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Targeting cancer-specific metabolic pathways for developing novel cancer therapeutics

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Cancer is a heterogeneous disease characterized by various genetic and phenotypic aberrations. Cancer cells undergo genetic modifications that promote their proliferation, survival, and dissemination as the disease progresses. The unabated proliferation of cancer cells incurs an enormous energy demand that is supplied by metabolic reprogramming. Cancer cells undergo metabolic alterations to provide for increased energy and metabolite requirement; these alterations also help drive the tumor progression. Dysregulation in glucose uptake and increased lactate production *via* "aerobic glycolysis" were described more than 100 years ago, and since then, the metabolic signature of various cancers has been extensively studied. However, the extensive research in this field has failed to translate into significant therapeutic intervention, except for treating childhood-ALL with amino acid metabolism inhibitor L-asparaginase. Despite the growing understanding of novel metabolic alterations in tumors, the therapeutic targeting of these tumor-specific dysregulations has largely been ineffective in clinical trials. This chapter discusses the major pathways involved in the metabolism of glucose, amino acids, and lipids and highlights the inter-twined nature of metabolic aberrations that promote tumorigenesis in different types of cancer. Finally, we summarise the therapeutic interventions which can be used as a combinational therapy to target metabolic dysregulations that are unique or common in blood, breast, colorectal, lung, and prostate cancer.

KEYWORDS

cancer, cancer metabolism, metabolic reprogramming, cancer microenvironment, targeted therapy

Introduction

Cancer is a multifactorial disease and one of the leading causes of death globally. According to the World Health Organization (WHO), cancer was responsible for approximately 10 million deaths in 2020 (1). Disruption in normal cellular functions is a feature of all cancer cells (2). Dysregulated cellular metabolism is one of the important hallmarks, and cancer cells alter their metabolism to overcome the cancer-associated cellular stress, thereby leading to "metabolic reprogramming" (3, 4). Metabolic reprogramming refers to the alteration in catabolic, anabolic, and redox pathways of the cells supported by the tumor microenvironment. Otto Warburg first described metabolic alteration in cancer cells; while normal cells convert glucose to pyruvate in the presence of oxygen (aerobic glycolysis) and redirect the pyruvate towards the tricarboxylic acid (TCA) cycle (5), cancer cells abnormally preferred to convert glucose to lactate irrespective of oxygen availability (6). Under normal circumstances, the pathway intermediates from glycolysis are used in different anabolic pathways; glyceraldehyde-3-phosphate is redirected towards fatty acid synthesis, while glucose-6-phosphate and fructose-6-phosphate are used for nucleotide biosynthesis through oxidative Pentose phosphate pathway (PPP) and non-oxidative PPP, respectively (7). Such anabolic pathways are activated only in nutrient-rich conditions. However, a metabolic shift occurs in the nutrient-deprived state, wherein the cells activate different catabolic pathways that can supply the required glycolytic and TCA cycle intermediates for energy production (Figure 1) (8).

The amino acid metabolic pathway is the major contributor to these intermediates. Additionally, cancer cells also show upregulation of lipogenesis and harness fatty acid oxidation to meet the energy requirements during nutrient-deprived conditions. These metabolic changes vary during different stages of cancer progression, from tumor initiation to metastasis. Pavlova et al. have discussed the six hallmarks of cancer metabolism, typical to all types of cancers (10).

The metabolic shift from TCA cycle mediated energy generation to glucose fermentation allows cancer cells to accumulate mutations in the involved enzymes. Some of these enzymes also function as tumor suppressors and their loss of function mutations can drive tumor progression as in the case of Isocitrate dehydrogenase (IDH) 1 and 2 (11), Fumarate hydratase (FH) (12), and succinate dehydrogenase (SDH) (13).

Due to the high metabolic activity, cancer cells produce copious amounts of reactive oxygen species (ROS) (14). Low levels of ROS can promote cellular proliferation, whereas high ROS levels can damage DNA and activate apoptotic pathways (15). Cancer cells circumvent these deleterious effects of high ROS by upregulating the synthesis of various ROS scavenging proteins and NADPH (7).

Further metabolomic studies in cancer have revealed that cancer cell metabolism is heterogeneous and may vary depending on the site and origin of cancer (3). One such instance is the diverse effect of MYC on glutamine metabolism, wherein MYC induces glutamine synthesis in liver cancer but drives glutamine catabolism in lung cancer (16). The metabolic interactions between the cancer cells and tumor microenvironment (TME) introduces further intricacies in the role of these alterations (17). The symbiotic relationship between the cancer cells and various component of the TME creates a hospitable niche for tumor progression which suppresses the immune system and promotes survival and metastasis of cancer cells. Furthermore, availability of new positron emission tomography (PET) probes will enable

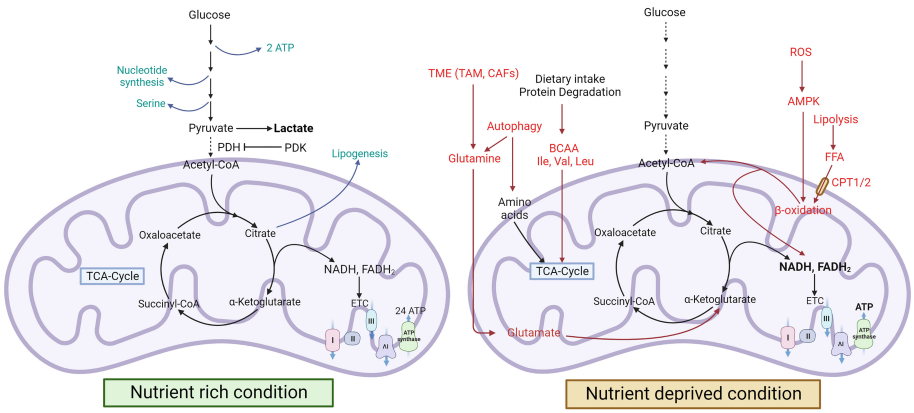

FIGURE 1
Cancer metabolism during nutrient-rich and stressed conditions. In nutrient-rich conditions, cancer cells use glucose to produce lactate, serine, and nucleotides, but in nutrient-deprived conditions, they induce FAO and autophagy for energy production (8, 9). Green colour indicates a nutrient-rich condition, and the red colour indicates a nutrient-deprived condition [FA, ,Fatty acid; Ile, Isoleucine; Val, Valine; Leu, Leucine; mTOR, Mammalian target of rapamycin].

characterisation of tumors on the basis of their active metabolic state, opening new possibilities of precision therapy (3). This chapter discusses the different metabolic signatures associated with various cancer types and how they may be targeted therapeutically.

Alterations in glucose metabolism

Glucose is the primary source for ATP production and synthesis of various macromolecules. Under physiological conditions, glucose is catabolized into pyruvate *via* the Embden-Meyerhof pathway, producing ATP and NADH (18). The fate of pyruvate is further dependent on oxygen availability, wherein aerobic (oxygen-rich) conditions facilitate the conversion of pyruvate into acetyl-CoA by pyruvate dehydrogenase (PDH). In contrast, anaerobic conditions (lack of oxygen) facilitate production of lactate from pyruvate by lactate dehydrogenase (LDH). In normal cells, acetyl-CoA enters the mitochondria and partakes in the tricarboxylic acid (TCA) cycle, also known as the citric acid cycle, to generate NADPH, FADH2, and GTP. These reducing equivalents (NADH and FADH2) enter the electron transport chain (ETC) to produce ATP with the help of ATP synthase through oxidative phosphorylation (OXPHOS). However, this metabolic pathway is altered in cancer cells to aid in cancer progression. The rapidly dividing cancer cells circumvent the time-consuming route of energy generation *via* the TCA cycle and instead undergo aerobic glycolysis even under an oxygen-rich state (6). The increased lactate production even under normoxic conditions, often dubbed as Warburg effect or aerobic glycolysis, is a common feature of all types of cancers, including brain, breast, lung, colorectal, hepatocellular, gastric, bladder, and blood cancer (19–25), with the exception of prostate cancer, wherein aerobic glycolysis is observed only in the later stages of tumor progression (26–28). By limiting energy generation *via* TCA cycle, cancer cells control their high ROS levels, thereby limiting oxidative stress induced apoptosis (29).

NADPH and FADH2 produced in the TCA cycle are used to produce adenosine triphosphate (ATP) through oxidative phosphorylation (OXPHOS) in the electron transport chain under physiological conditions. However, cancer cells exhibit dysregulation of OXPHOS, perhaps to further reduce the oxidative stress. In breast cancer (BC), gastric cancer (GC), hepatocellular carcinoma (HCC), and non-small cell lung carcinoma (NSCLC), various mutations have been reported in the mitochondrial DNA, which codes for 13 subunits involved in the ETC. Furthermore, Hepatitis C virus (HCV) infection and dysregulation of mitochondrial microRNAs downregulate the expression of OXPHOS-associated proteins in HCC (30). In the HCV-induced HCC mice model, upregulation of stem cell homeobox transcription factor NANOG suppresses OXPHOS to promote self-renewal and drug resistance (31). Ras-like GTPase, Rab3A, and TGF-β have also been reported to downregulate OXPHOS and induce migration and invasion in HCC (31–33). However, recent studies have shown that some cancer cells also rely on mitochondrial respiration. For instance, high expression of mitochondrial biogenesis gene, Peroxisome proliferator-activated receptor-gamma coactivator-1α (PGC-1α), promotes aerobic respiration in invasive circulating breast cancer cells (34). Intriguingly, differentiating enterocytes also show increased expression of PGC-1α as they migrate from the intestinal crypts towards the surface (35). However, unlike other tissue types wherein increased expression of PGC-1α also upregulates antioxidant genes like superoxide dismutase 2 (SOD2) and catalase (CAT) to cope with the ROS burden coupled with mitochondrial respiration, PGC-1α does not induce the expression of antioxidant genes in intestinal cells which results in ROS-induced apoptosis, thereby maintains the intestinal tissue homeostasis (35). Colorectal cancer (CRC) cells predominantly express PGC-1β, which can induce the expression of antioxidant genes, thereby maintain low ROS levels and normal glycolytic pathway, resulting in prolonged lifespan and accumulation of these cells (36). Similarly, several other cancer types maintain their dependence on OXPHOS and show increased mitochondrial content, such as in leukaemia, and prostate cancer (37, 38).

Lactate dehydrogenase (LDH) is overexpressed in cancer cells and promotes the conversion of pyruvate into lactate (39). Overexpression of lactate transporters, monocarboxylate transporter (MCT) 1 and 4 is a common feature of cancer cells that allows efflux of high amounts of lactate produced by oxygen-deprived cells. The normoxic cancer cells uptake this lactate from the microenvironment owing to their high expressions of MCT1 and utilise it for energy production *via* the TCA cycle (40).

