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Metabolism and epigenetics: a link cancer cells exploit

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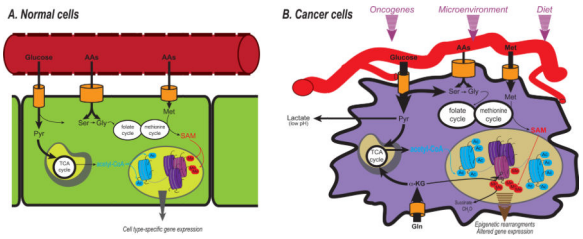
Abstract

Both cellular nutrient metabolism and chromatin organization are remodeled in cancer cells, and these alterations play key roles in tumor development and growth. Many chromatin modifying-enzymes utilize metabolic intermediates as cofactors or substrates, and recent studies have demonstrated that the epigenome is sensitive to cellular metabolism. The contribution of metabolic alterations to epigenetic deregulation in cancer cells is just beginning to emerge, as are the roles of the metabolism-epigenetics link in tumorigenesis. Here we review the roles of acetyl-CoA and S-adenosylmethionine (SAM), donor substrates for acetylation and methylation reactions, respectively, in regulating chromatin modifications in response to nutrient metabolism. We further discuss how oncogenic signaling, cell metabolism, and histone modifications are interconnected and how their relationship might impact tumor growth.

Graphical Abstract



Cancer cells must survive in and adapt to a changing and often harsh microenvironment. Despite the need to adapt to the extracellular environment, cancer cells are generally more self-reliant than their normal counterparts, with weakened dependence on exogenous growth factors and cell-to-cell interaction. This outlines an apparent paradox: how can intrinsically independent cell entities also possess an enhanced ability to adapt to extracellular signals? One mechanism may be through vigilant monitoring of intracellular metabolites.

Metabolism in cancer cells is impacted both by internal stimuli such as oncogenic signal transduction and external cues such as nutrient and oxygen availability. Hence, monitoring intracellular levels of metabolites is crucial for cells to appropriately gauge their nutritional

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resources, taking into account both signaling cues and microenvironmental conditions. Evolutionarily conserved “nutrient-sensing” mechanisms exist to detect and respond to metabolic changes. In this respect, the role of AMP-activated protein kinase (AMPK), which is activated when the AMP:ATP ratio rises, is illustrative of the ability of mammalian cells to switch to a more catabolic state when they perceive a nutrient stress[1]. Conversely, signaling through the mechanistic target of rapamycin (mTOR) promotes growth and is active when cells sense a favorable, nutrient-replete environment[2]. Certain post-translational modifications are also sensitive to the availability of specific metabolites and thus can provide additional mechanisms for the cell to gauge its metabolic status[3-5] (Figure 1).

Are metabolic and epigenetic alterations linked in cancer cells?

Cancer cells undergo extensive metabolic reprogramming to sustain tumor growth[6]. Most chromatin modifying enzymes utilize metabolites as cofactors or substrates, and accumulating evidence has shown that the epigenome (and ultimately the transcriptome) is sensitive to metabolic state[5,7,8]. At the same time, it is manifest that the epigenome is reorganized in tumor cells, a feature that is now considered an enabling characteristic of cancer[9,10]. Metabolic contributions to cancer cell epigenetic alterations are, with a few notable exceptions, largely unknown, however.

A prime example in which metabolic control of the epigenome has been demonstrated is in tumors harboring isocitrate dehydrogenase (*IDH1* or *IDH2*) mutations. In IDH mutant tumors, aberrant accumulation of the metabolite (*R*)-2 hydroxyglutarate competitively inhibits α-ketoglutarate-dependent JMJD histone demethylases and TET methylcytosine dioxygenases, thereby mediating a hypermethylation phenotype (reviewed in[6,11,12]). Less clear is how generalizable this paradigm will be to tumors without mutations in genes encoding metabolic enzymes. Does metabolic rewiring mediated by microenvironmental conditions or oncogenic signaling alter substrate availability to chromatin modifying enzymes to a sufficient extent to impact the cancer cell epigenome? If so, how does this impact cancer initiation, tumor growth, and treatment responses? In this Review, we will discuss the current evidence that oncogenic and microenvironment-mediated metabolic reprogramming impact tumor histone acetylation and methylation levels.

