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Review

A New Frontier in Studying Dietary Phytochemicals in Cancer and in Health: Metabolic and Epigenetic Reprogramming

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ABSTRACT: Metabolic rewiring and epigenetic reprogramming are closely inter-related, and mutually regulate each other to control cell growth in cancer initiation, promotion, progression, and metastasis. Epigenetics plays a crucial role in regulating normal cellular functions as well as pathological conditions in many diseases, including cancer. Conversely, certain mitochondrial metabolites are considered as essential cofactors and regulators of epigenetic mechanisms. Furthermore, dysregulation of metabolism promotes tumor cell growth and reprograms the cells to produce metabolites and bioenergy needed to support cancer cell proliferation. Hence, metabolic reprogramming which alters the metabolites/epigenetic cofactors, would drive the epigenetic landscape, including DNA methylation and histone modification, that could lead to cancer initiation, promotion, and progression. Recognizing the diverse array of benefits of phytochemicals, they are gaining increasing interest in cancer interception and treatment. One of the significant mechanisms of cancer interception and treatment by phytochemicals is reprogramming of the key metabolic pathways and remodeling of cancer epigenetics. This review focuses on the metabolic remodeling and epigenetics reprogramming in cancer and investigates the potential mechanisms by which phytochemicals can mitigate cancer.

Keywords: cancer, epigenetics, metabolism, phytochemicals

INTRODUCTION

Epigenetics is the study of genomic changes that modulate gene expression and the corresponding phenotype without altering the genetic nucleotide sequence. The mechanisms of epigenetics involve chemical changes to DNA and/or the packaging of histone protein that alters how the genetic material is stored in the nucleus or expressed (Hughes, 2014). Epigenetics has been shown to play an essential role in regulating critical normal cellular functions such as X-chromosome inactivation (Payer and Lee, 2008), tissue-specific gene expression (Illingworth et al., 2008), genomic imprinting (Li et al., 1993), non-coding DNA regulation (Jones and Takai, 2001), and long-term memory formation (Lubin et al., 2011). However, epigenetic alterations have also been associated with various pathological conditions, including cancer (Jones and Baylin, 2002), metabolic syndrome (Bruce and Cagampang, 2011), Alzheimer's disease (Stilling and Fischer, 2011), and neurological disorders (Gos, 2013). Interestingly, epigenetic mechanisms are highly affected by extrinsic environmental stimuli such as dietary phytochemicals, which can be a potential strategy for treating chronic life-threatening diseases such as cancer (Suter and Aagaard-Tillery, 2009; Wu et al., 2022). Along with dietary phytochemicals, some mitochondrial metabolites which are basic cofactors of the basic epigenetic machinery, are considered essential regulators of epigenetic mechanisms.

Mitochondrial metabolism is involved in the catabolism of biomolecules and energy production, as well as providing essential precursors for many biomolecules, which makes it a central hub for cellular bioenergetics (Spinelli and Haigis, 2018). Mitochondria can rapidly adapt to different environmental stimuli and metabolic conditions (Anderson et al., 2018). In cancer cells, mitochondrial metabolism plays an important function where it modifies metabolic pathways to obtain more energy and biomolecules to fuel cell proliferation. This phenomenon is known as metabolic reprogramming and is considered a hallmark of cancer (Hanahan and Weinberg, 2011). Furthermore, mitochondrial metabolism has been regarded as a major regulator of epigenetic modifications by sup-

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plying the epigenetic machinery with intermediary metabolites (Chisolm and Weinmann, 2018; Wang and Lei, 2018; Zheng et al., 2020). These metabolites act as cofactors or substrates for catalytic epigenetic modification and transcriptional regulation. Hence, targeting metabolic pathways engaged in cancer has gained increasing interest in targeting cancer interception and treatment. In this regard, dietary phytochemicals are considered as a potential chemoprevention and treatment strategy targeting metabolic reprogramming and epigenetic rewiring (Wu et al., 2022).

Biologically active phytochemicals are compounds with diverse chemical structures found in plants that exert many health beneficial biological effects and possess diverse molecular mechanisms including epigenetics (Table 1) (Fang et al., 2003; Chen et al., 2004; Fang et al., 2005; Druesne-Pecollo et al., 2007; Choi et al., 2009; Ho et al., 2009; Balasubramanian et al., 2010; Wu et al., 2011; Gong et al., 2012; An et al., 2013; Kang et al., 2013; Wang et al., 2014; Guo et al., 2015; Jiang et al., 2016; Kala and Tollefsbol, 2016; Li et al., 2017b; Gao and Tollefsbol, 2018; Cremonini et al., 2019; Kuo et al., 2019; Yang et al., 2019; Wu et al., 2020). For a long time, they have been used for the protection and treatment of various diseases, such as diabetic nephropathy (Hudlikar et al., 2021), obesity (Martin et al., 2013; Dincer and Yuksel, 2021; Li et al., 2022c), and cancer (Lee et al., 2011; Kotecha et al., 2016). In general, mounting evidence shows that dietary phytochemicals are potent chemopreventive/cancer interceptive agents due to their antioxidant, metabolic modulation, and epigenetic regulation properties (Gerhauser, 2013; Thakur et al., 2014; Russo et al., 2017; Wu et al., 2022). In this review, we will discuss the potential cancer interceptive effects of dietary phytochemicals by targeting metabolic rewiring and epigenetic reprogramming in cancer. Furthermore, we will summarize the metabolic pathways and epigenetic mechanisms involved in cancer and will attempt to integrate metabolism and epigenetics in cancer development and treatment.