In colorectal cancer (CRC) cells, an increase in aerobic glycolysis and downregulation of the TCA cycle can be attributed to the reduction in mitochondrial import of pyruvate due to low expression of mitochondrial pyruvate carrier 1 (MPC1) (41). Furthermore, in CRC and bladder cancer, the mitochondrial pyruvate fails to undergo the TCA cycle due to the inhibition of pyruvate dehydrogenase (PDH) by the overexpressed pyruvate dehydrogenase kinase 4 (PDK4) (42–44). On the other hand, energy generation without the involvement of the TCA cycle allows cancer cells to utilise the TCA cycle components for proliferation and invasion (45). A study of human lung biopsies using stable isotope resolved metabolomics (SIRM) revealed changes in glycolysis and mitochondrial function in non-small cell lung cancer (NSCLC), wherein cancer cells showed higher levels of TCA cycle intermediates than the surrounding normal tissue cells (46). In HCC, downregulation of PDK4 promotes the conversion of pyruvate into acetyl-CoA by PDH (47). Enhanced production of oxaloacetate from pyruvate due to overexpression of pyruvate carboxylase is reported in LC cells,

which results in increased production of downstream TCA cycle intermediates (48). Many of the TCA cycle moonlighting enzymes, such as Isocitrate dehydrogenase (IDH) 1 and 2, succinate dehydrogenase (SDH), and fumarate hydratase (FH), which function as tumor suppressors under physiological conditions, have a loss of function mutations in cancer cells. For instance, IDH1 and IDH2 convert isocitrate to α-ketoglutarate and 2-hydroxyglutarate, an inhibitor of histone demethylase and ten-eleven translocation (TET) proteins. In NSCLC, mutations in IDH1 and IDH2 result in various tumor-promoting epigenetic alterations (11).

Prostate cells pose another intriguing exception, where the TCA cycle is inhibited under the physiological condition to produce high amounts of citrate as a component of semen (49). The accumulation of citrate is attributed to high zinc concentration in the prostate cells, which inhibits the enzyme m-Aconitase required to convert citrate to isocitrate in the first step of the TCA cycle (49). Also, zinc acts as an anti-tumor/pro-apoptotic regulator by inducing the release of cytochrome-c from mitochondria (50, 51). This high zinc concentration is maintained by the upregulation of an ion channel called zinc or iron-regulated transporter like-protein 1 (ZIP1) in prostate cells (52). However, prostate cancer (PC) cells have atypical low zinc and citrate levels. In PC cell lines DU-145 and LNCaP, ZIP 1 channel is downregulated due to hypermethylation of its promoter at the binding site of transcription factor AP-1 (53). The resulting low zinc concentration allows completion of the TCA cycle by oxidising the citrate, increasing the energy output from 14 ATPs to 24 ATPs per glucose molecule. Therefore, unlike other cancers, the Warburg effect is not observed in the initial stages of PC.

Anaerobic glycolysis produces approximately 16-fold less energy per glucose molecule than its aerobic counterpart. To make up for this inefficiency, cancer cells have 15 times higher glycolytic flux than normal cells to meet their energy requirements (6, 24). The increased glucose demand is met by the upregulation of glucose transporters, such as GLUT2 in gastric and hepatocellular cancer and GLUT1 and GLUT3 in other cancer types (39). Upregulation of GLUT1 activity in CRC cells is attributed to dysregulation of RAS/MAPK pathway due to KRAS mutation (54). Similarly, CD147 upregulates GLUT1 in hepatocellular carcinoma (55). Furthermore, upregulation of hexokinase (HK) in cancer cells ensures retention of glucose by converting it into membrane impermeable glucose-6-phosphate (G6P) (39). Other key regulatory enzymes of the glycolytic pathway, such as phosphofructokinase (PFK), which converts G6P to fructose-6-phosphate (F6P), and pyruvate kinase (PK), which converts phosphoenolpyruvate to pyruvate are upregulated in cancer cells resulting in high glycolytic turnover (39, 56). Downregulation/deletion of sirtuin 6 (SIRT6), a known repressor of tumor driver MYC is associated with adenoma formation and increased glycolysis during all stages of colorectal adenomas (57, 58).

The increased glycolytic turnover is coupled with upregulation of the Pentose phosphate pathway (PPP) in many cancers. PPP provides pentose phosphate required for nucleic acid synthesis and NADPH needed for fatty acid synthesis and survival (59). Glucose-6-phosphate dehydrogenase (G6PD), which converts G6P to 6-phosphogluconate (6-PG), is the key regulatory enzyme for PPP and is upregulated in most cancers. Mammalian target of rapamycin 1 (mTORC1) and p21 activated kinase 4 (PAK4) modulates transcriptional and post-transcriptional regulation of G6PD and enhances Mdm2-mediated p53 ubiquitination and degradation. Furthermore, mutations in P53 and overexpression of Polo-like kinase 1 (Plk1) promote the dimerization and activation of G6PD in cancer cells. TP53-inducible glycolysis and apoptosis (TIGAR), which regulates the flux of glycolysis intermediates into PPP in normal injured tissue, is upregulated in CRC cells regardless of their P53 status and associated with the formation of adenomas (60). Similarly, the downstream PPP enzyme, 6-phosphogluconate hydrogenase (6-PGD), which converts 6-PG into ribulose-5-phosphate (Ru5P), is also upregulated in breast, lung, ovarian and blood cancers. Accumulation of PPP intermediates ribose-5-phosphate (R5P) and xylulose-5-phosphate is observed in various cancer types, particularly in HER2 positive BC. However, HCC is an exception where low levels of Ru5P and R5P are observed despite the upregulation of PPP enzymes (61, 62).

Molecular basis of glucose metabolic reprogramming

The metabolic state of the cell dictates its fate and functions. Under physiological conditions, the cellular metabolism is tightly regulated by various growth factors, which signal the cells to uptake nutrients from the extracellular space. But cancer cells carry oncogenic mutations that render their signal transduction independent of growth factor-mediated stimulation.

PI3K/AKT/mTOR pathway is one of the prominent signaling pathways which contributes to the import of nutrients to the cell. PI3K/AKT/mTOR pathway is among the commonly dysregulated pathway and is actively involved in the regulation of cancer cell survival, proliferation, growth and metabolism (63). Tumor suppressor PTEN antagonizes this signaling pathway by dephosphorylating PIP3 which leads to inhibition of downstream proteins phosphoinositide-dependent protein kinase (PDK1), AKT1 and mTOR. In normal cells, activation of PI3K/AKT/mTOR pathway induces glycolytic flux upon stimulation by growth factors like insulin. This is frequently altered (mutation in components of PI3K complex or by hyperactivation of RTKs) in cancer cells leading to a dysregulation of glucose metabolism (64–66). Loss of PTEN is observed in glioblastoma, melanoma, endometrial and prostate cancer. This results in activation of the downstream target proteins of PI3K signaling pathway inducing expression of

glycolytic enzymes like HK2, PFK1, and glucose transporter GLUT1 (67, 68). HK2 prevents release of apoptotic protein, cytochrome-c, by interacting with the mitochondrial pore to enable cell survival. Furthermore, AKT itself activates FOXO3a which promotes mitochondrial biogenesis (69, 70).

Oncogenes involved in these pathways are responsible for regulating the expression of glycolytic enzymes (71). HIF and c-Myc particularly, coordinate to promote glycolysis *via* activation of several glycolytic enzymes like hexokinase II (HK2), phosphopfructokinase I (PFK1), glyceraldehyde-3-phosphate dehydrogenase, enolase 1, pyruvate kinase, and LDH-A, and are known as master inducers of glycolysis (71–74). In normal cells, c-Myc is induced by growth factor stimulation, however, in cancer cells, it is aberrantly activated by gene mutations (single nucleotide polymorphism, chromosomal translocation) and induces energy production and anabolic processes even in absence of growth factor stimulation. To accomplish this, c-Myc induces expression of key glycolytic enzymes; it also increases the ratio of pyruvate kinase M2 (PK-M2) to pyruvate kinase M1 (PK-M1) by indirectly modulating exon splicing, thereby enforcing a shift toward lactic acid production, a prominent marker of cancer progression (75). c-Myc also induces NADPH production which further supports cancer proliferation (76).

Expression of hypoxia inducing factor-1 α (HIF-1α) is upregulated by PI3K and RAS/RAF/MEK/ERK kinase cascade (77–80). HIF-1α is stabilized by CREB binding protein (CBP)/p300 through ERK-mediated phosphorylation and also by ROS generated from ETC complex II and III (81–84). It induces the less efficient mode of glycolysis i.e., aerobic glycolysis, and also upregulates GLUT1 and GLUT3 expression resulting in uptake of glucose from the environment thereby increasing the rate of glycolysis in cancer cells (72, 85). It also upregulates PDK1 and LDH-A to prevent glucose flux into the TCA cycle thereby inhibiting OXPHOS and making pyruvate available for conversion into lactate by LDH-A (86, 87). Wnt signalling also acts as a driver of cellular proliferation in CRC by modulating the expression of PDK and inhibiting TCA cycle (88, 89). It is also a known driver for the upregulation of MCT1 in CRC (90). In tumor cells, elevated levels of c-Myc and HIF-1α, coupled with loss-of-function mutations in P53 leads to uncontrolled cell division, inhibition of apoptosis and cancer progression. P53, in normal cells, suppresses Warburg effect by decreasing glycolysis through repression of HK2 and glucose transporter (GLUT1, GLUT3) expression (91, 92). However, in cancer, P53 not only loses its function but it gains an oncogenic function (mutp53) which can inhibit AMPK and upregulate glucose transporters, GLUT1, GLUT3, and GLUT4, to proliferate under energy deficient conditions (93, 94). HIF-1α and HIF-2α are overexpressed in many types of cancers. In BC and high-grade bladder cancer, HIF-1α upregulates the expression of 6-phosphofructokinase/fructose-2,6-bisphosphatase (PFKB) 3 and 4, and controls the overall glycolysis rate by modulating the activity of phosphofructokinase 1 (PFK1) (95). This highlights the centrality of HIF-1α and c-Myc in the metabolic landscape of the tumor cells and their progression. c-Myc also plays a key role in glutamine metabolism and is responsible for glutamine addiction in cancer cells (Figure 2).

Dysregulations in amino acid metabolism

Amino acid metabolism is closely intertwined with the glycolytic pathway, where the amino acid pools can generate various components of the TCA cycle *via* anaplerotic pathways, along with other metabolites such as glucose, lipids, and precursors of purines and pyrimidines (98). Cancer cells utilize their amino acid pools during glucose deprivation to meet their energy requirements. Glutamine is the primary amino acid crucial for cancer proliferation and provides carbon and nitrogen that supports biosynthesis and cellular homeostasis in cancer cells (98). Cancer cells maintain high pools of glutamine by upregulating the expression of glutamine transporters, such as Alanine/Serine/Cysteine/Threonine Transporter 2 (ASCT2; SLC1A5) in PC and SLC7A5 in HC. Furthermore, glutamine synthetase (GS) that converts glutamate to glutamine is overexpressed in HCC and acts as a diagnostic biomarker which is correlated with more aggressive disease (99). Chronic hepatitis B (CHB) also leads to HCC and high expression of GS is also observed in CHB stage 1-4 (100). Glutamine synthase produced by glial cells also converts ammonia to glutamine in glioblastoma tissues thus providing an alternate source of glutamine (101). Glutamine depletion *via* shRNA-mediated silencing of ASCT2 inhibits tumor formation (102) and is a candidate for targeting amino acid dependence in cancer cells. In many cancers, including BC, LC, CRC, PC, GBM, HCC, GC, and leukaemia, Glutamine is used to produce glutamate by the process of glutaminolysis, which is later converted into TCA component α-KG by glutamate dehydrogenase (GDH) (62, 98, 103–107).

