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Mini-review

Epigenetics and cancer metabolism

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ABSTRACT

Cancer cells adapt their metabolism to support proliferation and survival. A hallmark of cancer, this alteration is characterized by dysfunctional metabolic enzymes, changes in nutrient availability, tumor microenvironment and oncogenic mutations. Metabolic rewiring in cancer is tightly connected to changes at the epigenetic level. Enzymes that mediate epigenetic status of cells catalyze posttranslational modifications of DNA and histones and influence metabolic gene expression. These enzymes require metabolites that are used as cofactors and substrates to carry out reactions. This interaction of epigenetics and metabolism constitutes a new avenue of cancer biology and could lead to new insights for the development of anti-cancer therapeutics.

1. Introduction

Conrad Waddington first established the concept of epigenetics in 1942 when he proposed that genes interact with their product to determine a phenotype [1]. This observation was later corroborated by findings from Barker and Osmond in 1986 that showed genes respond to environmental exposures during embryonic development [2]. They demonstrated that expectant mothers with poor eating habits give birth to children more susceptible to disease during childhood and well into their adulthood. This developmental response is characterized by changes in gene activity that is passed onto successive generations. Further evidence of transgenerational transmission of genetics emerged from the Bygren and Pembrey investigation into the possibility that some gene functions are not only passed on from mother to fetus during pregnancy but can be carried over from both male and female past exposures before conception [3,4]. These findings shaped the definition of the term "epigenetics" to become the study of modifications in gene expression that do not involve changes in DNA nucleotide sequences [5]. Hence, the epigenetic layer of gene regulation controls both normal cellular processes and abnormal events associated with disease, notably cancer [6,7].

It is widely recognized that cancer is a constellation of diseases manifested in various clinical subtypes, each characterized by distinct histopathological and biological features [8]. At the origin of all cancers remains abnormal cell proliferation, which has so far offered a useful but incomplete target for anticancer therapy [9,10]. Chemotherapeutic agents exerting cytotoxic effects on rapidly dividing cells are commonly used as first line of therapy, but become inefficient when tumors acquire resistant phenotypes and progress into a refractory phase. There is considerable need to circumvent tumor resistance to conventional therapy to achieve a more successful treatment. This goal is potentially attainable by exploiting intrinsic and extrinsic factors that contribute to tumorigenesis. One emerging possibility of new cancer therapy is to target the alteration of cell metabolism [11,12]. Over eighty years ago, Otto Warburg established that cancer cells metabolize increasing amounts of glucose through fermentation even in oxygen rich environments that originally suggested defective mitochondria [13]. Termed the Warburg Effect by Efraim Racker, this phenomenon was later shown to occur even with fully functional mitochondria [14]. It also has been observed that cancer cells utilize glutamine to support the synthesis of cellular building blocks (amino acids, ribonucleotides, and lipids) [15]. One mechanism of metabolic alteration in cancer cells is shown to occur at the epigenetic level [16]. Enzymes involved in epigenetic modulation necessitate a tightly regulated level of metabolic intermediates and cofactors, in addition to controlling genes implicated in metabolic reprogramming. In the context of cancer, these enzymes are dysregulated and promote functions conducive to tumor growth, namely, activation of oncogenes, and inactivation of tumor-suppressor genes [17]. In this review we will highlight the role of intermediate metabolites and cofactors in regulating epigenetic biochemical reactions. We will then address the significance of amino acid metabolism in mediating epigenetic changes. Furthermore, the role of environmental inputs such as nutrition in modulating the epigenome will be discussed. Finally, we will conclude with a

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discussion on pharmacologic intervention strategies for the reprogramming of metabolic pathways.

2. Metabolites and cofactors mediate activity of epigenetic-associated enzymes

Chromatin restructuring is a dynamic event that regulates gene transcription. Chromatin is composed of a nucleosome core made of a histone octamer (histone 2A, 2B, 3 and 4) wrapped by DNA. Posttranslational modifications of the DNA and histone tails dictate the configuration of chromatin whether open (euchromatin) and generally conducive to gene transcription, or condensed (heterochromatin) that promotes gene repression. These covalent modifications are crucial to the accessibility of DNA to transcriptional machinery, hence determining which genes are turned "on" or "off" [18]. These modifications can be retained across generations conferring properties of epigenetics to their associated DNA. Epigenetic regulation of gene expression occurs at the level of DNA, histones, and RNA. The most well characterized are DNA methylation, histone methylation, acetylation, and phosphorylation, and micrRNA-dependent gene silencing [19]. The activities of the many chromatin-modifying enzymes described herein are regulated in part by the concentrations of their required metabolic substrates or cofactors (Table 1) [16,20].