Table 1. Examples of phytochemicals regulating chromatin-modifying enzymes and their epigenetic effect in cancer cell

Class	Agent	Epigenetic effect	Biological and anti-cancer effects	Reference
Allyl sulfides	Diallyl disulfide	HDAC inhibitor	Activates Nrf2-mediating pathways and shows anti-proliferative properties	(Chen et al., 2004; Druesne-Pecollo et al., 2007)
Flavonoids	Epigallocatechin-3-gallate	HAT inhibitor DNMT inhibitor Histone methylation inhibitor	Changes methylation patterns in the ERα promoter, thereby reactivating ERα expression and re-sensitizing breast cancer cells to tamoxifen	(Fang et al., 2003; Balasubramanian et al., 2010; Choi et al., 2009; Li et al., 2017b)
	Resveratrol	DNMT and HDAC inhibitor Sirtuins activator	Inhibits proteins that contribute to oxidative stress and tumors	(Kala and Tollefsbol, 2016; Gao and Tollefsbol, 2018)
	Genistein	DNA hypomethylation Histone hyperacetylation	Reactivates tumor suppressor-related genes, such as p16, p21, RARβ, CCND2, GSTP1, MGMT, and BTG3	(Fang et al., 2005)
	Curcumin	DNMT inhibitor HDAC inhibitor HAT inhibitor	Modifies of CpG methylation; the demethylation was associated with reduced protein expression of DNMTs and HDACs and ultimately cancer prevention	(Guo et al., 2015; Wu et al., 2020)
	Anthocyanidins	DNMT inhibitor HDAC inhibitor	Activates of antioxidant Nrf2-ARE pathway and attenuates NF-κB and ERK1/2 redox pathways	(Cremonini et al., 2019; Kuo et al., 2019)
Isothiocyanates	Sulforaphane	HDAC inhibitor	Induces apoptosis and accumulation of cells at G0/G1 and G2/M and S phase arrest	(Ho et al., 2009; Jiang et al., 2016)
Triterpenoids	Urosolic acid	DNMT inhibitor HDAC inhibitor	Demethylates the CpG sites in the Nrf2 promoter region, which reduces tumorigenesis	(Yang et al., 2019)
Herbal medicinal product	Ginseng compounds (compound K and Ginsenoside Rh2)	Demethylation and miRNAs regulation	Reactivates RUNX3 and inhibits proliferation of HT29 and human glioma cells	(Wu et al., 2011; An et al., 2013; Kang et al., 2013)
	Salvia miltiorrhiza compounds (tanshinone I and IIA)	DNMTs inhibitor HDACs inhibitor Inhibited the over-expressed miR-155	Reduces the methylation of Nrf2 promoter, decreases inflammatory responses in LPS-induced macrophages, and triggers cell cycle arrest in breast cancer cells	(Gong et al., 2012; Wang et al., 2014)

HDAC, histone deacetylase; HAT, histone acetyltransferase; DNMT, DNA methyltransferase; ERα, estrogen receptor-α; LPS, lipopolysaccharide.