The upregulation of glutaminolysis in cancer cells can be attributed to increased activity of glutaminase 1 (GLS1) enzyme. Overexpression of TGF-β increases the levels of GLS1 in HCC (32) and in T-cell acute lymphoblastic leukaemia (T-ALL), increased glutaminolysis induces NOTCH1 signaling, promoting growth and survival of cancer cells (6, 107). N-methyl D-aspartate-associated protein 1a (GRINA), a glutamate receptor in GC cells, modulates aerobic glycolysis and is also involved in lipid and sterol synthesis, which ultimately promotes tumor progression (108, 109). A higher glutamine level further activates mTORC1, which helps in protein translation and nucleic acid biosynthesis required for cell growth and proliferation (110). On the other hand, amino acid deprivation in tumor cells promotes autophagy and cell survival *via* the mTOR pathway (111). In glutamine-deprived

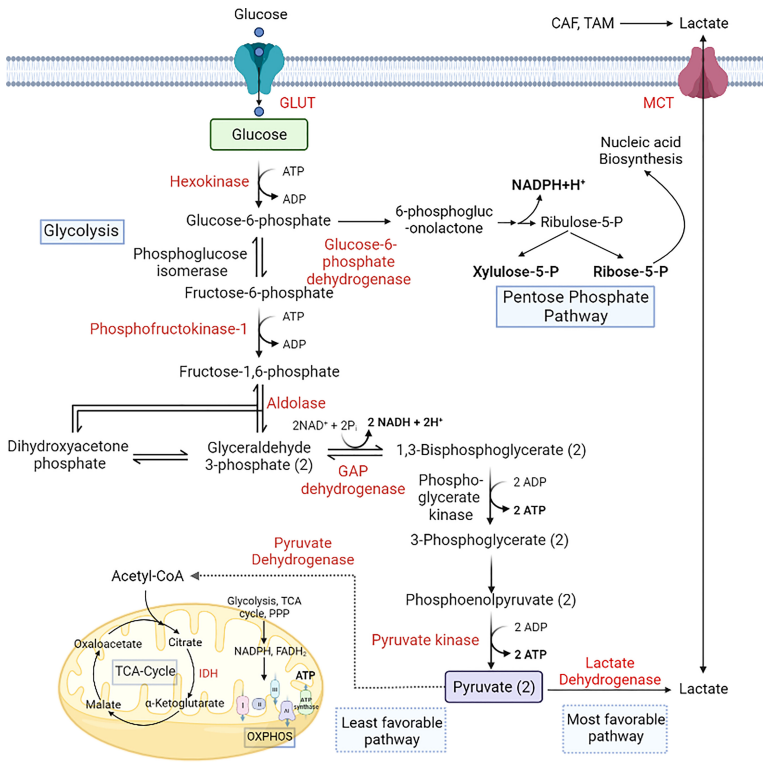

FIGURE 2
Alterations in glucose metabolism during cancer progression. Cancer cells utilize glucose as a primary energy source. GLUT overexpression helps the cells to uptake more glucose from the microenvironment, which is converted to lactate-by-lactate dehydrogenase. Lactate produced by the cells is secreted into the microenvironment *via* the upregulation of MCT1. PPP is also upregulated in cancer cells to produce NADPH and pentose phosphate for nucleic acid synthesis (18, 96, 97). [GLUT, Glucose transporter; IDH, Isocitrate dehydrogenase; MCT, Monocarboxylate transporter; OXPHOS, Oxidative phosphorylation].

conditions, upregulation of KRAS and asparagine synthetase (ASNS) induces asparagine synthesis from aspartate, thereby increasing the growth and proliferation of CRC (112). Asparagine can serve as an antiporter for the influx of other amino acids and induces the mTOR pathway during amino acid deprivation (113). Leukaemia and HCC have low levels of ASNS leading to asparagine deficiency, which rationalised the use of L-asparaginase, which converts asparagine into aspartate as an adjunct therapy (114, 115). Karpet-Massler et al. identified that L-asparaginase derived from E. coli decreases the cell growth in glioblastoma (116). However, as reviewed by Jiang et al., asparagine depletion further reduces the transcription of ASNS in a feedforward manner *via* p53 activation in tumor cells, warranting further studies on the role of p53 mutations in determining the efficacy of L-asparaginase therapy (113).

Serine and glycine are also noteworthy as they provide essential precursors for synthesising proteins, nucleic acids, and fats required by the cancer cells (117). In LC, upregulation of Na^+-dependent transporter, ASCT1 leads to increased serine uptake (98). Serine acts as a precursor for nonessential amino acids, glycine, and cysteine. It is also involved in the production of sphingolipids and supplies carbon to the one-carbon pool required for folate metabolism. The folate-methionine route is responsible for a variety of processes involving volatile carbons, such as the interconversion of serine and glycine and the creation of thymidine. Tetrahydrofolate, generated from folic acid, is a flexible carbon donor that can transport a range of one-carbon functional groups, such as methyl, methylene, and formyl groups. This property makes it a versatile cofactor in biosynthetic pathways. S-adenosylmethionine, a derivative of methionine, serves as another methyl donor. This metabolic route establishes a strong functional link between cellular metabolism and epigenetic regulation, which is essential for DNA methylation. The growth of glioma cells is restricted in the absence of methionine (118). Methylation by histone methyltransferase (HMT) and DNA methyltransferase (DNMT) is associated with poor prognosis in CRC. Puccini et al. reported overexpression of S-adenosylmethionine in all stages of CRC, which acts as a co-substrate for HMT and DNMT (119). Upregulation of the serine-glycine biosynthetic pathway due to overexpression of phosphoserine aminotransferase 1 (PSAT1) is associated with higher tumor proliferation and

poorer prognosis in CRC and BC (120, 121). Furthermore, downregulation of ζ isotype of protein kinase C (PKCζ) expression promotes the serine biosynthesis *via* increased activity of enzymes phosphoglycerate dehydrogenase (PHGDH) and PSAT1, leading to higher intestinal tumorigenesis. In addition, low expression of PKCζ in intestinal tumors correlates with poorer prognosis (122).

Similarly, arginine is a semi-essential amino acid therapeutically relevant in PC, HCC, and leukaemia, owing to the arginine auxotrophy of cancer cells. This dependency is due to the downregulation of key enzymes involved in arginine synthesis, such as arginosuccinate synthetase 1 (ASS1), ornithine transcarbamylase (OTC) and carbamoyl-phosphate synthetase 1 (CPS1) (114, 123, 124), which catalyses the conversion of citrulline to arginine *via* the ornithine cycle in normal cells. Arginine depletion using arginase (125) or pegylated arginine deiminase (126) induces cytotoxicity in prostate cancer cell lines. Arginine depletion also increases the efficacy of drugs such as docetaxel to treat prostate cancer (127).

Moreover, large neutral amino acid transporter 1 (LAT1 or SLC7A5), the primary transporter of branched-chain amino acids (BCAAs) that are not synthesised in the body, is also overexpressed in lung cancer, glioblastoma and the blast phase of chronic myeloid leukaemia (98), providing the nutrients necessary for tumor growth (101). Furthermore, the upregulation of branched-chain aminotransferase 1 (BCAT1) expression by H3K9 demethylation drives cancer progression by increasing the synthesis of branched-chain amino acids like valine, leucine, and isoleucine (128) and increases ROS scavengers and imparts chemoresistance against tyrosine kinase inhibitors (129). High cysteine levels increase the proliferation and chemoresistance in CML cells by maintaining cellular redox balance (114, 130). In CRC cells, upregulation of cystathionine-β-synthase (CBS) promotes proliferation (by upregulating glycolysis, PPP, and lipogenesis), invasion, and anoikis resistance by catalysing the condensation of homocysteine and cysteine to produce hydrogen sulphide (131). The CRC-specific biomarker CD110 also has an essential role in lysine catabolism and activates the Wnt signaling pathway by upregulating acetylated low-density lipoprotein receptor related-protein 6 (LRP6) and glutathione (132, 133). Tryptophan is an essential amino acid which is used by the immune cells, and tryptophan level decreased in the TME due to higher expression of indoleamine 2,3-dioxygenase 1 (IDO1). Lack of tryptophan leads to T-cell apoptosis or inhibit immune cell proliferation *via* downregulating mTOR signaling pathway and activating nonderepressible 2 (GCN2) (134, 135). GCN2 not only downregulate protein synthesis and T cell proliferation it can also induce differentiation of naïve T cells to T regulatory cells which ultimately create an immunosuppressive microenvironment (136). BC patients, particularly TNBC, show upregulation of tryptophan pathway metabolite Kynurenine, which promotes cancer progression by creating an immunosuppressive microenvironment (137, 138) (Figure 3).

Amino acid metabolism and autophagy

The inhibition of mTORC1 under nutrient-deprived conditions allows the cells to undergo autophagy, wherein macromolecules are recycled *via* autophagosome mediated lysosomal degradation (139). The Amino acid sensor proteins play a major role in regulation of mTORC1 activity which further modulates cellular metabolism, growth and survival (140). Rag GTPase is a regulator of mTOR that is controlled by different amino acid sensor proteins. Sestrin is the first identified amino acid sensor (response to cytosolic leucine levels) that regulates Rag GTPase, hence downregulating mTORC1 activity (141). Since, macropinocytosis is inhibited by mTORC1, sestrin-mediated inhibition of mTORC1 leads to increased import of extracellular macromolecules and therefore, increases survival of cells under low-nutrient conditions (142). Leucyl-tRNA synthetase (LARS) is an intracellular leucine sensor which interacts with Rag GTPase and activates mTORC1 activity (143). SLC38A9, a lysosomal transmembrane protein, which acts as an intra-lysosomal amino acid sensor for leucine, glutamine, tyrosine, and phenylalanine, also activates mTOR by Rag-GTPase (144–146). CASTOR 1/2, a GATOR2 binding protein, inhibits mTORC1 activity by forming homo- or hetero-dimer upon sensing arginine (147). s-adenosyl methionine (SAM), upon methionine sensing, induces S-adenosylmethionine sensor for the mTORC1 (SAMTOR) and GATOR1 dimerization leading to downregulation of mTORC1 (148). Intracellular amino acid-activated mTORC1 itself regulates amino acid availability and also phosphorylates S6 kinase 1 (S6K1) and eukaryotic translation initiation factor 4E binding protein 1 (4EBP1) which ultimately increase translation of metabolic enzymes and transcription factors (149).