DNA methylation is mediated by DNA methyltransferase (DNMT) enzymes, which rely on the methyl donor S-Adenosyl methionine (SAM). The methyl group is transferred to the fifth position carbon of cytosine within cytosine guanine (CpG) dinucleotides. Methylation of CpG motifs in gene promoter sequences often results in gene silencing [21]. This event could be reversed through a multistep demethylation reaction mediated by ten-eleven translocation (TET) proteins [22–24]. Global DNA hypomethylation and site-specific CpG promoter hypermethylation are common epigenetic features of cancer [25].

Methylation of histones occurs at the lysine or arginine residue and is catalyzed by histone methyltransferase (HMT) enzymes [26]. Like DNMT, HMT utilizes SAM as a key methyl donor. Two family proteins have been identified to reverse histone methylation events. The first is a flavin adenine dinucleotide (FAD)-dependent oxidase known as LSD1, and the second is alpha-ketoglutarate (αKG) and ferrous ion-dependent oxygenase known as JmjC-domain containing histone demethylase (JHDM) [27–30]. Histone demethylase activity is associated with context-dependent activation or repression of gene transcription [31–33].

Besides histone methylation, histone acetylation is another dynamic process that is regulated by two classes of enzymes: the histone acetyltransferases (HAT) and histone deacetylases (HDAC) [34]. HAT transfers the acetyl group of Acetyl-CoA to lysine residues of histones and is mostly associated with transcriptional activation [35,36]. Histone deacetylation is frequently carried by two broad classes of deacetylases. The first is zinc-dependent and the second is a nicotinamide adenine dinucleotide (NAD^+)-dependent family of proteins termed Sirtuins. The levels of these deacetylases have been shown to be elevated in several types of cancers and promote gene repression and silencing [37,38].

Additional routes of epigenetic modification are gaining interest. Molecules involved in intracellular signaling pathways have been known to affect nuclear transcription through indirect mechanisms. However, it is now recognized that direct mechanisms also exist, as some kinases are capable of translocating to the nucleus to directly phosphorylate histones [39]. One such example is AMP-activated protein kinase (AMPK), a kinase that serves as a metabolic sensor of ATP/AMP ratio [40]. During metabolic stress and in response to low ATP/AMP, AMPK phosphorylates histone H2B on serine 36 that triggers the expression of genes necessary for cell survival and adaptation to metabolic changes [41]. Additionally, modifications of the O-linked N-acetylglucosamine (GlcNAc) type have been reported to occur on histone H2B at serine 112. The glycosylation reaction is catalyzed by O-GlcNAc transferase (OGT) [42,43]. The implication of this type of epigenetic modification is not fully understood and warrants further investigation.

3. Genetic and epigenetic alteration of metabolic enzymes in cancer

Cancer initiation and progression are driven by alteration in gene expression as a result of specific activating mutations in oncogenes and prometastatic genes, or inactivating mutations in tumor suppressor genes. Compelling evidence implicates mutations in metabolic enzymes as a predisposition to tumorigenesis [44–46]. Among the metabolic enzymes reported to contribute to cancer pathogenesis we cite: $NADP^+$-dependent isocitrate dehydrogenase (cytosolic IDH1 and mitochondrial IDH2) in gliomas [47,48], acute myelogenous leukemia [49], and chondrosarcoma [50]; succinate dehydrogenase (SDH) in familial paragangliomas [51]; and fumarate hydratase (FH) in leiomyoma, leiomyosarcoma, and papillary renal cancers [52]. Mutational inactivation in these enzymes leads to the accumulation of 2-hydroxyglutarate, succinate, and fumarate, respectively [53]. At high concentrations, these metabolites inhibit the activity of histone and DNA demethylases and take on the role of oncometabolites [54] (Fig. 1). In recent work by Killian et al., a characteristic DNA hypermethylation pattern was observed in gastrointestinal stromal tumors with mutations in SDH. Such alterations were shown to be sufficient to drive oncogenesis [55]. Similar observations of genomic hypermethylation were reported by Letouze et al. in paragangliomas and pheochromocytomas carrying mutations in SDH. This phenotype associated with aggressive clinical behavior of the disease [56].

Phosphoglycerate dehydrogenase (PHGDH), a metabolic enzyme, is amplified in melanoma and breast cancer [57,58]. Mutational amplification in PHGDH directs the metabolic flux toward the serine biosynthetic pathway, which regulates one-carbon metabolism (Fig. 1). This event increases the concentration of the methyl donor methionine that can affect cellular epigenetics [59]. A current study by Ulanovskaya et al. uncovered a role for nicotinamide N-methyltransferase (NNMT) in regulating epigenetic events in cancer cells. NNMT is aberrantly expressed in various cancer types and is associated with increased cell invasive and migratory potentials. NNMT catalyzes the transfer of the methyl

Table 1
Interface of metabolic pathways and epigenetic regulation.

