. NADPH, a pyridine dinucleotide cofactor, is a key reservoir of electrons required for reductive biosynthesis and defence against oxidative stress (FIG. 5). Cancer cells upregulate NADPH-producing pathways to support an increased anabolic demand and to enhance their antioxidant capacity[122,141,142]. Recent studies have addressed the routes of consumption and production of NADPH using quantitative flux analysis[143–145]. These analyses have revealed that the majority of cytosolic NADPH is consumed by anabolic metabolism, and particularly by fatty acid synthesis[144] (FIG. 5). Indeed, de novo synthesis of a single molecule of one of the most abundant fatty acids in human plasma, palmitate, by the multifunctional enzyme fatty acid synthase (FASN) requires 14 molecules of NADPH. Ribonucleotide reductase (RNR) requires NADPH to catalyse the reduction of ribonucleotide 5′-diphosphates (NDPs) to deoxyribonucleotide diphosphates (dNDPs), which are subsequently converted to the dNTPs required for DNA replication[146]. Additionally, NADPH is required for the activity of dihydrofolate reductase to produce tetrahydrofolate for the reactions of one-carbon metabolism. NADPH is also required for synthesis of the amino acid proline, which has emerged as an important process for cancer cell growth and survival[147]. Several metabolic enzymes can reduce $NADP^+$ to replenish NADPH, the levels of which can be influenced by PI3K–AKT signalling (FIG. 5). The majority of the cytosolic NADPH pool is derived from reactions within the oxidative branch of PPP[145], which can be stimulated downstream of AKT signalling through the mTORC1–SREBP axis[68] (FIG. 5). SREBP also promotes the expression of malic enzyme 1 (ME1), which can contribute to the cytosolic NADPH pool[148]. Interestingly, both G6PD and ME1 expression are reciprocally repressed by the tumour suppressor p53, and their induction contributes to tumour growth in mouse models[149,150]. Finally, SREBP[151] and the FOXO transcription factors[152] have been found to control the expression of isocitrate dehydrogenase 1 (IDH1), another cytosolic enzyme that can produce NADPH. The relative importance of these three major sources of cytosolic NADPH to the oncogenic effects of PI3K–AKT signalling require further research.

The size of the cellular pool of $NADP^+$ and NADPH available for interconversion through reduction and oxidation (redox) reactions is determined, in part, by the activity of NAD kinase (NADK). NADK catalyses the phosphorylation of NAD^+ to produce $NADP^+$, which is the rate-limiting substrate for NADPH-producing enzymes. In response to growth factors, or in a growth factor-independent manner in cancer cells, AKT directly phosphorylates and acutely stimulates an increase in

Quantitative flux analysis
Measurement of the rate of consumption and production of metabolites in specific metabolic pathways, often achieved through the tracing of stable isotope-labelled nutrients and quantification via mass spectrometry.

