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Review

Crosstalk between metabolic and epigenetic modifications during cell carcinogenesis

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SUMMARY

Genetic mutations arising from various internal and external factors drive cells to become cancerous. Cancerous cells undergo numerous changes, including metabolic reprogramming and epigenetic modifications, to support their abnormal proliferation. This metabolic reprogramming leads to the altered expression of many metabolic enzymes and the accumulation of metabolites. Recent studies have shown that these enzymes and metabolites can serve as substrates or cofactors for chromatin-modifying enzymes, thereby participating in epigenetic modifications and promoting carcinogenesis. Additionally, epigenetic modifications play a role in the metabolic reprogramming and immune evasion of cancer cells, influencing cancer progression. This review focuses on the origins of cancer, particularly the metabolic reprogramming of cancer cells and changes in epigenetic modifications. We discuss how metabolites in cancer cells contribute to epigenetic remodeling, including lactylation, acetylation, succinylation, and crotonylation. Finally, we review the impact of epigenetic modifications on tumor immunity and the latest advancements in cancer therapies targeting these modifications.

INTRODUCTION

Cancer is a disease characterized by genomic instability in somatic cells. Genomic variation, including gene mutations, chromosomal rearrangements, and gene copy number variations, can directly or indirectly affect cell growth, differentiation, and death, promoting cancer development.[1] Genes regulate the synthesis of proteins, which play a vital role in maintaining normal cellular function. Mutations in cancer genes can result in the production of dysfunctional or deformed proteins, leading to abnormal signaling within cells and subsequent metabolic reprogramming in cancer cells.[2] In eukaryotic cells, including cancer cells, genomic DNA is packaged into chromatin by forming nucleosomes. Each nucleosome core particle consists of a histone octamer and approximately 146 base pairs of DNA, with the histone octamer comprising two copies each of the core histones H2A, H2B, H3, and H4.[3] The histone amino-terminal tails and globular histone cores protruding from the nucleosome undergo a variety of covalent modifications, including acetylation, ubiquitination, phosphorylation, methylation, succinylation, glycosylation, propionylation, borylation, and crotonylation.[4] Increasing evidence indicates that abnormal regulation of DNA modifications and histone post-translational modifications is closely related to cancer. These modifications can alter chromatin structure and protein-protein interactions, thereby regulating gene transcription and mediating cancer development by affecting critical physiological processes such as DNA damage repair, cell cycle progression, and epigenetic changes.[5]

Glucose, protein, and fat metabolism in cells is regulated by metabolic enzymes at the gene expression or protein level, responding to normal extracellular and intracellular signals. Cancer cells, however, meet their energy needs for abnormal proliferation and adapt to changing environments through metabolic reprogramming. Increased metabolic pathway activity leads to metabolite accumulation or changes in enzyme activity, which can serve as substrates or cofactors for chromatin-modifying enzymes, facilitating epigenetic modifications and contributing to cell carcinogenesis.[6] Consequently, the metabolic reprogramming in cancer cells, driven by metabolites and DNA-based epigenetic modifications, regulates physiological responses such as abnormal cell proliferation, immune escape, and surveillance. Dysregulation of these pathways, interconnected through abnormal proliferation signals, metabolites, and epigenetic modifications, can have significant effects and contribute to cancer progression.

THE CAUSE OF CANCER

Under the influence of various endogenous factors such as gene mutations, abnormal activation of oncogenes, and epigenetic changes, as well as exogenous factors such as carcinogens and viral microorganisms, tumor cells acquire a range of

markers. These markers enable signal transduction, evade growth inhibitors, resist cell death, achieve replication immortality, activate invasion and metastasis, reprogram cell metabolism, avoid immune destruction.[7] The acquisition of these abilities leads to uncontrolled growth of tumor cells. Abnormally proliferative tumor cells evade growth inhibition and induce malignant behavior by integrating various signaling pathways.[8] Activation of these pathway is caused by gene mutations interacting with energy metabolism pathways, prompting tumor cells to meet their energy needs through metabolic reprogramming.[9] Additionally, the energy metabolism required for cancer cell proliferation releases a series of metabolites into the tumor microenvironment (TME) and further mediates tumor immune escape.[10]