Thus, the dysregulated amino acid metabolism and the amino acid auxotrophy in several cancer cells can be exploited for therapeutic purpose.

Alterations in lipid metabolism

Lipid metabolism is instrumental for synthesising structural and functional lipids and generating energy during nutrient deficiency. Cancer cells generate fatty acids (FA) by lipogenesis during nutrient-rich conditions and use these stores as an alternate energy source during nutrient deprivation (150, 151). Fatty acid, cholesterol and lipids are primarily obtained from dietary intake, and *de-novo* synthesis of these molecules are restricted to the liver and adipocytes. However, the cancer cells have cholesterol *de-novo* synthesis, making them independent of

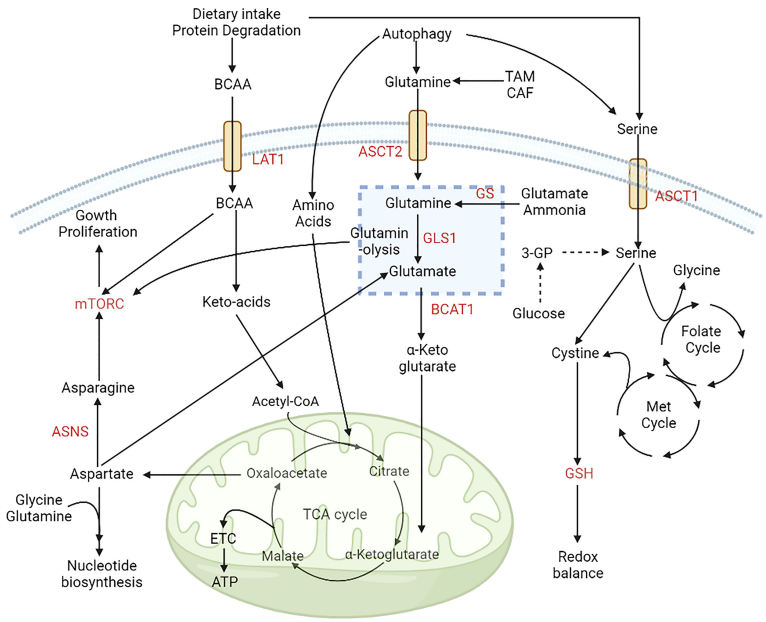

FIGURE 3
Alterations in amino acid metabolism during cancer progression. Amino acids are used by cancer cells as a source of carbon and nitrogen. The expression of ASCT2 increases glutamine uptake, and it is converted to glutamate *via* glutaminase and provides a TCA-cycle intermediate for energy production. Intake of BCAAs is also upregulated by the expression of LAT1. The folate methionine cycle is fuelled by serine, which helps maintain redox balance in the microenvironment. These alterations aid the growth and proliferation of cancer cells *via* upregulation of the mTOR signaling pathway (98). [LAT1, Large amino acid transporter 1; ASCT2, Alanine serine cysteine transporter 2; BCAA, Branch chain amino acids; BCAT1, Branch chain aminotransferase 1; ASNS, Asparagine synthetase; ETC, Electron transport chain; GSH, Glutathione; Met, Methionine; 3PG, Glyceraldehyde 3 phosphate].

extrinsic sources. In CRC, the expression of FASN increases in later stages (stage III, IV> stage I), which upregulates lipogenesis, mitochondrial respiration, and FA oxidation (152). For this, high amounts of FA are generated by the upregulation of one carbon metabolism resulting in increased proliferation of cancer cells (153).

Lipid metabolism is controlled by different oncogenes and tumor suppressors such as EGFR, PI3K, MAPK, Myc, and P53 (154, 155). 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR), a key regulatory enzyme in cholesterol biosynthesis (mevalonate pathway), is also upregulated in BC, GC, and HCC (156, 157). Enzymes involved in mevalonate pathway are upregulated in BC leading to the malignant transformation of benign epithelium (158–160). HMGCR is also responsible for the upregulation of Hedgehog signaling pathway - which plays a key role in tumor growth and proliferation - in GC (161). Additionally, HMGCR and not HIF, was observed to modulate YAP activation leading to chemoresistance in HCC under hypoxic conditions (158). Sterol regulatory element binding protein (SREBP) is a transcription factor which regulates genes involved in lipid synthesis. It has two variants: sterol regulatory element binding protein (SREBP1) which helps in lipid and fatty acid synthesis and energy generation, and sterol regulatory element binding protein 2 (SREBP2) which helps in cholesterol regulation (162). SREBP1 is the master regulator of fatty acid synthesis and controls the expression of FASN; both are regulated by PI3K-AKT and MAPK pathway (163, 164). SREBP1 is upregulated in PC, HCC and glioblastoma. Normally, SREBP1 activity depends on the intracellular cholesterol level; under high cholesterol conditions, SREBP1 remains attached to the endoplasmic reticulum (ER), but when intracellular cholesterol is low, SREBP1 is translocated to the Golgi apparatus and is activated. Activated SREBP1 upregulates lipogenic enzymes under the control of PI3K/AKT/mTOR signaling (156, 157, 165, 166). Brain is a cholesterol rich organ and consists of 20-25% of total body cholesterol, all of which is synthesised *de novo* by the astrocytes (167, 168). This characteristic is utilised by GBM cells where upregulation of lipogenesis due to high SREBP1 expression promotes their survival under hypoxic and lipid-deprived conditions and is associated with poor prognosis (169). Furthermore, dysregulated cholesterol synthesis in GBM cells also leads to high cholesterol availability for the invasive cells (89, 170). This dependence on lipid synthesis by SREBP1 for cellular growth in GBM is demonstrated by silencing sterol o-acyltransferase 1 (SOAT1)

which converts ER cholesterol to cholesterol esters leading to inhibition of SREBP1 activation and therefore suppressed growth (166).

Fatty acids are the primary source of energy production for glioblastoma cells, and their ability to cross the blood-brain barrier is an advantage for invasive cancer cells (171). In hypoxic conditions, glioblastoma cancer stem cells increase their FA uptake *via* upregulation of fatty acid transporter CD36 (172). Grube et al. and Lancaster et al. identified that inhibition of FA synthesis or β-oxidation decreases glioblastoma and neural stem cell proliferation and can be a target for treatment (173, 174).

Fatty acid synthase (FASN), the key regulatory enzyme of lipogenesis, and acetyl-CoA carboxylase (ACC), are upregulated in many cancer types. Expression of FASN is also controlled by Sp/KLF family transcription factor (in prostate cancer), p53 and lipogenesis related nuclear protein SPOT14 (175–177). Post-translational regulation of FASN is observed in prostate cancer by the isopeptidase, ubiquitin-specific protease-2a (USP2a), which removes ubiquitin from FASN preventing its degradation (178). FASN and ACCα expression are regulated at the translational level by PI3K-mTOR signaling pathway in HER2 overexpressing breast cancer cells (BT-474, SK-BR-3) (179). In lung adenocarcinoma, it was observed that ACC expression is regulated by LKB1-AMPK pathway (140). ACCα expression is induced by IGF-1 in colon cancer cells, but it is suppressed by ERK1/2 dependent signalling pathway (180). Stearoyl-CoA-desaturase (SCD) is another factor that is upregulated in PC and GC, which helps convert saturated fatty acids to unsaturated fatty acids (165, 181).

In nutrient-deprived conditions, cancer cells use free fatty acids for energy generation *via* fatty acid oxidation (FAO). Carnitine palmitoyl transferase (CPT) helps transport these free fatty acids to the mitochondria and undergo FAO. Peroxisome proliferator activator γ (PPARγ) is upregulated during cancer progression, which induces fatty acid trafficking and energy generation. In low-nutrient conditions, CRC cells upregulate the AMPK pathway to promote autophagy and mitochondrial FA oxidation (FAO). AMPK pathway activation inhibits lipogenesis *via* downregulation of acetyl CoA-carboxylase (ACC) and upregulates carnitine palmitoyl transferase 1 (CPT1) (182). Carnitine palmitoyl transferase 2 (CPT2), an isoform of CPT1, is also upregulated in leukaemia, PC, CRC, and HCC. Upregulation of FAO in CRC *via* overexpression of carnitine palmitoyl transferase 1A (CPT1A) decreases the ROS level and provides anoikis resistance (183) [Cell death due to loss of adhesion, called anoikis, is a major hurdle for cancer cells during metastasis]. ATP-citrate lyase (ACLY), which converts citrate to acetyl-CoA, is overexpressed in LC and HCC cells and acts as a bridge between glycolysis and fatty acid metabolism (184).

Dietary consumption of fats can also affect CRC tumorigenesis. A high-fat diet (HFD) induces PPAR-δ mediated activation of β-catenin target genes, which results in increased proliferation of intestinal stem cells (ISC) and expansion of TIC (tumor-initiating cells) (185). HCC caused by hepatitis-B virus (HBV) infection has higher levels of HBV protein HBx, which induces lipid accumulation in both mouse model and liver cell lines due to the increased expression of SREBP1 and PPARγ (186, 187). Breast cancer shows alterations in lipid metabolism depending on the type of BC. BC cells have increased catabolism of triglycerides and anabolism of linoleate, palmitate, and oleate. In the basal subtype BC, increased accumulation of monoacylglycerols *via* upregulation of monoacylglycerol lipase (MGAL) is crucial for epithelial to mesenchymal transition (EMT) and cancer progression (188, 189). Whereas, in the case of HER2, basal and luminal B subtypes, there is an accumulation of free fatty acids, palmitoyl carnitine, stearolycarnitine, and oleoyl carnitine. Additionally, accumulation of fatty acid oxidation product 3-hydroxybutyrate (3-HBA) is also reported in BC. The overall increase in FA anabolism promotes BC progression and cell survival. A high level of FA alters phospholipid biosynthesis and metabolism, which helps in the progression of HER2 and triple-negative breast cancer (TNBC) subtypes. Phosphatidylinositol 4-phosphate 5-kinase (PIPKIN) and phosphatidylcholine-specific phospholipase-C (PC-PLC) regulate FA metabolism and are overexpressed in all types of breast cancer, prominently in the TNBC (190–192). In GC, lysophosphatidic acid is converted to phosphatidic acid with the help of lysophosphatidylcholine acyltransferase 1 (LPCAT1) which correlates with tumor depth and lymph node metastasis (193). Nuclease receptor subfamily 1 group D member 1 protein (Rev-erbα) regulates lipid metabolism and decreases GC progression by augmenting glycolysis in GC (194) (Figure 4).