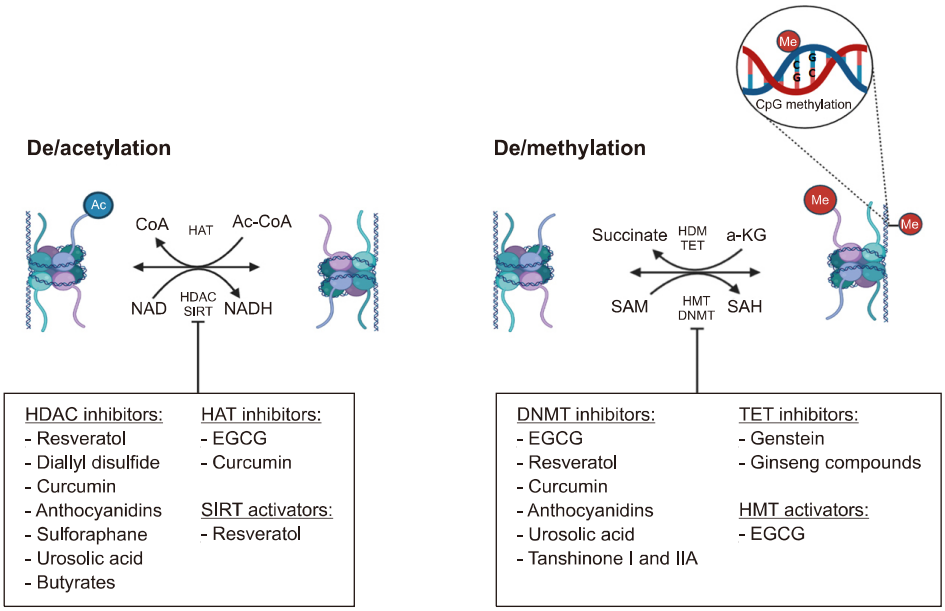

Fig. 1. Metabolites regulating major epigenetic mechanisms through phytochemicals. CoA, coenzyme A; NAD, nicotinamide adenine dinucleotide; NADH, nicotinamide adenine dinucleotide hydride; HDAC, histone deacetylase; HAT, histone acetyltransferase; EGCG, epigallocatechin-3-gallate; SIRT, sirtuin; HDM, histone demethylase; TET, ten-eleven translocation; SAM, *S*-adenosyl methionine; SAH, *S*-adenosyl-L-homocysteine; HMT, histone methyltransferase; DNMT, DNA methyltransferase.

ROLE OF PHYTOCHEMICALS IN EPIGENETIC REGULATION IN CANCER CELLS

While there are many epigenetic mechanisms have been revealed, three of the most prominent ones have been identified as major epigenetic modulators, which are DNA methylation, histone de/acetylation and de/methylation, and non-coding RNAs (Choudhuri, 2011). Here, we will summarize some of the major cancer epigenetic pathways and the role of different classes of phytochemicals in targeting these pathways (Table 1 and Fig. 1).

DNA methylation

DNA methylation is the transfer of a methyl group to the 5' position of cytosine residue that precedes guanine in a CG dinucleotide sequence (i.e., CpG island). This methylated sequence is found in abundant in the gene promoter region in the mammalian genome. The methylation reaction is enabled by a group of enzymes known as DNA methyltransferases (DNMTs). *S*-Adenosyl methionine (SAM), one of the mitochondrial metabolites, serves as the methyl group donor and is directly converted to *S*-adenosyl-L-homocysteine (SAH). SAM/SAH ratio is considered a universal biosensor of the cellular metabolic ability of DNA methylation state (Shyh-Chang et al., 2013). Hypermethylated CpG islands are usually linked with gene silencing in many cancer cells. For example, NRF2 is a nuclear factor that activates the expression of antioxidant genes, that protect the cells from oxidative stress-induced DNA or other damages in normal cells, but in advanced tumor cells, it could lead to cancer resistance against chemotherapeutic agents and or oxidative stress-induced cell death. In colorectal cancer (CRC) cells with a hypermethylated KEAP1's promoter, a negative regulator of NRF2, showed decreased mRNA levels, which suggests that mRNA level is regulated by the methylated KEAP1 promoter (Hanada et al., 2012; Wu et al., 2019). Furthermore, in 53% of tumor tissues from 40 surgical CRC specimens, hypermethylated KEAP1 promoter was revealed, potentially correlating to a decrease in the efficacy of anticancer drugs (Hanada et al., 2012). In this context, butyrate significantly decreases the KEAP1 promoter methylation and can promote the KEAP1 mRNA and protein expression levels resulting in decreased NRF2 protein levels and potentially contributing to the butyrate-mediated cancer prevention and treatment (Wang et al., 2022a). In the same study, butyrate treated cells showed decreased SAM/SAH ratios which is an indicator of potential reduced cellular methylation ability. These findings together support the interplay connections between mitochondrial metabolite and epigenetic regulation. On the other hand, epigallocatechin-3-gallate, a major polyphenolic constituent of green tea, is a potent demethylating agent by inhibiting DNMTs leading to the re-expression of epigenetically silenced tumor suppressor genes such as glutathione-S transferase (Fang et al., 2003; Pandey et al., 2010). Another example of a demethylation agent is sulphorafane. Sulphorafane successfully reversed the ultraviolet radiation B (UVB)-induced CpG methylation in HaCaT skin cancer cells (Li et al., 2022a). Furthermore, next generation sequencing (NGS) studies showed a significant increase in differentially methylated regions in the transgenic adenocarcinoma of the mouse prostate (TRAMP) cancer model as compared to wild type (Li et al., 2022a). However, this increase in DNA methylation was reversed in TRAMP mice fed diet enriched with 0.05% phenethyl isothiocyanate (PEITC), which is a phytochemical found abundant in cruciferous vegetables. Furthermore, 6 out of 7 TRAMP mice developed prostate cancer while wild type and PEITC fed TRAMP mice

both showed similar normal prostate appearance, which suggests potential protective effects of PEITC through DNA demethylation epigenetic mechanism (Wu et al., 2021).