Metabolic regulation of histone acetylation

Histone acetylation participates in multiple chromatin-dependent processes, including gene regulation, DNA replication, and DNA damage repair. Acetylation is catalyzed by lysine acetyltransferases (KATs), which transfer an acetyl group from acetyl-coenzyme A (acetyl-CoA) to lysine residues (Nε), with the concomitant production of CoA[13]. Histone deacetylases (HDACs) remove the acetyl group, generating acetate (class I/II HDACs).

Acetyl-CoA levels in cells fluctuate in response to several physiological cues, including nutrient availability, circadian rhythms, and changes in metabolic state[14-17]. Several KATs have been reported to exhibit physiological regulation based on cellular levels of acetyl-CoA[15,17,18]. In yeast, Gcn5 is highly responsive to acetyl-CoA availability, and the range of acetyl-CoA reported could plausibly regulate this KAT based on K_D for acetyl-

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CoA[17,19]. Many KATs are also inhibited by their product CoA, suggesting that the ratio of acetyl-CoA: CoA might be the physiological regulator of acetylation in response to metabolic changes [20]. Consistent with this model, the ratio of acetyl-CoA: CoA drops under conditions of glucose or growth factor deprivation, paralleling acetyl-CoA and overall histone acetylation levels[14]. Moreover, manipulation of either metabolite in isolated nuclei impacts histone acetylation levels, with high CoA suppressing histone acetylation[14].

In mammals, the nucleo-cytoplasmic pool of acetyl-CoA is produced largely by 2 enzymes; ATP-Citrate Lyase (ACLY), which produces acetyl-CoA from citrate, and acyl-CoA synthetase short-chain family member 2 (ACSS2, also known as AceCS1), which ligates coenzyme A to acetate to generate acetyl-CoA[4]. Generation of nuclear-cytoplasmic acetyl-CoA from breakdown of glucose, fatty acids, and amino acids relies on export of mitochondrial citrate to the cytoplasm and its subsequent cleavage by ACLY. Given the rapid turnover of histone acetylation (minutes to hours)[21,22], a close interplay between ACLY and ACSS2 likely occurs to maintain the nuclear-cytoplasmic acetyl-CoA pools, with ACLY responsible for net input of acetyl-CoA from nutrients, and ACSS2 playing a key role in acetyl group recycling after generation of acetate from deacetylation reactions (Figure 2). In addition to ACLY and ACSS2, production of nuclear acetyl-CoA has very recently also been attributed to the Pyruvate Dehydrogenase Complex (PDC), which normally functions to generate acetyl-CoA from pyruvate in mitochondria for TCA cycle entry, but has now been shown to also be present and enzymatically active within the nucleus[23]. All three enzymes, ACLY, ACSS2, and PDC, have been shown to contribute to histone acetylation[23-25].

Oncogenic control of acetyl-CoA metabolism and histone acetylation

Acetyl-CoA plays crucial roles in energy generation, as well as in lipid and amino acid metabolism[4]. Hence, it is not surprising that production and utilization of this central metabolite are impacted by oncogenic signal transduction. Not all oncogenic stimuli influence acetyl-CoA metabolism identically; for example, in a direct comparison of metabolic flux changes mediated by myr-AKT or H-RAS^{V12G}, AKT stimulated citrate to lipid conversion (which requires ACLY-dependent acetyl-CoA production), while H-RAS suppressed this flux[26].

AKT has long been recognized as a major regulator of glucose uptake and metabolism[6]. AKT also promotes the phosphorylation of ACLY on Ser455, thereby increasing its activity[27,28]. We have recently found that levels of AKT phosphorylation in human gliomas and prostate tumors correlate significantly with global levels of histone acetylation[14]. In support of a metabolic mechanism underlying this relationship, expression of myr-AKT or an ACLY phosphomimetic (S44D) facilitated sustained acetyl-CoA and histone acetylation levels during glucose limitation. Reciprocally, Akt inhibition suppressed acetyl-CoA and histone acetylation levels, which were partially restored upon acetate supplementation[14]. Importantly, elevated histone acetylation is also detectable upon AKT activation *in vivo*[14].