Alterations in nucleotide metabolism

Purine and pyrimidine metabolism are also altered in cancer cells. There are mainly two pathways by which purines and pyrimidines are synthesized – *de novo* synthesis which is the main source of nucleotides *in vivo*, and the salvage pathway which is a shortcut used by those cells which do not possess all of the enzyme machinery necessary for purine nucleotide synthesis from scratch (brain and bone marrow). Salvage pathway is primarily regulated *via* negative feedback (197–202). Key regulatory enzymes which control purine nucleotide metabolism are 5'-phosphoribosyl-1'-phosphate synthetase (PRS), glutamine phosphoribosyl pyrophosphate amido-transferase (GPRATase), IMP hypoxanthine dehydrogenase (IMPDH), adenyl succinate synthetase (ADSS) and key enzymes for pyrimidine nucleotide metabolism are carbamoyl phosphate synthetase II (CPSII) and dihydroorotate dehydrogenase (DHODH) (203–208). Pavlova et al. reported that increased nitrogen demand is one of the hallmarks of cancer cell proliferation which is fulfilled by synthesizing essential

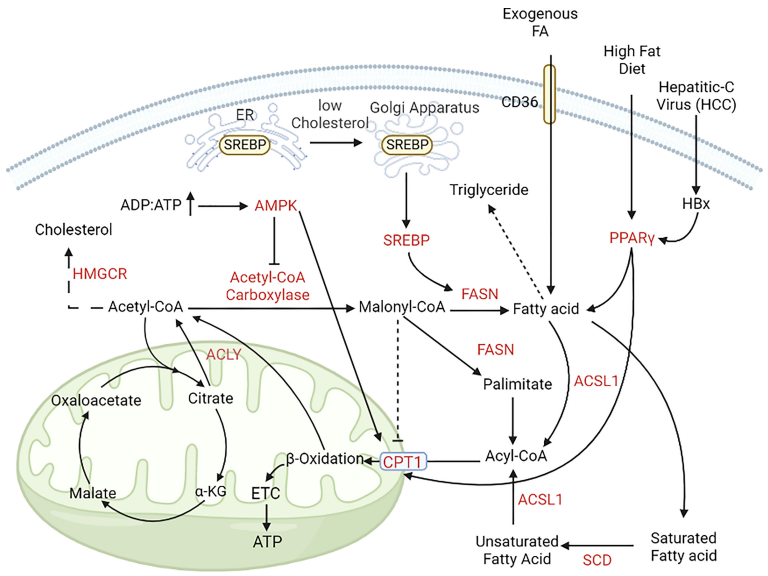

FIGURE 4
Alterations in lipid metabolism during cancer progression. In cancer cells, lipogenesis and lipolysis is controlled by the pool of ADP and ATP. In nutrient-rich conditions (ADP, ATP ratio is low); acetyl, CoA is converted to free fatty acids with the help of acetyl, CoA carboxylase and FASN. In nutrient-deprived conditions (ADP, ATP ratio is high), free fatty acids enter the mitochondria with the help of CPT1 and CPT1A and help in energy generation (195, 196). [FASN, Fatty acid synthase; CPT1, Carnitine palmitoyl transferase 1; CPT1A, Carnitine palmitoyl transferase 1A; GLUT, Glucose transporter; PPARγ, peroxisome proliferator activator receptor γ].

nitrogen-containing molecules like nucleotides (4, 10). Purine and pyrimidine nucleotides are raw materials that support cellular proliferation which is dysregulated in cancer cells to enhance the proliferation and progression of cancer cells (209). c-Myc induces increased expression of nucleotide synthesis pathway genes like carbamoyl phosphate synthetase/aspartyl transcarbamylase/dihydroorotase (CAD), thymidylate synthase (TS), inosine-5'-monophosphate dehydrogenase (IMPDH) expression (210–212). p53 mutation and pTEN loss result in mTORC1 activation which induces one-carbon metabolism and purine and pyrimidine synthesis *via* phosphorylation of S6K and transcription factor E2F1 (213, 214). S6K can activate CAD *via* phosphorylation on ser^{1859}, and E2F1 can induce the expression of TYSM which codes for TS (Pyrimidine anabolic), TK, and DPYD (Pyrimidine catabolic) (215, 216). Santana-Codina et al. identified that in pancreatic cancer KRAS drives tumor growth by activating pyrimidine nucleotide synthesis (217). Overexpression of CAD leads to poor clinical outcomes in BC, liver cancer, and CRC (218). Yu et al. identified higher expression of DHODH in Myc-amplified neuroblastoma and its inhibition led to suppressed neuroblastoma growth in animal models (219). Kollareddy et al. reported that mutant p53 (mutP53) can promote nucleotide metabolism genes, IMPDH and GMPS (220). mutP53 is stabilized by ubiquitin-specific protease 7 (USP7) which is regulated by nucleotide biosynthetic enzyme, guanosine 5'-monophosphate synthase thereby forming a feedback loop (GMPS) (220). Therefore, targeting different pathways of purine and pyrimidine nucleotide synthesis could be an effective strategy to increase the efficacy of cancer treatment.

Crosstalk between metabolic pathways in cancer cells

Glucose, amino acid, lipid, and nucleotide metabolism are linked to each other which is utilized by the cancer cells to support unlimited growth and progression. During initiation phase cancer cells mainly use glucose as a primary source of energy and produce high amount of lactate. Anaerobic glycolysis produces less amount of energy instead of aerobic respiration but cancer cells increase the rate of anaerobic glycolysis by upregulating glycolytic enzymes HK, PFK, LDH and inhibit aerobic glycolysis by upregulating PDK4 which inhibits the conversion of pyruvate to acetyl-CoA and push the pyruvate to produce more lactate. This transition from OXPHOS to aerobic glycolysis happens mainly due to hypoxic conditions resulting from less vascularization (221). Altered expression of P53, Myc, HIF-1 and activation of PI3K/AKT/mTOR in cancer are the key drivers of aerobic glycolysis (222). Here, HIF-1 act as a master regulator which can sense the oxygen concentration in the microenvironment and crosstalk with other signaling pathways (223, 224). During cancer progression when glucose is deficient in the

environment, cancer cells use other sources of carbon and nitrogen (amino acid, lipid, nucleotides) to produce TCA cycle intermediates and use OXPHOS for energy production. Therefore, metabolic plasticity of cancer cells allows them to switch or simultaneously use OXPHOS and glycolysis as per the need (223, 225, 226). OXPHOS is also observed in normoxic cancer cells which use lactate produced by the oxygen deprived cells, also known as reverse Warburg effect (23, 24).

Amino acids and lipids are the secondary source of energy which is used by the cancer cells in nutrient deprived condition. Glutamine, serine, and branch chain amino acids (leucine, valine, and isoleucine) produce TCA cycle intermediates α-ketoglutarate and pyruvate respectively, which produce NADH and FADH2 and undergo OXPHOS to produce ATP. In nutrient deprived condition, Myc binds to promoter of glutamine transporter SLC1A5 to increase glutamine uptake from the microenvironment, and increases GLS1 expression by suppressing the expression of microRNA miR-23a/b, leading to increased glutaminolysis (227, 228).

Flux of glucose to PPP pathway depends on glucose-6-phosphtae dehydrogenase (G6PD) which converts glucose-6-phospgate (a glycolytic intermediate) to 6-phosphogluconate (229). Expression of G6PD depends on the expression of PTEN, P53, AMPK which are mutated in most of the cancer types and increase flux of glucoe-6-phosphate to PPP and production of ribose-5-phosphate (substrate for purine metabolism) (59, 230). Nucleotide metabolism is also linked to PPP (ribose-5-phosphate) and amino acid metabolism (glutamine) which is required by the cancer cells to support DNA synthesis required proliferation and survival (231).

In nutrient replete conditions cancer cells undergo lipogenesis to produce lipid molecules from acetyl-CoA generated from acetate, glucose and glutamine, but during nutrient deprived condition lipolysis occurs to produce free fatty acids by breaking down lipid droplets which then undergo β-oxidation to produce energy for cancer cell survival and proliferation (232–234).

Due to these interlinking nodes between glucose, amino acid, lipid, and nucleotide metabolism, when one metabolic pathway is interrupted due to nutrient deficiency or other external stress, cancer cells compensate by upregulating other metabolic pathways to support their growth and proliferation. Therefore, targeting single metabolic pathway cannot be an effective therapeutic option for cancer treatment and focus should be shifted on combination therapy wherein multiple metabolic pathways which are upregulated in cancer cells are targeted simultaneously (Figure 5).

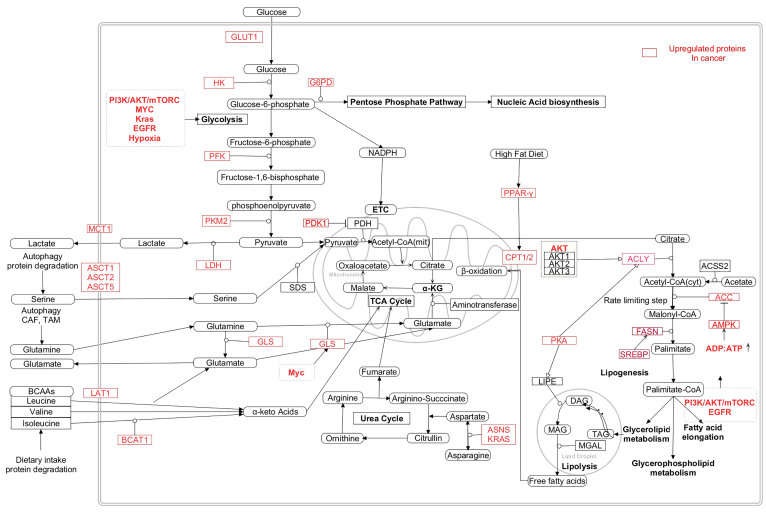

FIGURE 5
Interaction between the metabolic pathways and the dysregulated metabolic intermediates in cancer cells (24, 235–241). [HK: Hexokinase, PFK: Phosphofructokinase, PKM2: Pyruvate kinase M2, LDH: Lactate dehydrogenase, PDK1:Pyruvate dehydrogenase kinase 1, PDH: Pyruvate dehydrogenase, GLUT1: Glucossetransporter1, MCT1: Monocarboxylate transporter 1, ASCT: Alanine/Serine/Cysteine/Threonine transporter, LAT1: Large neutral amino acid transporter 1, GLS: Glutaminase, ASNS: Asparagine synthase, BCAT1: Branch chain aminotransferase 1, α-KG: α-ketoglutarate, BCAA: Branch chain amino acids, FASN: Fatty acid synthase, ACYL: ATP citrate lyase, SREBP: Sterol regulatory element binding protein, PKA: Protein kinase A, ACC: Acetyl-CoA carboxylase, TAG: Triacylglycerol, DAG: Diacylglycerol, Mag: Monoacylglycerol, PPAR-γ: Peroxisome proliferator activator receptor gamma, ASNS: Asparagine synthetase, CAD- Carbamoyl phosphate synthetase/aspartyl transcarbamylase/dihydroorotase, DHODH- Dihydroorotate dehydrogenase, PRPP- Phosphoribosyl diphosphate, IMPDH- IMP hypoxanthine dehydrogenase, GMPS- GMP synthetase, IMP- Inosine monophosphate, XMP-Xanthopsin monophosphate, GMP-Guanosine monophosphate, AMP-Adenosine monophosphate, UMP-uracil monophosphate, TMP-Thymine monophosphate].