Histone modification

Histone modification includes de/acetylation or de/methylation. Histone de/acetylation is carried on by two main groups of enzymes called histone deacetylases (HDACs) and histone acetyltransferases (HATs), which result in histone deacetylation and histone acetylation, respectively (Wang et al., 2009; Hassell, 2019). While lysine humane methyltransferases (KMTs), such as SETD7, catalyze histone methylation, and lysine demethylases (KDMs) demethylate histone (Chen et al., 2020). In eukaryotic chromatin, the DNA is wrapped around histone proteins. The acetylation and methylation status of the N-terminal of the histone proteins affect how the DNA is packed in the nucleus, affecting its interaction with different transcriptional factors and its expression (Strahl and Allis, 2000). HATs catalyze the addition of acetyl group on the N-terminal tail of histones, which neutralizes the positive charge. Consequently, histone acetylation relaxes the chromatin and facilitates the binding of transcriptional factors to the DNA and increases the corresponding gene expression (Struhl, 1998). Acetyl-coenzyme A (acetyl-CoA), a mitochondrial tricarboxylic acid (TCA) cycle metabolite, is required for the activity of all HATs, as it's the sole donor of acetyl moiety. Interestingly, acetyl-CoA availability for histone acetylation is influenced by chromatin recruitment of acetyl-CoA-producing enzymes, such as adenosine triphosphate (ATP)-citrate lyase (ACLY) and acyl-CoA synthetase short chain family member 2 (Sivanand et al., 2018). It is worth mentioning that besides acetyl-CoA there are four other acyl-CoA metabolites that are also known to modify histones: succinyl-CoA, propionyl-CoA, crotonoyl-CoA, and butyryl-CoA (Trefely et al., 2020).

In contrast, HDACs catalyze the deacetylation of histones resulting in the compaction of chromatin packaging suppressing the gene transcription (Kuo and Allis, 1998). HDACs are classified into zinc/iron-dependent deacetylases (class I, II, and IV HDACs) (Hassell, 2019) and NAD^+-dependent deacetylases (class III HDACs; known as sirtuins) (Sauve et al., 2006). Curcumin, a major bioactive phytochemical extracted from turmeric, was found to be a potent HDAC inhibitor (Bora-Tatar et al., 2009). For example, the treatment of B-NHL Raji cells with curcumin reduced HDAC-3, HDAC-8 and HDAC-1 protein expression in a concentration-dependent manner, resulting in elevated H4 acetylation and reduced p300/CREB binding protein (CBP) levels (Liu et al., 2005; Chen et al., 2007). This decrease in p300/CBP levels is related to curcumin-mediated inhibition of Notch1 and nuclear factor-κB, which resulted in decreased proliferation and apoptosis of Raji cells. Targeted inhibition of p300/CBP HAT by curcumin is deemed a potential target for the cancer treatment (Balasubramanyam et al., 2004; Marcu et al., 2006; Dekker and Haisma, 2009). This inhibition of HDACs by curcumin is also seen *in vivo*, in the rats (Boyanapalli et al., 2018) as well as in human healthy volunteers (Cheng et al., 2019). Histone methylating enzyme SETD7 knockdown decreases Nrf2 and Nrf2-target genes expression in prostate cancer LNCaP and PC-3 cell line (Wang et al., 2018). In the same study, PEITC and UA phytochemicals were reported to induce SETD7 expression.

ROLE OF PHYTOCHEMICALS IN METABOLIC REPROGRAMMING IN CANCER CELLS

Fast growing cancer cells require more energy and building blocks to proliferate. To meet these increased demands, tumor cells undergo metabolic reprogramming, which became a hallmark for all cancers (Park et al., 2020). It all started when Otto Warburg described the increased production of lactate even in the presence of oxygen in cancer cells (i.e., aerobic glycolysis), a phenomenon then termed Warburg effect (Warburg et al., 1927; Pavlova and Thompson, 2016). Now, more metabolic pathways have been discovered to be rewired in cancer cells such as deregulated uptake of various nutrients, TCA, nicotinamide adenine dinucleotide phosphate (NADP) and nicotinamide adenine dinucleotide phosphate hydrate ($NADPH^+$) biosynthesis, elevated nitrogen requirement, and metabolite-driven epigenetic reprogramming (Martinez-Outschoorn et al., 2017). Preclinical and clinical data indicate that targeting tumor metabolism approach is a promising field for the development and investigation of new chemotherapeutics potentially successfully mitigate tumor progression (Tennant et al., 2010; Vander Heiden, 2011). Still, targeting metabolism clinically is challenging and limited due to metabolic heterogeneity of different tumors even within the same entity, metabolic plasticity, drug resistance, systemic toxicity and unwanted side effects (Fendt et al., 2020).