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Elucidating the functional roles of metabolic regulation of histone acetylation will require further investigation. We speculate that oncogenes may exploit acetyl-CoA metabolism in part to modify chromatin in such a way to promote transformation and growth. In support of this possibility, work in yeast has shown that high acetyl-CoA stimulates promoter histone acetylation and expression of genes involved in cell growth and division[17,29]. Analogously, acetyl-CoA availability in glioblastoma cells regulates a gene expression signature enriched for genes involved in DNA replication and cell cycle[14]. While enabling acetyl-CoA production in glucose-limited conditions by providing cells with acetate does not *per se* accelerate proliferation, it does appear to poise cells for growth, potentially through gene regulation [14].

The proto-oncogene MYC has also been identified as a key regulator of acetyl-CoA metabolism and histone acetylation. Specifically, c-Myc was found to determine an increase in histone H4 acetylation in fibroblasts, an event that is coincident with and likely propaedeutic to cell cycle entry[30,31]. Myc-mediated histone acetylation relies on acetyl-CoA derived from mitochondria[31], presumably via citrate export and ACLY activity. In the absence of Myc, acetyl-CoA levels fall, despite compensatory increases in fatty acid oxidation[32]. Thus, both AKT and MYC have roles in promoting acetyl-CoA production and provision for histone acetylation.

Microenvironmental control of acetyl-CoA metabolism and histone acetylation

In addition to oncogenic controls, tumor microenvironmental conditions such as hypoxia, glucose deprivation, and pH changes also alter cellular metabolism and metabolite levels. Solid tumors expand and frequent incur a state of chronic hypoxia, due to poor or abnormal vascularization [33]. This activates a hypoxic response program coordinated by the hypoxia inducible factor (HIF) transcription factors, that includes enhanced glycolysis, reduced glucose entry into the TCA cycle, and upregulation of glutamine-dependent reductive carboxylation to produce citrate and lipogenic acetyl-CoA[34-36]. Hypoxia also increases the expression of ACSS2[37]. How hypoxia impacts acetyl-CoA availability for histone acetylation is not yet clear, but this could conceivably affect cellular responses and adaptability to a hypoxic environment.

Another distinguishing feature of the tumor microenvironment is the presence of a local acidic pH[38], due in part to elevated secretion of lactic acid by glycolytic cells. Extracellular acidosis also lowers intracellular pH (pHi), which promotes histone deacetylation [39]. Acidic pHi favors histone deacetylation as a mechanism to extrude protons from the cell; acetate is transported in a proton-coupled manner across the plasma membrane through monocarboxylate transporters. Chromatin has thus been proposed to function as a capacitor to ensure pHi balance[40]. Interestingly, hypoxia- and low pH-activated genes generally favor an aggressive, pro-metastatic phenotype [38], and likewise low histone acetylation levels are associated with poor patient prognosis [41]. This at first may seem at odds with the notion discussed above that nutrient-regulated histone acetylation appears to promote growth. One potential explanation is that these divergent effects may dominate at different disease stages. For example, histone acetylation changes are detected

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early in disease progression as a consequence of oncogene activation and may serve to initially facilitate growth. As disease progresses and pH in the microenvironment drops, acetate is mobilized from chromatin. Hence, the low histone acetylation that correlates with poor prognosis may be a consequence rather than a mediator of disease progression.

Tissue-specific environmental conditions can also play a major role in acetyl-CoA metabolism. This is exemplified by the role of butyrate, which is produced by commensal microorganisms in the gut, through fermentation of diet-derived fibers [42]. A short chain fatty acid, butyrate is a major energy source of normal colonocytes. Butyrate contributes to the mitochondrial acetyl-CoA pool after undergoing β-oxidation; consistently, in normal colonocytes butyrate promotes ACLY-dependent increase in histone acetylation and cell proliferation[43]. On the other hand, in cancer cells, butyrate is not oxidized but instead enters the nucleus and functions as an HDAC inhibitor, underlying the selective toxicity of butyrate to cancer cells. Notably, gene expression profiles mediated by butyrate are strikingly different whether elevated histone acetylation results from increased acetyl-CoA production or from HDAC inhibition[43], highlighting that the consequences of shifts in overall histone acetylation levels can be markedly different depending on the underlying mechanisms. Importantly, high fiber diet was shown to suppress colorectal tumorigenesis in mice, in a manner dependent on the presence of butyrate-producing gut bacteria[42]. Moreover, both butyrate and histone acetylation levels are elevated in human colon tumors compared to surrounding normal tissue[42].