Metabolic reprogramming in tumor-microenvironment

Stromal cells

The tumor microenvironment plays a critical role in tumor progression as the cancer cells evolve beyond the initial proliferative stage into metastatic stages. The bidirectional crosstalk modulates the metabolic reprogramming of cancer cells and various stromal and immune cells present in their microenvironment. Cancer-associated fibroblasts (CAFs), adipocytes, and immune cells in the CRC microenvironment are involved in tumorigenesis (242). Cancer cells are known to induce an "activated" state in fibroblasts, either by secretion of various growth factors and cytokines or *via* direct cell-cell contact mediated by Notch1. This transformation of fibroblasts into cancer associated fibroblasts (CAFs) is akin to activation of quiescent fibroblasts into proliferative myofibroblasts in the advent of tissue injury (243). CAFs can constitute a major fraction of the tumor population, however their origin and role can vary vastly at different stages of cancer progression (244). Quiescent fibroblasts are reported to have anti-tumorigenic properties, however, it is believed that CAFs are the central architecture of tumorigenesis and are responsible for metabolic reprogramming *via* secretion of growth factors such as EGF, transforming growth factor 1 (TGF1), PGE2 and exosomes (242, 245). CAFs create a catabolic microenvironment that promotes tumor-initiating cells ($CD133^+/CXCR4^+/EpCAM^+$) and induces stemness in cancer cells by activating sonic hedgehog and GLI signaling (246, 247). Gorchs et al. found that CAFs isolated from NSCLC tissue maintain their immunosuppressive effects *via* secretion of various immunomodulatory cytokines such as TGF-β, IL-6, and PGE2, even after high dose irradiation (248). Furthermore, CAFs can support the metabolic requirements of the tumor cells by providing various metabolites like lactate, amino acids and fatty acids (249, 250). Pavlides et al. proposed the reverse Warburg effect, where they observed that lactate produced by CAFs, due to upregulation of glycolytic enzymes, can be used by the cancer cells for respiratory metabolism (251). ROS generated by CRC cells stimulates lactate secretion by CAFs, and this lactate is utilized by CRC cells, which have high expression of lactate transporter MCT1 (252). Adipocytes in the cancer microenvironment regulate the switching between glucose and FA metabolism in cancer cells. Wen et al. reported that adipocytes transfer free fatty acids to the CRC cells and promote their survival by upregulating the AMPK pathway (250). Such metabolic coupling with the tumor-associated stroma promotes ATP generation and survival of cancer cells and can serve as a novel biomarker of cancer progression (253). In BC and GBM, a metabolic symbiosis also exists between tumor subpopulations in the oxygenated and hypoxic regions of the tumor, wherein hypoxic cells metabolise glucose to secrete lactate (through lactate transporter MCT4) which in turn is internalized by the oxygenated cells *via* MCT1 to produce energy through OXPHOS (254–259). This symbiosis permits the survival of heterogenic populations within a tumor while circumventing any competition over resources. Cancer progression of solid tumors requires the formation of new blood vessels to meet the oxygen and nutrient requirements of the tumor mass. Stromal cells secrete and induce the expression of proangiogenic factors VEGF and PGE2 in CRC cells (260). Additionally, CAFs can also modulate the extracellular matrix composition at tumor site to promote cancer cell motility (261).

The human gut microbiome also plays a significant role in reprogramming CRC metabolism. The gut microbiome expresses approximately 9.9 million genes, which is 150 times greater than the human transcriptome (262). CRC patients show alterations in the diversity of gut flora as harmful microbiome populations like- Fusobacterium and Prevotella increase, and populations of good bacteria like- butyrate-producing bacteria plummet (263).

Immune cells

Along with CAFs and adipocytes, the metabolic signature of cancer cells is also influenced by surrounding immune cells, which include tumor-associated macrophages (TAM), tumor-infiltrating lymphocytes (TIL), and myeloid-derived suppressor cells (MDSC) (264). Macrophage infiltration is associated with poor prognosis in BC. Metabolic reprogramming in BC cells influences TAM differentiation, and increases glycolysis mediated by upregulation of hexokinase-2, PFK2 (ATP-dependent-6-phosphofructokinase), and enolase-1. These observations indicate that metabolically altered cancer cells can also reprogram the metabolism of associated macrophages to favour cancer progression (265).

Moreover, the accumulated lactate stabilizes the oxygen-regulated protein NDGR3, which can bind to c-Raf and promotes angiogenesis *via* the Raf-ERK signaling cascade (266). Lactate also activates breast cancer-associated macrophages and upregulates CCL5 and CCR5 expression by activating the NOTCH, TGFβ, and AMPK pathways, promoting EMT, migration, and aerobic glycolysis in BC cells through a positive feedback loop (267). BC cells induce the expression of hypoxia and stress response protein REDD1 in TAMs, which inhibits glycolysis *via* mTOR inhibition (268). Inhibition of glycolysis hinders the secretion of angiogenic factors by TAMs, leading to leaky, abnormal blood vessels that allow tumor metastasis (269). Coculture with TNBC cells induces the differentiation of monocytes into M2-like macrophages (M2-TAMs) and downregulates citrulline metabolism, nitric oxide synthase (iNOS), and nitric oxide (NO) (270, 271). The anti-inflammatory nature of M2-TAMs enables the cancer cells to evade immune recognition and promotes their survival. Increased glucose uptake and subsequent lactate accumulation by BC cells

acidify the tumor microenvironment and impair the cytolytic activity of T-lymphocytes, thereby promoting tumorigenesis. The NK cell function is also hampered under high lactate conditions enabling cancer cells to evade immune surveillance (272, 273). MDSCs in the BC microenvironment promote immune evasion and upregulate glycolysis and phosphoenolpyruvate (PEP) accumulation, protecting BC cells from ROS-induced apoptosis (274). Furthermore, a higher number of MDSCs in the BC microenvironment is associated with increased metastasis (275).

Similarly, lung cancer progression is modulated by stromal and immune cells found in the lung microenvironment (276). Tumor-associated macrophages (TAMs) crosstalk with LC cells *via* the C-C chemokine receptor type-2 (CCR2) and CX3C chemokine receptor 1 (CX3CR1). LC cells also promote the conversion of TAMs into anti-inflammatory, tumor-supporting M2 phenotype, promoting cancer cell migration and survival (277). TAMs exhibit a glycolytic phenotype in the early stages of lung cancer, and tumor extract stimulates the expression of aerobic glycolysis and glycolytic enzymes HK2 and ENO1 in macrophages (265). The pro-tumoral TAMs secrete arginase II (ARG 2), which converts arginine to ornithine and urea and impairs T-cell response (278). TAMs also degrade tryptophan in the tumor microenvironment in lung cancer by upregulating indoleamine 2,3-dioxygenase (IDO) (279). Lack of arginine and tryptophan in the TME impairs T-cell response, whereas, the downstream metabolic product, Kynurenine, produced by tryptophan degradation increases the number of immunosuppressive regulatory T cells (Tregs) (280). Similarly, glutamine addiction of tumor cells deprives T cells of the glutamine supply, which is necessary for T-cell activation (281).

M2 polarization of TAMs is also observed in HCC, inducing an immunosuppressive microenvironment (282). M2 macrophages secrete IL-1β, which induces FAO and increases the proliferation and metastatic potential of HCC cells. M2-like TAMs in HCC-TME also show a reduction in glycolysis and PPP with enhanced OXPHOS and FAO (283). Metabolic modifications in tumor-associated neutrophils (TANs) also play a key role in tumor growth, invasion, and metastasis. Neutrophils derive energy from glycolysis to maintain their function at low oxygen levels (284, 285). However, lack of glucose in the TME obligates neutrophils to utilize mitochondrial FAO and produce NOX-2-dependent ROS, which further increases immune tolerance in the TME (286). Like TANs, the dependence of regulatory T cells on FAO for their survival in TME also plays an immunosuppressive role (287, 288). Of note, the glycolytic nature of the TME inhibits the functions of effector T-cells, but maintains the proliferation and function of regulatory T cells (289, 290). Thus, tumor-associated stromal cells and immune cells play a crucial role in tumor progression in several cancers, and effective strategies should be derived to inhibit the metabolic crosstalk between the tumor cells and microenvironment cells (Figure 6).

Metabolic targets for cancer therapy

Metabolic targeting of cancer is a new era of precision therapy that aims to exploit the dependence of malignancies on specific metabolic alterations. The excess glycolysis, the first described metabolic dysregulation in cancers, has been targeted in multiple ways to induce growth arrest and apoptosis in tumor cells. Using 2-deoxyglucose (2-DG) was one of the earliest attempts to inhibit glycolysis in cancer cells. 2-DG is transported by hexose transporters and converted to 2-DG-6-phosphate by hexokinase, which cannot be metabolised further, and its accumulation impedes glycolysis by inhibiting hexokinase and phospho-glucose isomerase. However, 2-DG did not show clinical benefits due to its low therapeutic index (302–304), and 2-DG inhibits the necessary high glucose metabolism in the brain (305). However, studies have shown that the biological effects of 2-DG are not solely due to its metabolic block; therefore, targeting glucose metabolism *via* other means might still have therapeutic benefits (306). For instance, other glycolysis inhibitors such as 3-bromopyruvate (3-BP) (307) and lonidamine (308) are being explored to treat cancers with minimal side-effects like alopecia and bone-marrow suppression observed with conventional chemotherapies (302, 309, 310). Phosphofructokinases and their regulatory gene PFKFB are also dysregulated in transformed cells and primary cancers (311). Upregulation of PFKFB3 promotes glycolysis, helps in cell cycle transition by phosphorylating p27, and is associated with poor overall survival in BC patients making it a potential target for treatment (312, 313). 3-(3-pyridinyl)-1-(4-pyridinyl)-2-propen-1-one (3-PO) is a PFKFB3 inhibitor that interacts with its functional subunit and depletes fructose-2,6-bisphosphate, but has limited application due to its water insolubility. However, PFK15 and PFH158, the functional derivatives of 3-PO, are tested in the clinical trial as PFKFB inhibitors (314, 315). Furthermore, inhibition of glucose uptake by targeting upregulated GLUTs using WZB117, silibinin or cytochalasin B induces metabolic crisis in breast, lung, and colorectal cancer cells (238, 316, 317). Similarly, AR-C155858 and AZD3965, inhibitors of lactate transporters MCT1 and 2, normalise the TME pH and inhibit tumor proliferation (318, 319). LDH upregulation has also been targeted with quinoline-3-sulfonamide, Oxamate and GNE-140 to inhibit conversion of pyruvate into lactate. Specific targeting of mutant enzymes such as IDH1 and IDH2, using enasidenib (AG-221) or ivosidenib (AG-88), is another approach to target glucose metabolism without affecting the function of normal cells. However, the relevance of such mutations to tumor survival and proliferation largely depends on the cancer stage and might not be an effective strategy during later stages.