	Glucose			Glucose/gluta mine	Serine/glycine/threonine
Hexosamine Pathway	Glycolysis	TCA Cycle	TCA Cycle	TCA Cycle	One carbon metabolism/folate–methionine cycle
GlcNac	NAD+/NADH	Acetyl CoA	AMP/ATP	αKG	SAM
OGT	SIRT	HAT	AMPK	HDM/TET	HMT/DNMT
GlcNacylation	Deacetylation	Acetylation	Phosphorylation	Demethylation	Methylation

*GlcNac, O-linked N-acetylglucosamine; OGT, O-linked N-acetylglucosamine transferase; SIRT, sirtuins; TCA cycle, tricarboxylic acid cycle; HAT, histone acetyltransferase; AMPK, 5′ adenosine monophosphate-activated protein kinase; αKG, alpha ketoglutarate; HDM, histone demethylase; SAM, S-Adenosyl methionine; HMT, histone methyltransferase; DNMT, DNA methyltransferase.

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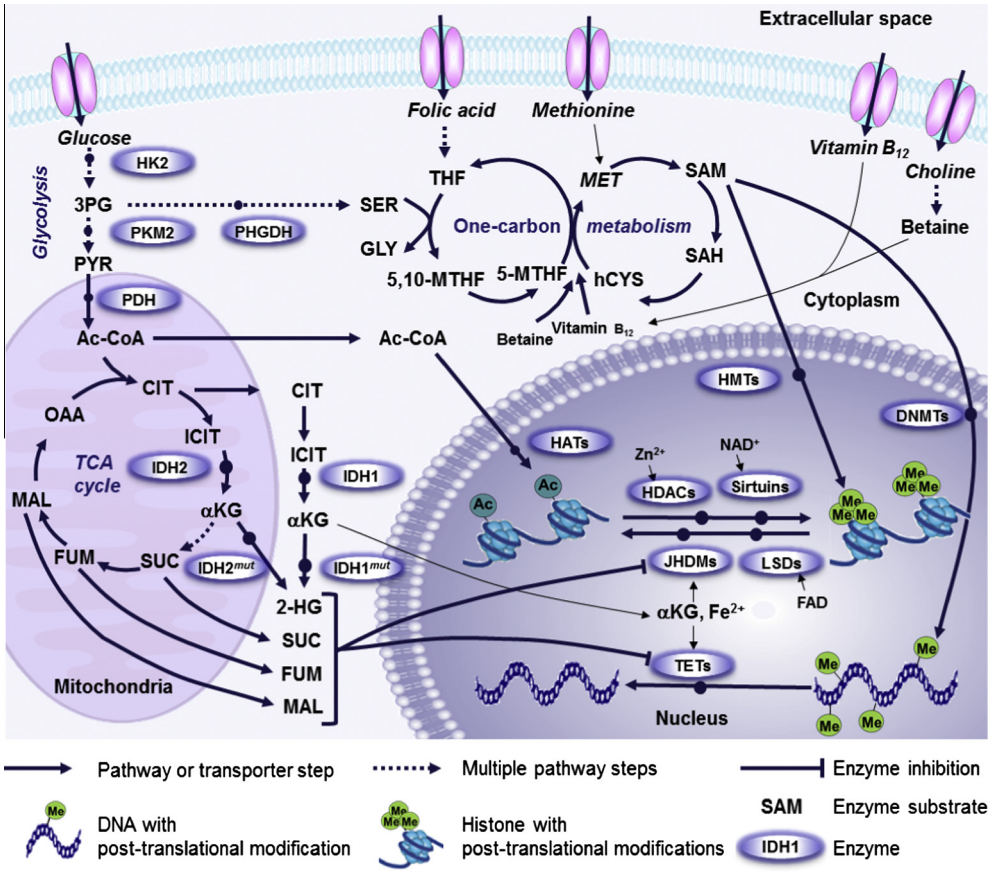