Phytochemicals inhibiting major cancer metabolic pathways

To overcome challenges associated with traditional approaches (surgery and chemotherapy), such as organ damage, toxicity, and cancer resistance, a wide range of relatively safe phytochemicals can be used in the interception and treatment of cancer. Among the advantages of these phytochemicals are immune-modulatory activity, selective toxicity, oral administration, and synergistic effects in combination with other drugs (Liu, 2004; Samec

Table 2. Examples of phytochemicals regulating major cancer metabolic pathways and their target enzymes and biological effects

Metabolic pathway/ metabolites	Phytochemical	Affected enzyme	Biological effect	Reference
Glycolysis	Hesperetin Apigenin Bavachinin Galbanic acid	Reduce GLUT	Reduce glucose uptake and cancer cell apoptosis	(Yang et al., 2013; Xu et al., 2014; Fang et al., 2015)
	Oroxylin Deguelin Curcumin	HK inhibitor		(Wei et al., 2015; Geng et al., 2016; Li et al., 2017a)
	Resveratrol Epigallocatechin-3-gallate Berberine	Inhibiting PFK1		(Gomez et al., 2013; Tan et al., 2015; Li et al., 2016)
Pentose phosphate pathway	Polydatin Epicatechin gallate Resveratrol	Inhibiting G6PD	Depletion of cellular $NADPH^+$ levels and induction of oxidative stress in cancer cells	(Vanamala et al., 2011; Sánchez-Tena et al., 2013; Mele et al., 2019)
Amino acid metabolism	Resveratrol Morin Esculetin	Solute carrier family 1 member 5 transporters	Decreased intake of glutamine	(van Geldermalsen et al., 2016; Sharma et al., 2017; Liu et al., 2018)
	Diallyl sulphide		Reversed the NNK-upregulated amino acid such as tyrosine, proline, serine, etc.	(Hudlikar et al., 2022)
Glutathione metabolism	SFN	Upregulation of GCLC and NQO1	UVB-regulated metabolites such as N-acetyl-leucine, hypoxanthine, 3-methyl-2-oxovalerate, and creatine were reversed by SFN	(Li et al., 2022a)
	Fucoxanthin		Blocked TPA-induced ROS and oxidized GSSG/reduced GSH in Nfe2l2 wild-type but not Nfe2l2-knockdown cells	(Wang et al., 2022b)
Methionine metabolism	Butyric acid		Inhibited SAM/SAH ratios in colon cancer HCT 116 cell line indicated the reduced cellular methylation potential	(Wang et al., 2022a)
	Ursolic acid		Regulated (SAM) and methionine	(Li et al., 2022b)

GLUT, glucose transporter; HK, hexokinase; PFK1, 6-phosphofructo 1-kinase; G6PD, glucose-6-phosphate dehydrogenase; NADPH, nicotinamide adenine dinucleotide phosphate hydrate; NNK, 4-[methyl(nitroso)amino]-1-(3-pyridinyl)-1-butanone; SFN, suphoraphane; GCLC, glutamate-cysteine ligase catalytic subunit; NQO1, NAD(P)H quinone oxidoreductase-1; UVB, ultraviolet radiation B; TPA, 12-*O*-tetradecanoylphorbol-13-acetate; ROS, reactive oxygen species; GSSG, oxidized glutathione; GSH, glutathione; SAM, *S*-adenosyl methionine; SAH, *S*-adenosyl-L-homocysteine.

et al., 2020). Recognizing this vast array of benefits offered by phytochemicals, they are gaining interest and are steadily being listed under the drugs effective in the cancer interception and treatment (Wang et al., 2012; Guerra et al., 2018). However, there are caveats in translating these potentially health beneficial effects in many animal models to human patients. Hence more clinical studies would need to be done in the future to prove their utility in clinical medicine. One of the potential mechanisms of cancer interception and treatment by phytochemicals is the reprogramming of the key metabolic pathways (Khan et al., 2021). Here, we will summarize some of the major cancer metabolic pathways and the role of different classes of phytochemicals in targeting these pathways (Table 2) (Vanamala et al., 2011; Gomez et al., 2013; Sánchez-Tena et al., 2013; Yang et al., 2013; Xu et al., 2014; Fang et al., 2015; Tan et al., 2015; Wei et al., 2015; Geng et al., 2016; Li et al., 2016; van Geldermalsen et al., 2016; Li et al., 2017a; Sharma et al., 2017; Liu et al., 2018; Mele et al., 2019; Hudlikar et al., 2022; Li et al., 2022a; Li et al., 2022b; Wang et al., 2022a; Wang et al., 2022b).