These data underscore the concept that acetyl-CoA serves not only as a metabolic intermediate, but also as signaling molecule that confers metabolic information to chromatin (Figure 3). Beyond chromatin and gene regulation, recent studies have also shown that acetyl-CoA levels impact acetylation of many other proteins, influencing autophagy and multiple metabolic processes[44]. How oncogenic control of acetyl-CoA metabolism and acetylation influence gene expression programs, differentiation state, and stress responses in cancer will be exciting areas for further investigation.

Metabolic control of histone methylation

Histone lysines can be mono-, di- or tri-methylated and are recognized by particular chromatin-binding proteins, which locally orchestrate the gene expression machinery to either repress or activate neighboring genes. The universal methyl donor in mammals is S-adenosylmethionine (SAM), synthesized from methionine and ATP. SAM is an intermediate of one-carbon metabolism, constituted of two interconnected cycles of reactions, the folate and methionine cycles, which have metabolic inputs from methionine, serine and glycine metabolism, and folate[45,46]. Transfer of the methyl unit from SAM results in the production of S-adenosylhomocysteine (SAH), which is then recycled in the methionine cycle, but also acts as competitive inhibitor of methyltransferases. Hence, the SAM: SAH ratio is considered an indicator of the “methylation potential” of a cell [47].

Metabolic alterations, SAM levels, and histone methylation

Like acetyl-CoA, 1-carbon metabolism also plays key roles in biosynthetic reactions, including nucleotide and phospholipid synthesis[45,46]. Moreover, regulation of the

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availability of 1-carbon units is influenced by at least two major control points that are altered frequently in cancer cells. First, cellular uptake of methionine occurs through solute transporters such as Lat1 (Slc7a5), which is overexpressed in many tumors[48]. Secondly, the serine-glycine biosynthesis pathway, which donates 1-carbon units to regenerate methionine from homocysteine, is also frequently enhanced in cancer cells via amplification of 3-Phospoglycerate Dehydrogenase (PHGDH), a gatekeeper enzyme of the pathway[49,50]. Suppression of PHGDH in cancer cells with PHGDH amplification impairs proliferation[49,50], although its impact on histone methylation has not yet been addressed. Interestingly, overexpression of PHGDH in normal breast acini causes disruption of acinar organization, hinting at possible chromatin rearrangements[50].

Alterations in SAM and histone methylation levels have been described in cancer cells overexpressing nicotinamide N-methyltransferase (NNMT), an enzyme that catabolizes SAM to 1-Methyl Nicotinamide (1MNA). The NNMT reaction drains SAM and traps it into 1MNA, a highly stable metabolite that is not known to be further utilized by the cell. Hence, increased NNMT activity in cancer cells lowers SAM and histone methylation levels, and this is associated with the acquisition of a more aggressive phenotype[47].

Another striking example of metabolic control of histone methylation is in the context of stem cell pluripotency. SAM-dependent regulation of histone methylation is required for maintenance of pluripotency. In mouse ES cells, this occurs through threonine catabolism into glycine to generate 1-carbon units[51]. In human ES cells, methionine consumption is crucial for sustaining histone methylation and pluripotency[52]. It is not yet known whether SAM-dependent control of histone methylation regulates cellular plasticity or differentiation in the context of tumor development.

Perspectives

Metabolites such as acetyl-CoA and SAM connect nutritional status to signaling and gene expression. This connection is impacted by oncogenic and microenvironmental stimuli, thereby contributing to chromatin organization in cancer cells. The biological programs regulated by metabolic control of the epigenome are still largely elusive. Contributions to growth and proliferation, cellular plasticity, and differentiation will be intriguing areas for future investigation. Also poorly understood is whether diet induces changes in cellular metabolite levels that could help explain the increasingly clear link between overnutrition and cancer. Further elucidation of the connections between metabolism, oncogenic signaling and chromatin organization is expected to enhance our understanding of the basic biology of cancer and to potentially point towards new therapeutic approaches.