Fig. 1. Metabolic pathways involved in epigenetic regulation through acetylation and methylation. Pyruvate (PYR), one of the end products of glycolysis, is converted to Acetyl-Co-EnzymeA (Ac-CoA) by pyruvate dehydrogenase (PDH) and serves as the acetyl donor for histone acetylation by histone acetyl transferases (HATs). Accumulated 2-hydroxyglutarate (2-HG) generated by mutated isocitrate dehydrogenase (IDH1mut, cytosol; IDH2mut, mitochondria) inhibits alpha-ketoglutarate (αKG)-dependent DNA- and histone-demethylases. Several additional mutated TCA cycle enzymes lead to accumulation of succinate (SUC), fumarate (FUM) and malate (MAL) which leads to a similar inhibition of demethylases. FAD-dependent Lysine (K)-specific demethylases (LSDs) are also involved in histone demethylation but are not subject to inhibition by 2-HG and TCA cycle intermediates. Phosphoglycerate dehydrogenase (PHGDH) diverts 3-phosphoglycerate (3PG) away from glycolysis into the tetrahydrofolate (THF) and methionine (MET) cycles. Dietary uptake of folate, cobalamine, choline and methionine also contribute to one-carbon metabolism. The methionine cycle intermediate S-adenosylmethionine (SAM) serves as the methyl donor during DNA methyl transferase (DNMT) and histone methyl transferase (HMT) reactions. Histone deacetylation is performed by either zink dependent histone deacetylases (HDACs) or NAD + dependent Sirtuins. CIT, citrate; ICIT, isocitrate; OAA, Oxaloacetate; SER, Serine; GLY, Glycine; 5,10-MTHF, 5,10-methylene-THF; 5-MTHF, 5-methyl-THF; TET, ten-eleven translocation; JmjC-domain containing histone demethylases (JHDMs); homocysteine, hCYS; SAH, S-adenosylhomocysteine; TCA cycle, tricarboxylic acid cycle; FAD, Flavin adenine dinucleotide.

group from SAM to nicotinamide, a sequestration process that impairs SAM-mediated methylation of histone and DNA [60].

A number of metabolic enzymes is reported to be altered by epigenetic events rather than genetic mutations in cancer cells. Hexokinase isoform 2 (HK2) upregulation in liver cancer and glioblastoma is believed to be the result of hypomethylation of its promoter [61,62]. Elevated levels of HK2 in cancers promote increased glycolytic flux. Along the same line, pyruvate kinase M2 (PKM2), the enzyme that carries out the final step in glycolysis, is subject to acetylation reactions that decrease its activity, favoring trafficking of glycolytic intermediates into biosynthetic processes of nucleic acids, lipids, and amino acids [63,64]. This event appears to be required for proliferation in certain contexts. Fructose-1,6-bisphosphatase (FBP1) regulates gluconeogenesis and is silenced through promoter methylation in gastric, colon, and liver cancers [65,66]. The inhibition of gluconeogenesis leads to higher glycolytic rates, which are advantageous to tumor cells.

4. Amino acid metabolic pathways in epigenetic regulation

One-carbon metabolism is a network of interrelated biological reactions with integral roles in DNA synthesis and methylation (Fig. 1). A key metabolite in one-carbon metabolism is S-Adenosyl methionine (SAM). The ability to donate a methyl group gives SAM its role in cells as a universal methyl donor. Many enzymes that carry out nucleic acid modifications undergo a methyltransfer reaction. For example, DNA and lysine methylation enzymes that regulate DNA transcription during chromatin remodeling are methyl group acceptors. A number of metabolites feed into the one-carbon metabolism and facilitate the availability of SAM. Glucose and glutamine are the most studied factors contributing to the understanding of cancer cell metabolism [67]. Non-essential amino acids (NEAA) also play a significant role by feeding into pathways that generate the cell's building blocks and provide substrates or cofactors for epigenetic processes [58,68]. For example, serine and glycine are metabolized through the one-carbon metabolism pathway that has been reviewed elsewhere[70]. On the other hand, proline's metabolic system is distinct in that it is catabolized by proline dehydrogenase (PRODH) to produce pyrroline-5-carboxylate (P5C) [68]. P5C is then sequentially converted to glutamate and αKG potentially influencing epigenetic mechanisms. Overexpression of PRODH in immunodeficient mice exhibited tumor-suppressive properties and could be negatively regulated by microRNA-23b [66]. Such crosstalk emphasizes the complexity of cancer cell metabolism. Further studies on NEAA metabolism and

Table 2
Pharmacological agents and natural compounds for epigenetic cancer therapy.