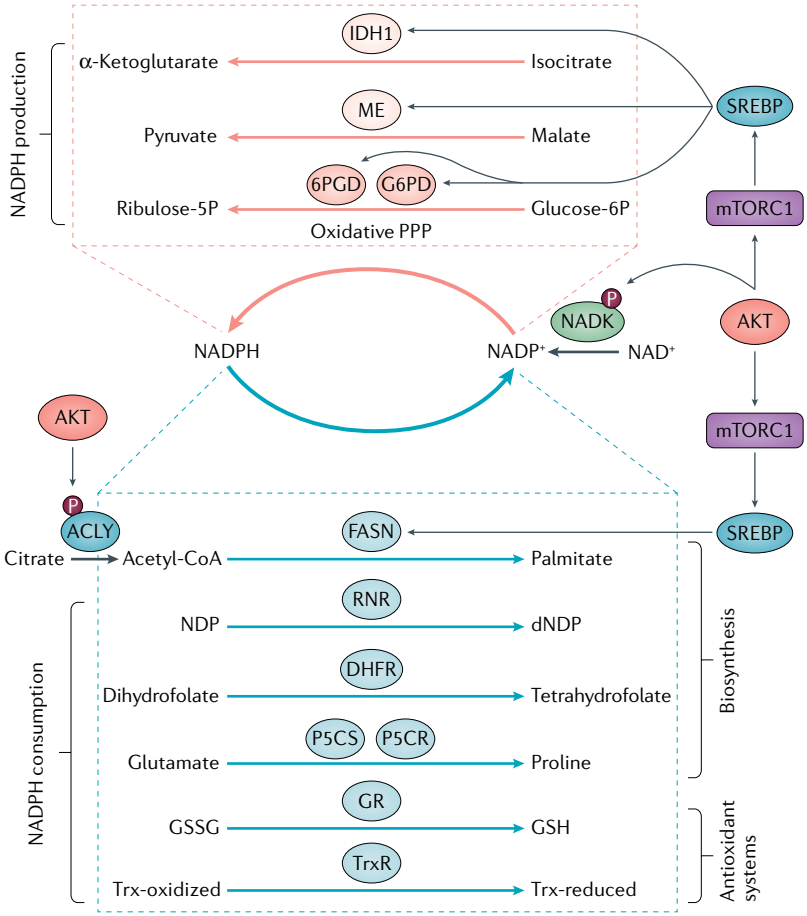


Fig. 5 | **AKT signalling and control of NADPH production and consumption.** Reduced nicotinamide adenine dinucleotide (NAD) phosphate (NADPH) serves as a major electron donor for reductive biosynthesis and defence against reactive oxygen species (ROS), which yields its oxidized form, $NADP^+$. In the cytosol, NADPH can be regenerated from $NADP^+$ through reactions involving two enzymes of the oxidative pentose phosphate pathway (PPP; glucose-6-phosphate (glucose-6P) dehydrogenase (G6PD) and 6-phosphogluconate dehydrogenase (6PGD)), isocitrate dehydrogenase 1 (IDH1) and malic enzyme (ME). Downstream of AKT and mechanistic target of rapamycin complex 1 (mTORC1), sterol regulatory element binding protein (SREBP) induces expression of these enzymes to enhance NADPH production. AKT-mediated phosphorylation of NAD kinase (NADK) serves to boost $NADP^+$ abundance and to further enhance the production of NADPH through these redox reactions. Many cellular reactions consume NADPH as the reducing power. NADPH is required for key reactions in the biosynthesis of macromolecules, including fatty acid synthase (FASN) to produce palmitate, ribonucleotide reductase (RNR) to convert ribonucleotide diphosphates (NDPs) into deoxyribonucleotide diphosphates (dNDPs), dihydrofolate reductase (DHFR) for tetrahydrofolate synthesis, and the proline synthesis enzymes pyrroline-5-carboxylate synthase (P5CS) and pyrroline-5-carboxylate reductase (P5CR). NADPH also serves as the essential reducing power for antioxidant enzymes including glutathione reductase (GR), which reduces the oxidized glutathione disulfide (GSSG) to glutathione (GSH), and thioredoxin (Trx) reductase (TrxR), which transfers electrons from NADPH to reduce Trx for subsequent reduction of oxidized cysteines. ACLY, ATP citrate lyase.

NADK activity, resulting in increased production of $NADP^+$ and, subsequently, NADPH[153] (FIGS 2,5). The AKT-mediated phosphorylation of NADK facilitates the anchorage-independent growth of cancer cells[153]. This finding might help explain the key role of PI3K signalling in the survival of cells detached from the extracellular matrix, which requires a robust antioxidant response[154]. The stimulated increase in NADK activity is also likely to serve as a key part of the broader anabolic programme induced by the PI3K–AKT pathway, providing reducing cofactors in high demand for the biosynthetic processes underlying cell growth. Loss of NADK attenuates tumour growth in xenograft models[155,156], and an activating mutation in NADK, identified in pancreatic ductal adenocarcinoma, was found to increase tumour growth in a xenograft model[155]. Future research will be needed to define the role of NADK as a downstream target of AKT signalling in cancer development and progression and whether this enzyme is a viable metabolic target for cancer therapies.