OXPHOS is generally downregulated in cancer cells (breast cancer, gastric cancer), but due to mutations in mitochondrial

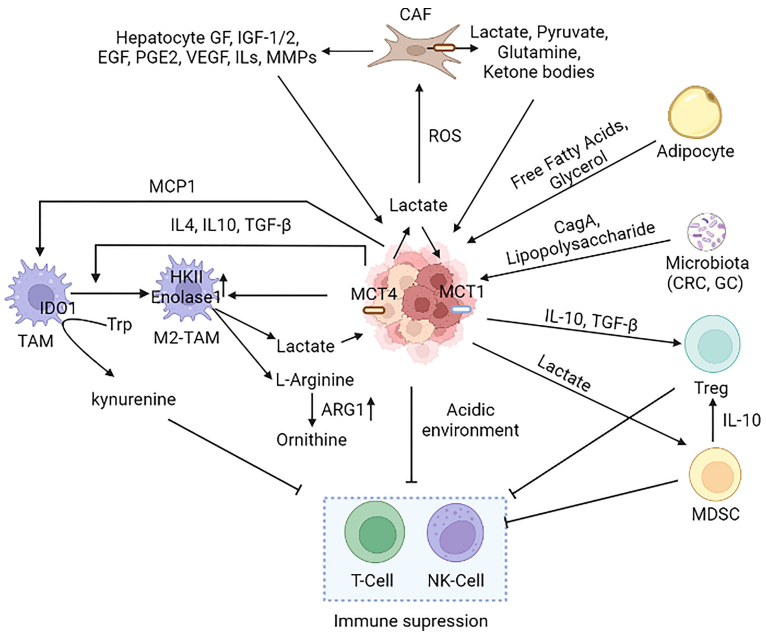

FIGURE 6
Cancer microenvironment in metabolic reprogramming. Several cell types such as macrophages, neutrophils, MDSCs, Treg, DC, T-cell, NK-cell, adipocytes, and CAFs present in the tumor microenvironment alter the metabolic reprogramming of cancer cells. Immune cells present in the TME have both pro and anti-tumor effects; however, the cancer cells induce the pro-tumorigenic phenotype (M2-TAM and M2-TAN). Cancer cells induce CAFs to secrete lactate in the TME leading to an acidic environment that suppresses the immune cells (242, 250, 252, 291–301). [MCT1: Monocarboxylate transporter 1, MCT4, Monocarboxylate transporter 4; CAF, Cancer-associated fibroblast; M2-TAM, M2 Type Tumor-associated macrophages; NK cell, Natural killer cell; MCP1/CCL2, Monocyte chemoattractant protein-1/Chemokine (C-C motif) ligand 2; IDO, Indoleamine-pyrrole 2,3-dioxygenase; MDSC, Myeloid-derived suppressor cells; Treg, T regulatory cells; IGF, Insulin-like Growth Factor; EGF, Epidermal growth factor; VEGF, Vascular endothelial growth factor; IL-Interleukin, PGE2-Prostaglandin E2; TGF-β, Transforming growth factor beta, MMP: Matrix metalloproteases, CRC, Colorectal cancer; GC, Gastric cancer].

DNA, OXPHOS is upregulated in some cancer types (leukaemia, endometrial carcinoma) (38). Targeting OXPHOS requires inhibition of the ETC complexes. Metformin inhibits ETC complex I and reduces tumor growth by reducing NADH oxidation, resulting in ATP depletion and loss of proton gradient across the inner mitochondrial membrane (320, 321). In addition to metformin, drugs such as tamoxifen, Vitamin E derivative α-tocopheryl succinate, and 3-BP target ETC complexes (322). On the other hand, the independence of cancer cells from mitochondrial respiration mediates their resistance to the mitochondria-controlled apoptotic pathway. PDK regulates the activity of PDH to limit the production of acetyl-CoA from pyruvate and is a potential target for cancer therapy. Dichloroacetate inhibits PDK, upregulates the activity of PDH, and restores the mitochondrial dependence of cancer cells (323).

Downregulation of PPP to inhibit nucleotide biosynthesis is another therapeutic approach to limit the proliferation of cancer cells. Dehydroepiandrosterone, an endogenous precursor for steroid hormones, can inhibit G6PD, the key regulator of PPP, but has limited therapeutic application due to its immediate conversion into steroid hormones *in vivo* (324). 6-aminonicotinamide is reported to inhibit G6PD and showed promising results in inhibiting tumor growth *in vitro* (325–327), but its inclusion within tolerable doses in subsequent clinical trials showed no significant benefit (328).

Glutamine addiction is another prominent characteristic of cancer cells that can be targeted therapeutically. Glutaminase1 (GLS1) inhibitor, Bis-2-(5-phenylacetamido-1,3,4-thiadazol-2-yl) ethyl sulphide reduces cancer cell proliferation *in vivo* (329–331). Several other molecules, such as acivicin, azaserine, 6-diazo-5-oxo-I-norleucine (DON), which can inhibit glutaminolysis, can be used for cancer treatment (329, 332). L-asparaginase, which depletes asparagine and glutamine in the microenvironment of ALL cells to inhibit their growth, have been found to be effective in several patients (333). Serine, a precursor for nonessential amino acids glycine and cysteine, is synthesised from glucose or imported from the extracellular environment by the cancer cells to promote their survival (334–336). Upregulation of phosphoglycerate dehydrogenase (PHGD), which converts 3-phosphoglycerate to serine, can be targeted using PHGD inhibitors CBR-588 and NCT-503 in BC and LC (305).

Many cancer types, such as glioblastoma, are dependent on lipid metabolism. In nutrient-deprived conditions, cancer cells use FAO to produce NADH and FADH2 *via* OXPHOS (337).

During cancer progression, upregulation of CPT1 increases the transport of fatty acids into the mitochondria. CPT1A inhibitor, etomoxir (ETO), induces growth arrest in bladder cancer cells (338) and increases the effectiveness of hormonal therapeutic drugs like enzalutamide in prostate cancer (339). Further studies identified that etomoxir has off target effects which leads to oxidative stress, therefore, using other CPT1A inhibitor (S1326) might yield better therapeutic results (340, 341). Furthermore, FAO is upregulated due to the increased activity of enzymes like ACLY, ACC1 and ACC2 that are crucial for cancer cell growth and proliferation, making them a potential target for GC, LC, and BC treatment (342). Drugs like SB-204990 and simvastatin inhibit ACLY and decrease acetyl-CoA availability for FAO (82, 343–345). FASN is overexpressed in most cancer types to promote lipogenesis (154, 346).

Like other metabolic pathways nucleotide metabolism is also dysregulated in cancer. Targeting nucleotide metabolic enzymes or using purine and pyrimidine analogs has been long sought therapeutic approach for cancer treatment. Thiopurines (6-mercaptopurine, thioguanine), deoxy-purines (cladribine, Clofarabine), arabinose purine analogs (nelarabine, fludarabine) and base modified purine nucleotides (8-chloro-adenosine, tocladesine and forodesine) are purine analog antimetabolites which are used for cancer treatment (347). 6-mercaptopurine was approved by FDA for the treatment of childhood leukaemia in early 1953 and thioguanine in 1996 for the treatment of non-lymphocytic leukaemia (347–350). Cladribine is approved for the treatment of hairy cell leukaemia and its improved version is clofarabine a second-generation deoxyadenosine analog (351–354). Arabinose purine analogs are used for the treatment of acute and chronic lymphocytic leukaemia and in relapsed T cell lymphoblastic leukaemia, and base modified purine nucleotides have not yet approved by FDA (351–357). Fluorinated pyrimidines (5-Fluro uracil, capecitabine, floxuridine), azanucleosides (decitabine, azacytidine), ribose sugar modified cytidine analogs (gemcitabine), cytarabine are used as a pyrimidine analogue for treatment of cancer (347). 5-FU was approved by FDA in 1960 for hepatic carcinogenesis and is currently under study for gastrointestinal, breast and renal cancer (358–360). Gemcitabine, a ribose sugar modified cytidine analog, disrupts DNA biosynthesis through cell cycle arrest and is currently approved by FDA for the treatment of breast, ovarian, lung and pancreatic cancer (361–363). Azanucleosides induce epigenetic modification (inhibit DNA methylation) to achieve antitumor effects (364–366). Along with the purine and pyrimidine nucleotide analogs there are enzymatic blockers which can disrupt nucleotide metabolism in cancer cells. Mizoribine, merimepodib and mycophenolic mofetil (phase I trial in pancreatic cancer) are inhibitors of IMDPH an enzyme involved in purine metabolism (367–370). Thymidylate synthase (TS) and glycinamide ribonucleotide transformylase (GART) which are involved in thymidine and purine nucleotide synthesis is inhibited by an anti-folate drug called pemetrexed. MLN4924 can be used in melanoma, acute myeloid leukemia and lymphoma, as it inhibits carcinogenesis by inhibiting proteasomal degradation (371, 372). Teriflunomide and leflunomide, inhibitor of DHODH a key enzyme in nucleotide synthesis, have antiproliferative effects in NSCLC, myeloma and neuroblastoma but has not yet been approved by FDA for clinical use (373, 374). TVB-3166, TVB-2640, and omeprazole inhibit the FASN to inhibit cancer proliferation. Several signaling pathways (PI3K/AKT/mTORC, MAPK, PI3K/AKT/FOXO) are also involved in the metabolic alteration of cancer cells, which can be targeted to downregulate the metabolic pathways and ultimately inhibit cancer growth and proliferation.

Dysregulation of GLUT-1/3, HK II, PFK-1 CPT1/2, FASN and GLS1 is common in most cancer types, and the interlinked metabolic pathways compensate for the deprivation of nutrients to maintain cancer growth, proliferation, and metastasis. Therefore, combination therapies targeting more than one metabolic pathway will be more effective with a better therapeutic index to treat cancer. Kalyanaraman et al. reported that targeting both glycolysis and OXPHOS is a promising therapeutic approach and observed good outcomes with a combination of Metformin and 2-DG treatment in pancreatic cancer which depleted the ATP pool and cancer proliferation (375). L-asparaginase can be combined with other glutamine metabolism inhibitors, which can increase the effectiveness of the treatment. Tanaka et al. observed that a combination treatment of mTOR and GLS inhibitors induced tumor cell death in a mice model (376).

Along with metabolic and signaling pathways, targeting TME cells can be a potential therapeutic option by which we can produce a synergistic effect against the cancer cells. CAF present in the microenvironment undergo aerobic glycolysis and produce lactate which is released into the microenvironment by MCT4 and imported by the cancer cells *via* MCT1 to fuel up the OXPHOS during nutrient deprived conditions (377, 378). Syrosingopine, which can inhibit both MCT1 and MCT4 and LDH has been shown to induce higher cytotoxicity than AZD3965 which can only inhibit MCT-1 in liver cancer cells (377). CAFs are also a source of glutamine in the TME so targeting glutamine synthetase (GLUL) in CAFs along with GS in cancer cells leads to synergistic effect which reduces metastatic potential of ovarian cancer (379). Endothelial cells are reprogrammed to undergo excessive glycolysis in the TME leading to their impaired function, so targeting glycolytic activator PFKFB3 with 3-PO, can be a multimodal therapeutic option for cancer treatment (380, 381).