Gene mutation

Cancer is characterized by cellular abnormalities and uncontrolled growth caused by genetic mutations. Genes play a crucial role in regulating protein synthesis, which is essential for maintaining proper cellular function. Mutations in oncogenes lead to the synthesis of proteins with abnormal functions or deformities, changing their expression levels and functions, thereby inducing carcinogenesis. While a single gene mutation may cause cancer, most cancers result from the accumulation of mutations in multiple genes.[11] Previous studies have found that passenger mutations corresponding to passenger genes do not induce or promote tumor occurrence and development. In contrast, mutations in cancer-driving genes promote cancer occurrence and development. For example, researchers observed deviation between cross-tumor somatic mutation patterns and expected neutral mutation patterns through the Integrative OncoGenomics (IntOGen) channel, constituting a positive selection signal driven by cancer. These cancer-driving genes play a key role in regulating cell growth, the cell cycle, and DNA replication.[12] More importantly, mutations in genes lead to changes in enzymes or proteins that regulate epigenetic modifications in cancer cells, and the latter participate in cancer development by modulating epigenetic modifications. Conversely, changes in epigenetic modifications also modulate changes in chromatin to mediate mutations in genes. This in part creates a close link between gene mutations and epigenetic modifications.

During carcinogenesis, driving genes can be divided into proto-oncogenes and tumor suppressor genes. Proto-oncogenes promote the growth and division of normal cells. When overexpressed or mutated, they lead to excessive cell proliferation and tumorigenesis. For example, *RAS* gene mutations, particularly *KRAS* mutations, are common in various human cancers.[13] The small GTPase enzyme encoded by the *KRAS* gene regulates many cellular activities, including proliferation, differentiation, and death. Missense mutations in the KRAS protein continuously activate downstream signaling pathways, resulting in uncontrolled cell proliferation and tumor formation. For instance, in pancreatic ductal adenocarcinoma, the amino-terminal 12 position of the KRAS protein is the most frequently mutated site, with $KRAS^{G120D}$ and $KRAS^{G120V}$ being the most common mutations. Studies have shown that inhibitors can significantly reduce cancer cell growth by targeting wild-type KRAS, various KRAS mutants, and downstream signaling pathways of KRAS mutant cancer cells.[14–16] Although KRAS is widely regarded as the most common mutant proto-oncogene, epidemiological estimates indicate that PIK3CA mutations are more prevalent. In contrast, BRAF mutations are less common,[17] and the abnormal activation of the *PIK3CA* gene leads to the p110 catalytic subunit of class I phosphatidylinositol 3-kinase, known as PI3Kp110a. In tumor cells, enhanced PI3K kinase activity continuously stimulates downstream protein kinase B (AKT) signaling pathways, making cells independent of growth factors and enhancing the ability of cancer cells to invade and metastasize[18] (Figure 1). Additionally, the RAS-RAF-MAPK pathway, a classic mitogen-activated protein kinase (MAPK) signaling pathway, integrates growth signals transmitted by various receptors across the membrane. Activation of this pathway facilitates intracellular transmission of growth signals, contributing to cell proliferation and differentiation. The B-Raf proto-oncogene (BRAF) mutation has the highest downstream mutation rate of RAS. BRAF is one of the three members of the RAF protein family (ARAF, BRAF, and CRAF). Mutations in BRAF are found in melanoma, thyroid adenoma and colorectal cancer (BRAF).[19–21] BRAF mutations can continuously activate MAPK signals as monomers or dimers independent of RAS, promoting cancer development.[22] Besides proto-oncogenes, the tumor suppressor gene *TP53*, which encodes the p53 protein, is frequently mutated in humans. *TP53* mutations are associated with higher metastasis rates and poorer patient survival. Notably, the dominant negative effect of mutant p53 (mutp53) not only results in the loss of the anti-tumor function of the wild-type p53 protein but also interferes with other signaling pathways through gain-of-function mechanisms, regulating cell metabolism, metastasis, and invasion. The p53 hot spot mutant protein $p53^{R175H}$ can bind to the transcription factor BACH1 (BTB domain and CNC homolog 1) *in vivo*, inhibiting ferroptosis and promoting tumor metastasis.[23] Furthermore, studies have shown that p53 inactivation causes genomic instability, and TP53 mutations usually occur earlier than other genome rearrangement events. The absence of p53 not only causes genetic instability but also induces predictable, orderly evolution of the cancer genome.[24] This further indicates that driving gene mutations play a crucial role in carcinogenesis.