Glycolysis

To meet the increased demands of energy and biomolecules, almost all cancer cells show an upregulated glycolysis which gives tumor cells the ability to produce energy regardless of oxygen availability and ultimately supports the accelerated growth (Vander Heiden et al., 2009; Lunt and Vander Heiden, 2011). Cancer cells reprogram glycolysis by regulating several transporters and enzymes related to glucose transportation and metabolism.

Cancer cells showed significantly upregulated expression of glucose transporters (GLUTs) compared to normal cells, which supports the continuous uptake of glucose (Moreno-Sánchez et al., 2007; Harshani et al., 2014). After entering the cell, glucose is first converted to glucose-6-phosphate (G6P) by the rate-limiting enzyme hex-

okinase (HK). Then, G6P can be further oxidized to produce the major cellular energy macromolecule ATP through glycolysis or pentose phosphate pathway (PPP). Glycolysis is performed through several steps; each step is catalyzed by a specific enzyme such as 6-phosphofructo 1-kinase (PFK1), aldolase, phosphoglycerate mutase, enolase, and lastly pyruvate kinase. Targeting these enzymes and transporters by phytochemicals could be a potential anticancer strategy.

Many phytochemicals were found to diminish tumor growth by interfering with glucose uptake. *In vivo* and *in vitro* cancer studies showed apigenin and hesperetin reduce GLUT1 protein expression and induce apoptosis (Yang et al., 2013; Xu et al., 2014; Fang et al., 2015). Particularly, hesperetin not only plummeted the expression of GLUT1 but also decreased the translocation of GLUT4 to the cytoplasmic membrane (Yang et al., 2013). Galbanic acid and bavachinin inhibit GLUT1 by downregulating its transcriptional factor HIF-α (Nepal et al., 2012; Eskandani et al., 2015). HK has been shown to be downregulated by many phytochemicals, including oroxylin (Wei et al., 2015), deguelin (Li et al., 2017a), and curcumin (Geng et al., 2016). Resveratrol, epigallocatechin-3-gallate, and berberine induced apoptosis potentially by inhibiting PFK1 (Gomez et al., 2013; Tan et al., 2015; Li et al., 2016).

PPP

The PPP is a crucial anabolic pathway for cancer cells that generates not only ATP as an energy unit but also other essential biomolecules $NADPH^+$ and ribose sugar. Ribose sugar is required for nucleotide synthesis, and $NADPH^+$ is essential for fatty acid synthesis and is considered a key component of the antioxidant defense system against the increased oxidative stress in cancer tissues (Patra and Hay, 2014). In the first step in PPP, G6P is irreversibly converted to 6-phosphogluconolactone catalyzed by G6P dehydrogenase (G6PD) (Kruger and von Schaewen, 2003). G6PD, among a group of PPP-regulating enzymes, was reported to be upregulated in many cancer types (Jiang et al., 2013; Zhang et al., 2017).

Polydatin, epicatechin gallate, and resveratrol inhibited G6PD activity in breast and colon cancer (Vanamala et al., 2011; Sánchez-Tena et al., 2013; Mele et al., 2019). Targeting the PPP pathway by these phytochemicals may result in reduced nucleic acid production and depletion of cellular $NADPH^+$ levels, which induce oxidative stress in cancer cells. Ultimately, this can lead to apoptosis and mitigate cancer cell proliferation.

Amino acid metabolism

Amino acids are biomolecules for both anabolic and catabolic pathways. They are the building units of proteins and one of the energy sources in cells. Isoleucine amino acid was reported to be a primary metabolic source of propionyl-CoA and histone propionylation, which revealed a new mechanism of crosstalk between amino acid metabolism and epigenetics (Trefely et al., 2022). Amino acids are more important in cancer cells as they provide an alternative bioenergetic and biosynthetic source. Therefore, cancer cells rewire amino acid metabolism to their advantage, adapting it to the available nutrient conditions and thus supporting their growth and survival. For instance, glutamine is the second most required nutrient by tumor cells, coming just after glucose (Yang et al., 2017). Phytochemicals such as resveratrol, morin, and esculetin showed decreased intake of glutamine through downregulation of solute carrier family 1 member 5 transporters, which is reported to be elevated in cancer cells (van Geldermalsen et al., 2016; Sharma et al., 2017; Liu et al., 2018). Nonetheless, Poillet-Perez et al. (2018) showed that autophagy-deficient (Atg7-deficient) hosts attenuated tumor xenograft growth, and dietary supplementation with arginine partially restored tumor growth.