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Highlights

- Oncogenic and microenvironmental stimuli rewire metabolism in cancer cells.
- Many chromatin-modifying enzymes rely on metabolites as cofactors or substrates.
- Histone acetylation is sensitive to acetyl-CoA levels, and linked to growth and proliferation.
- Histone methylation is sensitive to the methyl donor S-adenosylmethionine.

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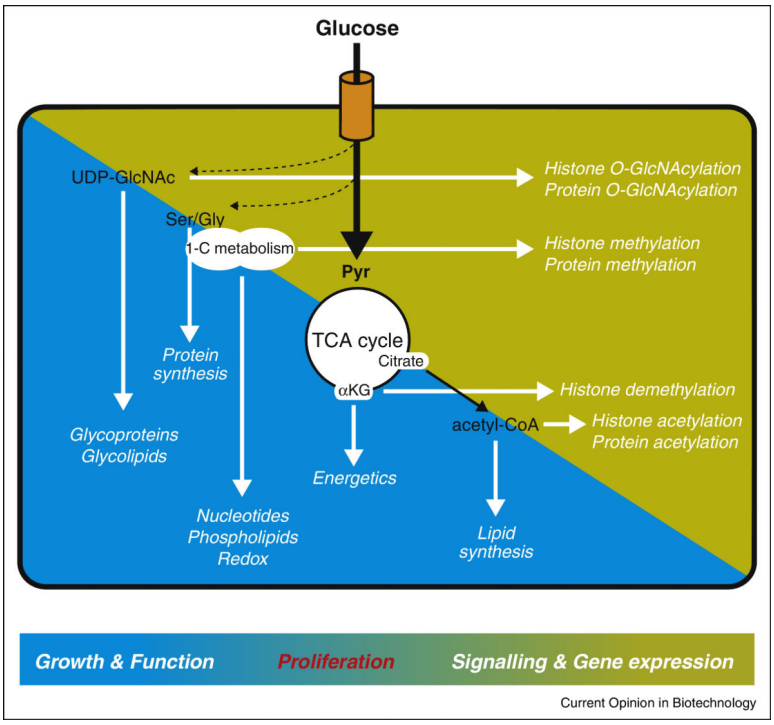

Figure 1.

Glucose-derived metabolic intermediates provide energy, reducing equivalents and building blocks to sustain normal cell functions and biomass accumulation (blue background). The same intermediates impact numerous signaling events, serving as substrates or cofactor for post-translational modifications of histones or proteins (yellow background). Through dual roles in the regulation of biomass generation and signal transduction, cellular metabolism is central in the decision to grow and proliferate or to remain quiescent.

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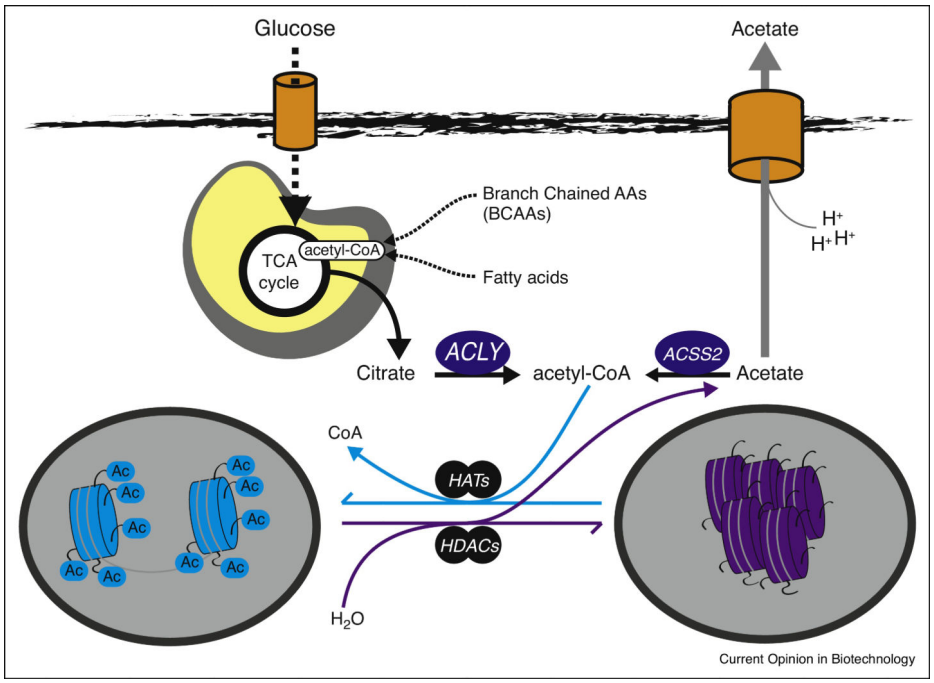