Exome-based analyses have successfully mapped somatic mutations in protein-coding regions. However, numerous mutations occur in the vast non-coding regions, which are more than 50 times larger than the coding exome. As the activity of driving genes in cancer often changes through transcriptional activation or inactivation, non-coding point mutations and small insertion or deletions can lead to cancer through various pathways. These include altering enhancer sequence, disrupting chromatin structure, and affecting mRNA stability or protein translation in the 5′ or 3’ untranslated regions (UTRs).[25] For instance, single nucleotide variant (SNV) in regulatory regions (enhancers, promoters, 5′ or 3’ UTRs of cancer genomes may affect cancer-related genes and phenotypes.[26] For example, to uncover the relationship between nucleotide polymorphisms in the non-coding region and carcinogenesis, researchers analyzed the HaploReg database. They found that the glioma susceptibility gene variant (rs55705857) at the 8q24 site was located in a brain-specific enhancer. The risk allele mutation disrupted the binding of OCT transcription factors, enhancing interaction with the Myc

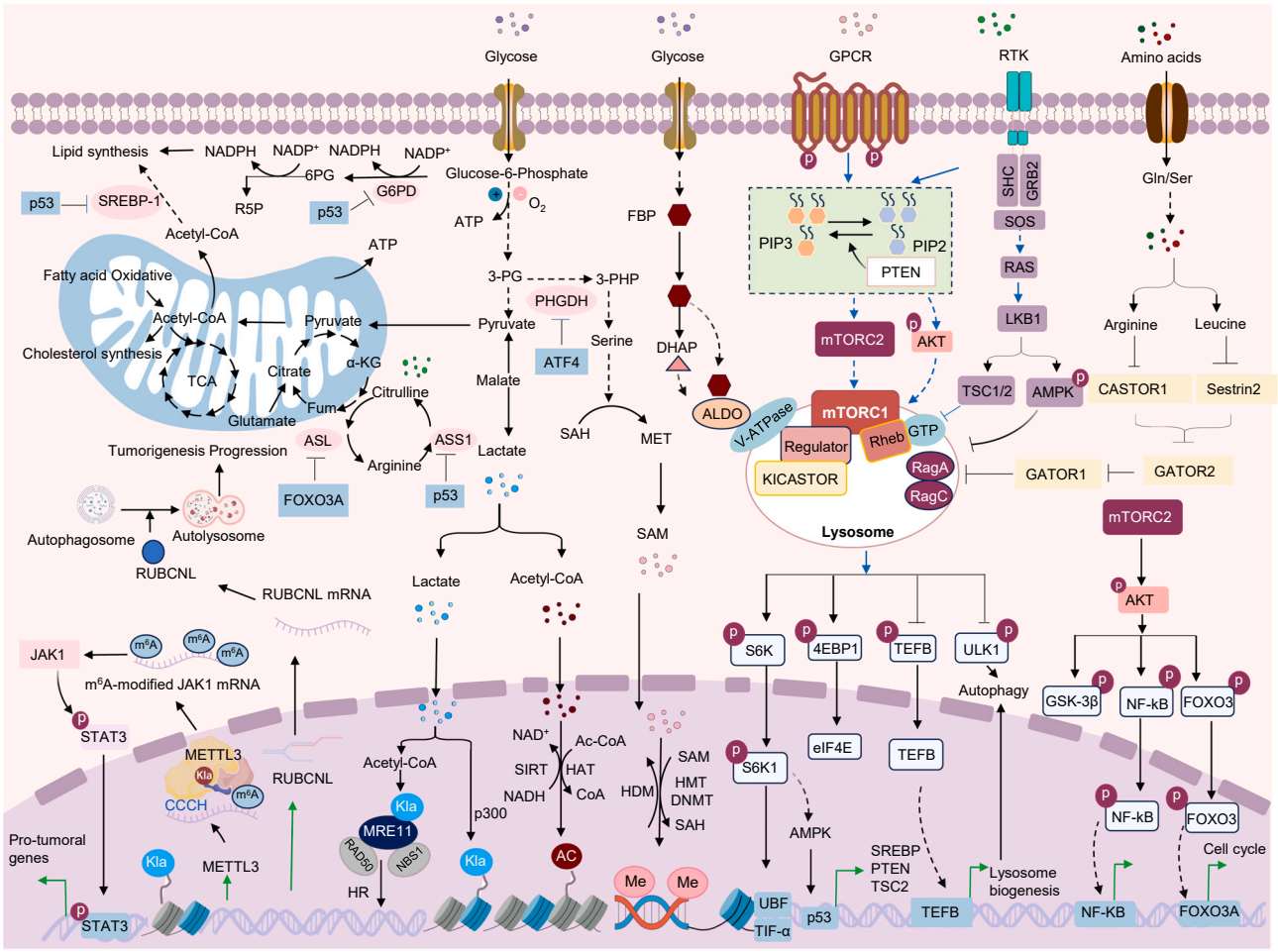

Figure 1. Cancer-related signaling molecules drive metabolic reprogramming and mediate epigenetic inheritance