TCA cycle

The TCA cycle acts as a central metabolic hub for aerobic organisms, and it generates energy and intermediates for cellular anabolic pathways. Once the glucose is initially oxidized into pyruvate in the cytoplasm, pyruvate enters the mitochondrion to be further metabolized through the TCA cycle. Through oxidative phosphorylation, the reduced equivalents in nicotinamide adenine dinucleotide hydride and reduced form of flavin adenine dinucleotide produced by the TCA cycle are utilized for the ATP generation (Eniafe and Jiang, 2021). In addition to their roles in biosynthesis and bioenergetics, the TCA cycle is also known to modulate different characteristics of cancer progression. They may go out of their way as metabolites to act as effector molecules, thereby modulating cellular or systemic responses that can impact cellular processes including cancer epigenetics.

α-Ketoglutarate (α-KG) and succinate are vital TCA cycle intermediates that are considered cofactors in DNA and histone demethylation reaction catalyzed by lysine demethylase, histone arginine residues demethylase, and ten-eleven translocation family enzymes (Fang et al., 2010; Pastor et al., 2013; Walport et al., 2016; Blanc and Richard, 2017). In oxygen-dependent reactions, these enzymes are α-KG-dependent enzymes that demethylate DNA and histone to produce succinate (Tsukada et al., 2006). ACLY enzyme catalyzes the production of acetyl-CoA and oxaloacetate from citrate and CoA in the cytosol and nucleus. Furanodiene inhibits ACLY activity in adenosine monophosphate-activated protein kinase dependent manner, which resulted in attenuated proliferation in doxorubicin-resistance tumor cells (Zhong et al., 2016).

Glutathione metabolism

Dysregulation of cellular glutathione concentrations is associated with tumor development. Glutathione is the most important endogenous antioxidant system that plays important role in detoxification of carcinogens and scavenging of reactive oxygen species. γ-Glutamylcysteine synthetase is the rate-limiting enzyme in the synthesis of glutathione. One report showed that flavonoids increase expression of γ-glutamylcysteine synthetase with a parallel increase in the intracellular glutathione levels (Moskaug et al., 2005). Another phytochemical, N-acetylcysteine, is clinically investigated and suggested as a glutathione support supplement (Parcell, 2002).

Methionine and one-carbon metabolism

Many nutrients, including glucose, serine, glycine, and threonine, fuel one-carbon metabolism, where they are converted to SAM via the folate and methionine cycles. High levels of the methyl donor SAM influence the DNA (discussed earlier) and histone methylation (Newman and Maddocks, 2017). Histone methylation occurs on lysine and arginine residues (Du et al., 2015). Lysine methyltransferase (KMT) and arginine methyltransferase (PRMT), with the aid of SAM as the methyl donor, methylate histones. This methylation can repress or activate different genes' transcription (Cheng, 2014). In colon cancer cell line HCT 116, butyric acid inhibits methionine metabolism showing a decreased SAM/SAH ratio which indicates attenuated cellular methylation potential. This finding was validated with NGS data (i.e., RNA-seq and methyl-seq) showing a correlation between tumor suppressor gene ATP binding cassette transporter 1 and its promoters' CpG methylation (Wang et al., 2022a). In the prostate cancer xenograft animal model, ursolic acid regulated SAM and methionine pathway, decreased global CpG methylation, and attenuated the growth of the xenograft tumor (Li et al., 2022b). Finally, Folate deficiency, may be associated with the development of genomic DNA hypomethylation, an early epigenetic event found in many cancers, through inhibition of one-carbon metabolism (Liu and Ward, 2010).

INTEGRATION OF METABOLISM AND EPIGENETICS IN CANCER

There are many challenges to understand the complex connectivity of metabolism-epigenetics and the regulation of the metabolic pathways and chromatin modifications. However, several universal principles underlie this relationship and illustrate the evolution of particular molecular mechanisms that promote epigenomic dynamics in the presence of metabolic changes. The innate thermodynamics parameters of chromatin-modifying enzymes enable epigenetics to react to oscillations in metabolic modifying activities. The addition and deletion of most of these modifications are catalyzed by 'writers' and 'erasers' enzymes that utilize metabolites as substrates or cofactors. These metabolites are called chromatin-modifying metabolites.

Metabolic enzymes involved in producing chromatin-modifying metabolites are repeatedly reported to be mutated in many cancers, implying that the metabolically regulated epigenomic landscape could play critical roles in cancer. One of the relevant examples is the mutation of isocitrate dehydrogenase (IDH)1 or IDH2, which can result in accumulation in (R)-2-hydroxyglutarate (Bailey et al., 2018). Consequently, this can lead to hypermethylation of DNA and histones, hence, downregulation of tumor suppressor genes (Lu et al., 2012; Losman et al., 2013). According to The Cancer Genome Atlas project, mutant IDH1 functions as an oncogene in at least seven cancer types (Bailey et al., 2018). Another example of metabolic-derived DNA and histone hypermethylation is the mutation in FH and SDH, whose deficiency results in the accumulation of fumarate and succinate, respectively (King et al., 2006; Cervera et al., 2009; Kaelin, 2009).