Oxidative stress response. Activation of the PI3K–AKT pathway stimulates both ROS-producing and ROS-scavenging mechanisms that vary between cellular settings. For instance, in neutrophils and macrophages, activation of PI3K–AKT signalling stimulates ROS production through regulation of the p47phox component of the NADPH oxidase NOX, thereby generating the respiratory burst required to eliminate extracellular and phagocytosed pathogens[157,158]. In addition, AKT directly phosphorylates and activates endothelial nitric oxide (NO) synthase (eNOS), another NADPH oxidase, which produces NO in endothelial cells to control vascular tone, but can also generate ROS[159,160]. However, whether these or other specialized mechanisms downstream of PI3K–AKT signalling contribute to ROS production within cancer cells is unknown. Instead, most of the evidence to date supports an antioxidant role for PI3K–AKT signalling in cancer.

Elevated ROS, including superoxide (O_2^-) and hydrogen peroxide (H_2O_2), can oxidize and damage lipids, proteins and nucleic acids and have detrimental consequences on cell growth and survival[140]. Cells have multiple enzymes and systems to neutralize ROS, including superoxide dismutase (SOD), which converts O_2^- to H_2O_2; catalase, which reduces H_2O_2 into water; and the peroxiredoxin (Prx)/thioredoxin (Trx) and glutathione peroxidase (GPx)/glutathione (GSH) antioxidant systems, which utilize NADPH to reduce H_2O_2 into water and repair macromolecules oxidized by exposure to ROS[140]. It is interesting to note that the FOXO transcription factors, which are negatively regulated by AKT, can also function to detoxify ROS through the induction of several ROS-scavenging systems[161–163]. However, more research will be necessary to understand the significance of the PI3K–AKT–FOXO circuit in redox control in the context of cancer.

Consistent with PI3K signalling playing an important role in the cellular response to ROS, an increase in ROS levels can activate the pathway through various mechanisms. H_2O_2 can influence cell signalling events by oxidizing cysteine residues on proteins, including the catalytic cysteine of protein and lipid phosphatases. These ROS-sensitive phosphatases include negative regulators of PI3K signalling, such as protein tyrosine phosphatase 1B, protein phosphatase 2A and PTEN[164–166], the inhibitory oxidation of which can activate AKT in response to a rise in H_2O_2 (REFS[165,167]) (FIG. 6). Thus, together with downstream mechanisms to mitigate ROS levels, the PI3K–AKT pathway can serve as part of an adaptive oxidative stress response pathway.

As we described above, AKT signalling increases the cellular reducing power (NADPH) available for antioxidant responses (FIG. 5). However, the PI3K–AKT pathway also contributes to ROS detoxification through sustained activation of nuclear factor erythroid 2-related factor 2 (NRF2), a transcription factor that controls the expression of numerous genes involved in the antioxidant response, including enzymes involved in glutathione synthesis and function, the thioredoxin system, NADPH regeneration and ROS detoxification[168]. NRF2 is a cellular sensor of both oxidative stress and growth factor signalling through mechanisms that control its protein stability. NRF2 is targeted for rapid proteasome-mediated degradation through two distinct E3 ubiquitin ligases, Kelch-like ECH-associated protein 1 (KEAP1) and β-transducin repeat-containing protein (β-TrCP) (FIG. 6). Oxidative stress directly inhibits the binding of KEAP1 to NRF2, leading to increased abundance of NRF2 (REFS[169,170]). Activation of the PI3K pathway also results in the stabilization and activation of NRF2. AKT inhibits GSK3, which directly phosphorylates NRF2 and targets it for degradation by β-TrCP[171] (FIG. 6). In addition, AKT has been proposed to phosphorylate and stabilize p21$^{Cip1/WAF1}$, allowing it to compete with KEAP1 for NRF2 binding, thus leading to NRF2 stabilization and activation of antioxidant gene targets[172,173].