Tumor signaling pathways regulated by oncogenes or tumor suppressor genes will drive metabolic reprogramming, and the corresponding metabolites will further mediate epigenetic changes, thus interfering with the expression of target genes, and ultimately promoting the occurrence of cancer in the way of metabolic and epigenetic interaction. GPCR: G protein-coupled receptor; RTK: receptor tyrosine kinase; NADPH: Nicotinamide adenine dinucleotide phosphate; SREBP-1: sterol regulatory element binding transcription factor 1; 6PG: 6-paradol-beta-glucoside; G6PD: Glucose-6-phosphate dehydrogenase; ATP: Adenosine triphosphate; TCA cycle: trichloroacetic acid cycle; α-KG: alpha-ketoglutarate; ASL: argininosuccinate lyase; ASS1: argininosuccinate synthetase 1; RUBCNL: regulate rubicon-like autophagy enhancer; JAK1: Janus Kinase-1; m6A: N6-methyladenosine; STAT3: signal transducer and activator of transcription 3; METTL3: methyltransferase-like 3; CCCH: Cysteine3Histidine; 6PG: 6-paradol-beta-glucoside; R5P: ribose 5-phosphate; 3-PG: 3-phosphoglycerate; 3-PHP: 3-phosphohydroxypyruvate; PHGDH: phosphoglycerate dehydrogenase; ATF4: activating transcription factor 4; SAH: subarachnoid hemorrhage; MET: cellular-mesenchymal to epithelial transition factor; Kla: lysine lactylation; MRE11: meiotic recombination 11 homolog 1; RAD50: double-strand break repair protein; NBS1: Nijmegen breakage syndrome protein 1; HRR: homologous recombination repair; FBP: fructose 1,6-bisphosphate; DHAP: dihydroxyacetone phosphate; SAM: S-adenosylmethionine; ALDO: Aldosterone; SIRT: sirtuins; HAT: hydrogen atom transfer; Ac-CoA: acetyl-coenzyme A; AC: adenylyl cyclase; HDM: histone demethylase; Me: methylation; DNMT: DNA methyltransferases; HMT: histone methyltransferase; GPCR: G protein-coupled receptor; RTK: receptor tyrosine kinase; PIP3: phosphatidylinositol 3,4,5-trisphosphate; PIP2:phosphatidylinositol 4,5-biphosphate; PTEN: Phosphatase and tensin homolog; mTORC2: mechanistic target of rapamycin complex 2; AKT: protein kinase B; mTORC1: mechanistic target of rapamycin complex 1; Rheb: Ras homolog protein enriched in brain; GTP: guanosine triphosphate; RagA: Ras-related GTP-binding protein A; RagC: Ras-related GTP-binding protein C; S6K: S6 kinase; 4EBP1: eIF4E-binding protein; TEFB: transcription elongation factor b; ULK1: UNC-52-like kinase 1; S6K1: S6 Kinase 1; eIF4E: eukaryotic translation initiation factor 4E; AMPK: adenosine monophosphate-activated protein kinase; UBF: upstream binding factor; TNF-α: tumor necrosis factor-α; SREBP: sterol regulatory element-binding proteins; TSC2: tuberous sclerosis complex subunit 2; SHC: Src homology and collagen; GRB2: growth factor receptor-bound protein-2; SOS: Son of Sevenless; RAS: rat sarcoma; LKB1: liver kinase B1; CASTOR1: mTORC1 subunit 1; CASTOR2: mTORC1 subunit 2; GSK-3β: glycogen synthase kinase 3 β; NF-κB: nuclear factor κB.