However, caution needs to be exercised as inhibiting certain metabolic pathways can severely impair the immune cell function, which in turn might promote tumor progression. Furthermore, tumor microenvironment components are also being explored as a viable target to disrupt the metabolic cooperation that promotes tumor progression (17) (Table 1).

TABLE 1 List of metabolic pathway drugs which were evaluated clinically.

Drug	Target molecule	Mode of action in different cancer types
AZD3965 AR-C155858	MCT1	Inhibition of lactate transporter and glycolysis in CRC (235) and LC (236).
WZB117 Silibinin Cytochalasin B Fasentin, phloretin, STF-3, Dapagliflozin	GLUT SGLT	Downregulates GLUT1 expression in CRC (235), Inhibits glucose uptake in cells preferentially expressing GLUT1 or GLUT4 and inhibits active transport of glucose into cells by SGLT1 and SGLT2 in LC (382–385), Inhibit glucose reabsorption in the kidney in BC (386)
2-DG Lonidamine Bromopyruvate	HK	Sensitizes CRC cells to TRAIL-induced apoptosis (310). *Inhibits* glycolysis in hypoxic cancer cells and inhibits mitochondrial pyruvate oxidation in BC (302) and LC (302, 309, 387).
Metformin, Mito-Metformin	Mitochondrial electron transporter complex 1	AMPK activation, PKM2 inhibition, and ATP depletion in CRC (388, 389) Inactivates phosphorylation of the E1 alpha-subunit of PDC and inhibits alpha-ketoglutarate dehydrogenase in BC (390).
Dichloroacetate AZD7545	PDK	Fostering oxidative phosphorylation in BC (391). Increases oxidative phosphorylation, thereby increasing Krebs cycle intermediate concentration in LC (392, 393)
CPI-613 ME-344	PDH	Inactivate phosphorylation of the E1 alpha-subunit of PDC; and inhibits alpha-ketoglutarate dehydrogenase and decreases mitochondrial ATP production in BC (394, 395).
Indoximod, Epacadostat, BMS-986205, KHK2455, Epacadostat, INCB001158	Indoleamine 2,3 dioxygenase (IDO1)	Increases tryptophan concentration and activates T cell-mediated immunity In BC (106, 396). Induces host immune system mainly T-cell mediated response in BLC (397, 398).
3PO PFK3 PFK158	PFKFB3	Reduces glucose uptake and ATP production in LC (399, 400).
Bromop-yruvate	GAPDH	Inhibit glycolysis, thereby suppressing the production of ATP and inducing cell death in LC (401, 402).
Shikonin	PKM2	Inhibits cell aerobic glycolysis in LC (403).
FX11 Quinoline-3-sulfonamide Oxamate GNE-140 PSTMB	LDH	Inhibits the ability of LDH to convert pyruvate into lactate in LC (237, 404–407).
Enasidenib Ivosedinib GSK864 GSK321	IDH	Potent IDH1 inhibitor used in LC and approved in relapsed/refractory IDH2 mutant AML (408, 409).
Lonidamine SiRNA	VDAC1	Induces apoptosis by rewiring tumor cell metabolism, reduces cancer stem cells, and induces differentiation in LC (410, 411).
Simvastatin	3-hydroxy-3-methylglutaryl coenzyme A reductase	Inhibit conversion of HMG-CoA to mevalonate, the rate limiting step of steroidogenesis in PC (412).
INCB001158	Arginase	Induces proliferation of cytotoxic T-cells and natural killer (NK) cells that kill the tumor cells In BLC (413).
L-NMMA	Nitric oxide synthase	Inhibits NOS in BLC (397).
ADI-PEG20	Arginine deiminase	Starves tumor cells by *arginine* depletion in BC (414).
CB-839	Glutaminase	Inhibits hydrolysis of glutamine in BC (415)
DON, BPTES, Acivicin, Azaserine	GLS1	Inhibits Gln metabolism in CRC (416, 417) and reduces glucose uptake in PC (418).
L-aspartate + Rapamycin	ASNs, mTOR	Inhibits asparagine biosynthesis in CRC (112)
TVB-3166, TVB-2640, Omeprazole, Conjugated Linoleic Acid (CLA), Orlistat,	FASN	Inhibits de novo palmitate synthesis in CRC (343). Supresses denovo lipogenesis in BC (82, 344, 345). Form a covalent bond with the enzyme FASN and inhibits its function, thereby inhibiting lipogenesis in PC (419–421).

(Continued)

TABLE 1 Continued

Drug	Target molecule	Mode of action in different cancer types
C75, cerulenin, and C93, 3-aryl-4 hydroxyquinoline-2 (1H)-one derivatives, GlaxoSmithKline produced GSK837149		
SB-204990 and simvastatin	ATP citrate lyase	RNA interference and inhibits proliferation and survival of tumor cells in PC (422).
Ficlatuzumab	FGF	Inhibits glucose uptake and blocks HGF activity in CRC (106).
RO5126766	RAF/MEK	Downregulates GLUT1 expression in CRC (133).
Metformin, 5-aminoimidazole-4-carboxamide-1-b-ribofuranoside (AICAR), A-769662, PT1, and OSU-53	AMPK	Reduces the expression of gluconeogenic enzymes, decreases AMP/ATP ratio, and activates AMPK in PC (421, 423–425).
Mercaptopurine	Hypoxanthine–guanine phosphoribosyltransferase, amidophosphoribosyltransferase, Inosine-5'-monophosphate dehydrogenase	Acute lymphatic leukemia (347, 348)
Fluorouracil	Thymidylate synthase	Colon, esophageal, gastric, rectum, breast, biliary tract, stomach, head and neck, cervical, pancreas and renal cell cancer (302, 359)
Thioguanine Carboplatin Oxaliplatin	DNA	Acute non-lymphocytic leukemias (347, 350) Testicular tumors, ovarian tumors, and bladder cancer CRC (426)
Gemcitabine	Ribonucleoside-diphosphate reductase, thymidylate synthase, UMP-CMP kinase	Ovarian, lung, breast, and pancreas cancer (361, 362)
Pemetrexed	Thymidylate synthase, Bifunctional purine biosynthesis protein PURH, Dihydrofolate reductase, Trifunctional purine biosynthetic protein adenosine 3	Mesothelioma, NSCLC (427)

Conclusion

Metabolic dysregulations in cancer cells were first described by Otto Warburg, who identified and hypothesised that excessive glucose uptake and lactate formation is the root cause of tumorigenesis (6). Since then, numerous studies have identified alterations in all major metabolic pathways, including glucose, amino acids, lipid, and nucleotide metabolism.

The current understanding of tumor progression suggests that while metabolic reprogramming does not lead to tumor initiation, it is the most critical driver of tumor progression in later stages. But in some cases, mutation in metabolic enzymes leads to tumorigenesis. Oncometabolites (succinate, fumarate, D-2-hydroxyglutarate) produced from mutations in TCA cycle enzymes succinate dehydrogenase (SDH), fumarate hydratase (FH) and IDH1/2 lead to epigenetic alterations and affect gene expression by inhibition of Jumanji-C-domain containing histone lysine demethylase (KDMs) and ten-eleven translocation (TET) family of 5-methylcytosine (5mC) hydroxylase (428–430). These oncometabolites are observed across different cancer types such as renal cancer, gastrointestinal cancers, leukaemia gliomas and glioblastomas (430). In some cases, risk factors like obesity, may also lead to tumorigenesis, mediated by increased leptin and decreased adiponectin. Leptin leads to the activation of PI3K-AKT-mTOR pathway, whereas downregulation of adiponectin reduces AMPK levels, thereby increasing mTORC1 activity, which induces cell proliferation (431, 432).

Induced glucose fermentation, also referred to as "aerobic glycolysis" or the Warburg effect, provides for the high energy requirements of the cancer cells. The upregulation of glucose consumption forms the basis of tumor screening by fluorodeoxyglucose positron emission tomography (FDG-PET) (433). This increase in glycolytic flux is due to the upregulation of various glucose importers (GLUTs) and downstream metabolising enzymes like HK, PFK, PKM2, and LDH, observed in many cancer types (39, 55, 433, 434). Furthermore, high glycolytic flux is coupled with upregulation of PPP, increasing nucleic acid biosynthesis required for unabated proliferation of cancer cells (59). Cancer cells derive energy *via* oxidative phosphorylation of TCA cycle intermediates produced by amino acid metabolism or *via* beta-oxidation of fatty acids (98, 150, 151). Increased metabolism of

glutamine and auxotrophic dependence on other amino acids is a prominent characteristic of cancer cells. The exclusive sensitivity of ALL cells towards L-asparaginase treatment was the first therapeutic intervention that targeted metabolic dysregulation in tumor cells. Since then, various other approaches that limit the availability of amino acids, such as treatment with arginase, inhibition of AA metabolism, such as glutaminase1 inhibitors and inhibition of amino acid transporters like ASCT, have shown promising results in inhibiting tumor growth. Glutaminase inhibitors, IPN60090, a small molecule, and Telaglenastat are in phase 1 clinical trial for CRC, NSCLC and PC (435, 436). There are also other drugs available which are in clinical trial for targeting different cancer types such as- sirpiglenastat an antagonist of glutamine (phase I/II for solid tumors and NSCLC), AZD5965 inhibitor of MCT1 (phase II for solid tumors and lymphoma), IACS-010759 inhibitor of mitochondrial respiratory complex 1 (phase I for AML) (436). Similarly, various aspects of fatty acid metabolism and lipogenesis upregulated in cancer cells are targeted by inhibiting the regulatory enzymes such as FASN. In glioblastoma, cancer cells do not depend on extrinsic sources of fatty acid and instead upregulate *de novo* synthesis of cholesterol. Under such circumstances targeting specific regulators of lipogenesis such as SREBP1 shows high therapeutic specificity and efficacy (167, 169).

Furthermore, the tumor microenvironment comprises various immune cells and tumor-associated stromal cells, which extensively modulate the metabolic state of the cancer cells. The symbiotic relationship between cancer and TME cells supports the metabolic dysregulations resulting in a tumorigenic and metastasis-promoting niche. Various metabolites secreted by cancer cells induce tumor suppressive phenotype in the macrophages and regulatory T-cells. Furthermore, cooperative metabolic coupling within different subpopulations of tumor cells are also observed. Secretion of various metabolites by the TME cells induces signaling pathways such as AMPK/mTORC1, PI3K/AKT and Raf-ERK, which promote the survival of cancer cells.

Therefore, further studies aimed at a better sub-classification of cancers depending on the type of interactions that exist between the cancer cells and its TME might allow targeting of TME-induced metabolic alterations.

Author contributions

SP, AS, SM and BJ wrote the manuscript and approved the final version of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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