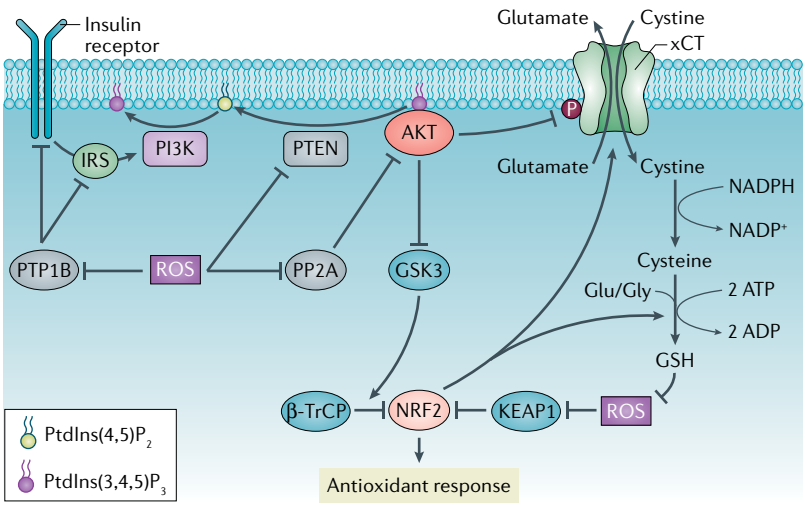


Fig. 6 | **Interplay between ROS and the PI3K–AKT pathway.** Reactive oxygen species (ROS) in the form of hydrogen peroxide can activate the phosphoinositide 3 kinase (PI3K)–AKT pathway through the inactivation of protein phosphatases, including protein tyrosine phosphatase 1B (PTP1B), which attenuates the activity of insulin receptor and insulin receptor substrate (IRS), and protein phosphatase 2A (PP2A), which normally dephosphorylates T308 on AKT, thus leading to enhanced AKT phosphorylation and activation in response to ROS. ROS also inhibit the phosphatase and tensin homologue (PTEN) lipid phosphatase, resulting in the accumulation of phosphatidylinositol 3,4,5-trisphosphate (PtdIns(3,4,5)P_3) and the activation of AKT. AKT activation can facilitate adaptation to ROS by activating the nuclear factor erythroid 2-related factor 2 (NRF2) transcription factor, which stimulates numerous enzymes to mount an antioxidant response. Downstream of AKT, glycogen synthase kinase 3 (GSK3) phosphorylates NRF2 and marks it for ubiquitylation by the β-transducin repeat-containing protein (β-TrCP) E3 ligase, leading to subsequent proteasomal degradation. Thus, through its inhibition of GSK3, AKT signalling can stabilize NRF2. NRF2 is stabilized and activated by ROS via cysteine oxidation of the E3 ligase Kelch-like ECH-associated protein 1 (KEAP1), thereby disrupting its binding of NRF2. AKT also directly phosphorylates and inhibits the cystine–glutamate antiporter xCT, which transports cystine into cells that, upon nicotinamide adenine dinucleotide phosphate (reduced) (NADPH)-dependent reduction of the cystine to cysteine, can be used to produce glutathione (GSH) for ROS neutralization. xCT and the enzymes of GSH synthesis are encoded by gene targets of NRF2 as part of its antioxidant response. $NADP^+$, nicotinamide adenine dinucleotide phosphate.

Accumulating evidence indicates that NRF2 confers an advantage for aggressive cancer cell survival and proliferation by upregulating metabolic and antioxidant pathways[174]. Recently, the PI3K–AKT–NRF2 axis was reported to contribute to both anabolic metabolism and ROS detoxification through control of the metabolic genes involved in NADPH regeneration[175]. Activation of AKT signalling through loss of PTEN induces NRF2 target genes to support proliferation and tumorigenesis[175,176]. Moreover, oncogenic activation of the PI3K–AKT pathway in breast cancer induces an NRF2-dependent transcriptional programme, which enhances glutathione biosynthesis to support tumour growth and confer resistance to oxidative stress[177]. Interestingly, inhibition of glutathione biosynthesis was found to synergize with the chemotherapeutic agent cisplatin and to induce tumour regression in PI3K-driven breast cancer models[177], suggesting that the antioxidant response downstream of PI3K–AKT signalling represents a targetable metabolic vulnerability.