Figure 2.

Acetyl-CoA production and utilization for histone acetylation. ATP-citrate lyase (ACLY) generates nuclear-cytoplasmic acetyl-CoA from nutrients such as glucose, amino acids, and fatty acids. Each of these nutrients generates acetyl-CoA within mitochondria. Transfer of these acetyl units from mitochondria to cytoplasm involves mitochondrial synthesis of citrate from oxaloacetate and acetyl-CoA, then subsequent mitochondrial export and then cleavage of citrate into acetyl-CoA and oxaloacetate by ACLY. Acetyl-CoA serves as the substrate for lysine acetyltransferases (KATs). Histone deacetylases (HDACs) remove acetyl moieties from histones, leading to local production of acetate, which in turn can be recycled back into acetyl-CoA by ACSS2 or exported in a proton-coupled manner to facilitate pH balance. Not shown, the pyruvate dehydrogenase complex has also recently been shown to be present within the nucleus and to provide an additional source of nuclear acetyl-CoA for histone acetylation.

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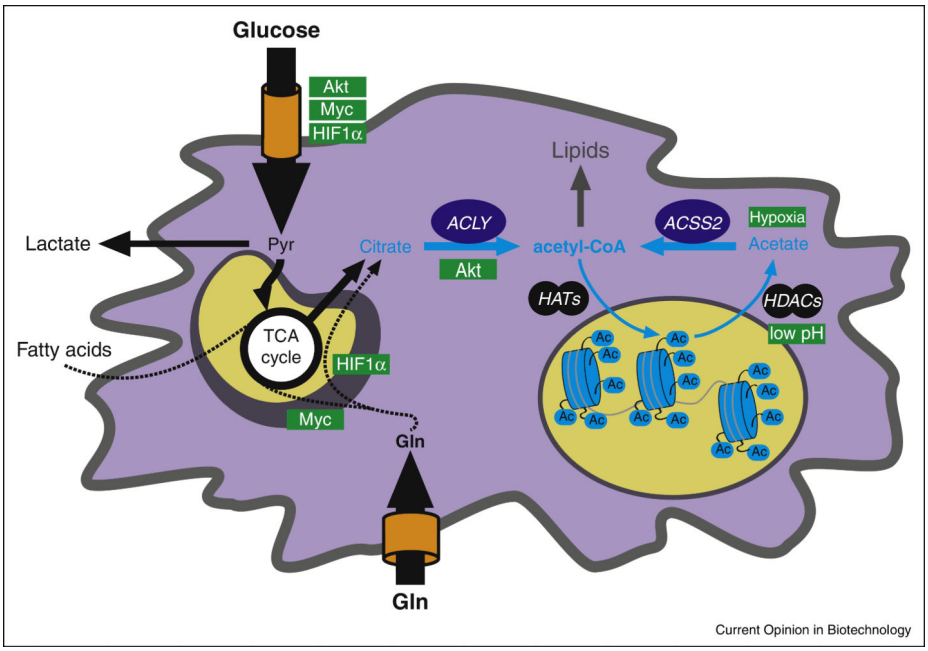

Figure 3.

Acetyl-CoA metabolism is impacted by oncogenes and microenvironmental cues (positive regulators indicated in green boxes).