Target pathway	Pharmacological agents and Natural compounds	Metabolic/epigenetic Mechanism of action	Stage of therapy development
Glucose metabolism	2-deoxyglucose	Reduce glycolysis	Clinical and preclinical data [84,85]
	Mannoheptulose		Preclinical data [86]
Glutamine/amino acid Metabolism	L-asparagine	Depletion of asparagine and Glutamine	Approved
Serine/Glycine metabolism	shRNA to PHGDH	Inhibitor of *de novo* serine synthesis	Preclinical data [57,58]
Lipid metabolism	Betulin	Inhibitor of SREBP	Preclinical data [87]
	Hydroxycitrate	Inhibitor of ATP Citrate lyase	Preclinical data [88]
	Statins	Inhibitor of HMG-CoA reductase	Approved
Nucleotide metabolism	5-fluorouracil	Impair DNA synthesis	Approved
	Methotrexate		Approved
Epigenetic modifications	Folate, choline, methionine, Betaine, selected B vitamins, Flavonoids, EGCG, genistein	Inhibitors of DNA Methyltransferases	Lab studies
	Butyrate, sulforaphane, Allylmercaptan, 3,3-Diindolylmethane	Inhibitors of Histone deacetylases	Lab studies
	Anacardic acid, garcinol, Curcumin, EGCG, Genistein	Inhibitors of Histone Acetyltransferases	Lab studies
	Butyrate, cambinol, Dihydrocoumarin, genistein	Inhibitors of acetylation of non-Histone proteins	Lab studies

PHGDH, phosphoglycerate dehydrogenase; SREBP, sterol regulatory element-binding protein; EGCG, epigallocatechin-3-gallate; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A.

their regulation of epigenetic events in cancer will provide a new avenue for the development of anti-cancer therapeutics.

5. Bioactive food compounds targeting the epigenome

Metabolism is a regulatory interface shaped by the environment. Food exposure plays a direct role in resetting genes for wellness or illness by targeting different elements of the epigenetic machinery [70]. A variety of natural compounds from different sources have been shown to directly regulate metabolism related to epigenetics [71]. Of the micronutrients with direct effects on one-carbon metabolism, folate, cobalamine, choline, flavonoids, methionine, and betaine are metabolized in pathways that mediate epigenetic events [72]. Bioactive food compounds such as polyphenols found in plants are claimed to regulate DNMT expression and activity, increase HAT activity, and activate sirtuins to elicit antioxidative, anti-tumorigenic, and anti-metastatic properties [72,73]. Fatty acids are also emerging as important regulators of post-translational modifications and have been implicated in cancer progression [74,75]. We refer the reader to a detailed review by Ong et al. on the role of dietary compounds on epigenetic regulation in cancer [76]. There is increased interest in harnessing the benefits of these compounds to affect the epigenetic reprogramming of cancer cell metabolism. However, the field faces a technical challenge in determining metabolite bioavailability and dose-dependent effects in humans. It is not clear whether any of these factors affect metabolism at orally available doses. It is important to note concentrations used for studies *in vitro* do not recapitulate the levels of metabolites provided through diet. Primary factors that should be considered in future investigations include the effective doses and dose timing of bioactive food compounds to attain epigenetic effects [77,78].

6. Epigenetic therapeutic targets for the treatment of cancer

Epigenetics and metabolism are highly interconnected in a reciprocal fashion. The importance of these relationships are accentuated by the reversibility of both processes [79]. This feature has attracted a significant amount of attention in the prevention and treatment of many illnesses including cancer. As epigenetic abnormalities have been shown to be both causative and contributing factors in cancer, chemical agents and natural compounds that are direct or indirect regulators of the epigenome constitute an excellent approach in cancer prevention and potentially in anti-cancer therapy [80–83] (summarized in Table 2).

With every potential therapy comes a challenge. Targeting cancer cell metabolism aims to reestablish normal cell metabolism, correct signaling cascades, and reverse epigenetic reactions. As our understanding of cancer cell metabolism expands, more combination therapy targeting different branches of metabolic pathways should be considered. In addition to targeting metabolic pathways that support biosynthesis [15], a new direction is to modulate metabolic pathways involved in epigenetic reprogramming that contributes to tumor progression. It is important to note that metabolic events occur in multiple cellular compartments, thus learning the transport of metabolites between cytoplasm, mitochondria and nucleus may be important for developing effective targeting. Of importance is also the artificial culturing conditions used experimentally to study cancer cell biology. These growth media are complex in composition and not fully defined. Changes in media composition are predicted to have dramatic effects on metabolism. It is therefore imperative to carefully interpret data pertaining to quantitative metabolic flux prior to extrapolating to human disease. Nevertheless it is anticipated that with rapid technological advances, refinement of current protocols, and the surge of interest in the field, the intervention of cancer cell metabolism may contribute to a breakthrough in the prevention and treatment of cancer in the near future.

Conflict of Interest

Each author has no conflict of interest to disclose.

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