NRF2 also enhances glutathione synthesis through transcriptional induction of the cystine–glutamate antiporter xCT (or SLC7A11)[178], which imports cystine molecules (oxidized dimers of cysteine) that are subsequently reduced to cysteine, an essential substrate for glutathione synthesis. Paradoxically, xCT function has been shown to be attenuated downstream of growth factor-stimulated and oncogenic PI3K signalling[179,180]. AKT was found to directly phosphorylate xCT and to decrease its cystine transport activity[179], thereby rendering cells with oncogenic PI3K signalling dependent on endogenous cysteine synthesis (FIG. 6). Since cystine reduction to cysteine requires NADPH[181], acute inhibition of xCT by AKT could serve to preserve NADPH for use in lipid synthesis downstream of AKT-mediated activation of ACLY. Inhibition of the xCT antiporter could also serve to spare glutamate and glutamine nitrogen to be used for nitrogen-dependent synthesis of amino acids and nucleotides. Perturbations in the balance between the antioxidant and biosynthetic activities of cancer cells imposed by oncogenic PI3K–AKT signalling is a particularly interesting and active area of investigation, with potential to reveal new therapeutic approaches.

Clinical perspective

The PI3K–AKT pathway has emerged as one of the most frequently activated drivers of human cancer, making it a prime candidate for therapeutic intervention. Specific inhibitors targeting both PI3K and AKT have been developed as cancer therapies, with most trials demonstrating limited therapeutic benefit of these drugs as single agents[182]. Due to the critical role of PI3K–AKT signalling in insulin-responsive glucose uptake into tissues, such as skeletal muscle, pan-PI3K inhibitors inevitably cause hyperglycaemia, with the consequent hyperinsulinaemia being shown to overcome pathway inhibition and reactivate PI3K signalling in tumours[183]. Dietary interventions, such as a ketogenic diet, have been found to alleviate this hyperglycaemia and hyperinsulinaemia

and improve responses to these inhibitors in mouse cancer models[183]. Furthermore, resistance to PI3K inhibitors can arise due to redundant regulation of key downstream effectors such as mTORC1 (REF.[184]). Importantly, patient stratification for oncogenic *PIK3CA* mutations, which are found in approximately 40% of ER$^+$, HER2$^-$ breast cancers, together with the use of a p110α-selective PI3K inhibitor (BYL719, trade named Piqray) yielded improved clinical responses when used in combination with an oestrogen receptor antagonist[185]. Preclinical and clinical studies continue to focus on understanding the tumour response to PI3K inhibitors and to identify both combination therapies and unique vulnerabilities arising from uncontrolled PI3K signalling in distinct cancer settings. As we discussed above for nucleotide synthesis, pharmacological targeting of specific metabolic enzymes and pathways induced downstream of PI3K–AKT signalling in cancer may offer effective therapeutic alternatives to PI3K inhibitors for cancer treatment.

Conclusion

Research in the past two decades has defined how aberrant activation of the PI3K signalling pathway drives tumorigenesis, at least in part, through the control of metabolism. Future research aimed at refining our molecular map of the critical regulatory nodes connecting the oncogenic PI3K signalling network to the metabolic networks in different cancers will help reveal metabolic dependencies and novel therapeutic strategies. One example of this is the finding that PI3K inhibitors can deplete intracellular nucleotide pools and cause DNA replication stress, which when combined with inhibitors of poly(ADP-ribose) polymerase (PARP), an enzyme involved in DNA repair, increases the anticancer efficacy of PI3K inhibitors in tumour models and in a subset of cancer patients[118,186–188]. Metabolic enzymes are inherently druggable and offer a wealth of new targets to which specific pharmacological inhibitors can be developed, as new metabolic outcomes and vulnerabilities are identified. Finally, while we have focused here on the cancer cell-intrinsic regulation of metabolism, it is clear that the physiological features of the tissue of origin for a given tumour, the stromal cell milieu, the nutritional and metabolic status of the host and the distinct metabolic niches of sites of distant metastases will all differentially influence cancer cell metabolism and metabolic dependencies as they relate to cancers with oncogenic PI3K–AKT signalling.

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