On the other hand, cancer cells often display metabolism changes in response to upstream drivers that can also reprogram the epigenome. Research by Kottakis et al. (2016) on a mouse model of Kirsten rat sarcoma viral oncogene homolog-mutant pancreatic cancer showed that the inactivation of liver kinase B1, a tumor suppressor resulted in the upregulation of methionine and one-carbon metabolism and DNA hypermethylation through the accumulation of SAM. Another study by Morris et al. (2019)

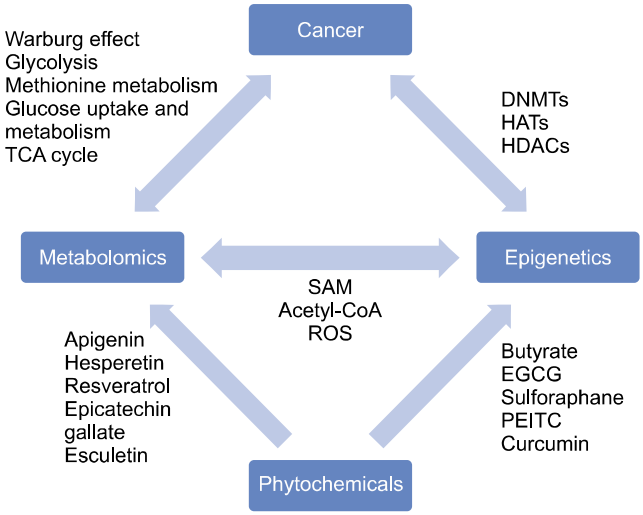

Fig. 2. Epigenetic and metabolomic effects of phytochemicals in cancer interception and treatment. TCA, tricarboxylic acid; DNMT, DNA methyltransferase; HAT, histone acetyltransferase; HDAC, histone deacetylase; SAM, *S*-adenosyl methionine; CoA, coenzyme A; ROS, reactive oxygen species; EGCG, epigallocatechin-3-gallate; PEITC, phenethyl isothiocyanate.

showed that the elevation levels of αKG and 5hmC, due to the expression of the tumor suppressor p53 which resulted in tumor suppression and premalignant differentiation.

Phytochemicals can enhance this reciprocal relationship between metabolism and epigenetics in cancer interception and treatment (Fig. 2). Recent research from our lab and others have shown that dietary phytochemicals can intervene multiple epigenetic and metabolic pathways to potentially prevent and treat various types of cancer. For instance, our recent publication reported that naturally occurring organosulphur compound, diallyl sulphide, can reverse the cigarette smoking carcinogen 4-[methyl(nitroso)amino]-1-(3-pyridinyl)-1-butanone-induced alterations of metabolomics, epigenomics and transcriptomics in the protection of early-stages lung carcinogenesis (Hudlikar et al., 2022). On the other hand, triterpenoid ursolic acid regulates metabolic rewiring of metabolism including SAM to drive epigenetic CpG methylation reprogramming and transcriptomic signaling resulting in the overall anticancer chemopreventive effect in prostate cancer (Li et al., 2022b). Our recent research shows that sulforaphane attenuates the UVB-induced aberrations in metabolic rewiring, epigenetic reprograming, and phenotypic transcriptomic alterations to protect UVB-induced skin cancer (Li et al., 2022a).

CONCLUSION

In summary, this review briefly discusses how metabolism could structure the epigenomic landscape in cancer. Phytochemicals have been found to elicit both epigenetics and metabolic capability in cells. Further work is required to describe the kinetic and thermodynamic characteristics of epigenetic-related enzymes and their context-specific dynamics in response to metabolic perturbation.

Cancer metabolism is considerably differential between normal and tumor cells; hence, it holds great potential for anticancer strategies. The ability of phytochemicals to modulate metabolic preprogramming in cancer cells makes them a potential contributor in therapeutic strategies. Undoubtedly, further research with systematic preclinical and clinical evaluation of phytochemicals is needed to unravel the capability of plant-based targeting metabolic and epigenetic reprogramming in cancer. Expanding our knowledge of phytochemicals and their potential to rewire metabolism and interact with epigenomes in cancer may pave the way for improved clinical outcomes. Although we discussed many potential phytochemicals regulating epigenetics and metabolic pathways, still there are many other relevant compounds which could be addressed.

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The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Concept and design: AS, ANTK. Analysis and interpretation: AS. Data collection: AS. Writing the article: AS. Critical revision of the article: all authors. Final approval of the article: all authors. Obtained funding: ANTK. Overall responsibility: AS.

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