promoter and increasing Myc expression. This leads to isocitrate dehydrogenase (IDH) mutations, increasing the risk of low-grade gliomas.[27] This suggests a causal relationship between non-coding single nucleotide polymorphisms and cancer risk. Similarly, based on RNA sequencing and exome data, our previous studies found that in many cancer types, abnormal intronic polyadenylation (IPA)-related somatic SNVs are enriched in tumor suppressor gene (TSG), including PTEN and CDH1.[28] This

suggests that carcinogenic cell SNVs may have an unexpected function in regulating the expression of tumor suppressors. Besides IPA events, alternative polyadenylation (APA) has emerged as a new paradigm for the post-transcriptional regulation of human genes. Using different poly (A) sites, genes can shorten or extend the 3′ UTR containing *cis*-regulatory elements, affecting target gene translation, localization of gene products, and protein-protein interactions. Interestingly, this event occurs independently of mRNA expression levels or splicing.[29] In a recent study, based on APA transcriptome-wide association studies (TWAS) and experimental methods, we identified several important cancer susceptibility genes that increase protein expression through APA, thereby increasing cancer risk.[30,31] These studies reveal that mutations in the coding regions of driving genes can lead to cancer; however, mutations in the large non-coding regions also seem to promote cancer. This indicates that mutations in the non-coding regions of genes play an indispensable role in promoting cancer progression. In addition, mutations in some genes encoding important enzymes or proteins lead to alterations in epigenetic modifications within the cell. For example, *p300* and its cognate gene, CREB-binding protein (CBP), are transcriptional co-activators that play important roles in transcriptional regulation. Mutations in p300/CBP or chromosomal translocations can lead to gene expression disorders and disease development.[32,33] Similarly, the deacetylase SIRT6 can use its deacetylase activity to deacetylate proteins important for recognizing damage in the Nucleotide excision repair (NER) pathway, which in turn promotes their ubiquitination and segregation from the chromatin, and ultimately facilitates the signaling of the NER pathway and completes the repair. However, in melanoma, SIRT6 mutations inhibit the NER pathway and promote tumorigenesis.[34] This seems to imply that mutations in some important genes can lead to changes in enzymes or signaling pathways that regulate epigenetic modifications, which can cause abnormal epigenetic modifications or tumorigenesis.

Abnormalities of epigenetic modification

Although genetic mutations can induce cancer, many cells with DNA mutations do not develop cancer. This is because, in addition to proto-oncogene/tumor suppressor gene mutations, epigenetic regulatory elements in cells play an important role in carcinogenesis.[35] When researchers revealed differences in mutations across various cancers and their inherent correlations, they found many coexisting mutations in the epigenetic pathway. The accumulation of epigenetic regulatory factor mutations leads to increased transcriptome characteristics related to proliferation. Additionally, mutations in epigenetic regulators often coexist with PI3K signaling pathway molecules.[36] Recently, a drosophila model was used to transiently knock down PH, a key component of polycomb (PcG) family proteins that act as chromatin transcriptional repressors, during larval development using a temperature-induced RNAi system. Transient PH knockdown irreversibly upregulated the expression of several genes, some of which are involved in the JAK-STAT pathway. This potentially driving tumorigenesis through activation of transcription factors that act as proto-oncogenes.[37] This suggests that epigenetic modifications (DNA/RNA methylation, histone modification, nucleosome localization, non-coding RNA, and the three-dimensional structure of chromatin) significantly affect chromatin structure, gene expression, and basic cellular activities, making them key factors in cancer induction.

DNA/RNA methylation

DNA methylation is a form of chemical modification of DNA that can alter genetic expression without changing the DNA sequence. DNA methylation includes (5-methylcytosine (5mC), 5-hydroxymethylcytosine (5hmC), N6-methyladenine (6mA), and 7-methylguanine (7mG)). Generally, the promoter region of active genes is demethylated, whereas that of silent genes is hypermethylated. Consequently, abnormal DNA methylation of the promoter can silence tumor suppressor genes or activate proto-oncogenes. Researchers constructed a pan-tumor map by analyzing the transcriptomes of tumor and adjacent tissues, identifying abnormal DNA methylation related to changes in RNA and protein abundance. DNA methylation is complex and specific to the regulation of gene expression, with specific DNA methylation contributing to tumor-positive selection and histone changes.[38] This means that a decrease in DNA methylation levels throughout the genome can reduce its stability and further deteriorate cancer by activating the expression of various proto-oncogenes. Interestingly, recent research using single-cell multi-omics sequencing, cytogenetic sequencing, and nanopore third-generation sequencing, combined with a mouse tumor model, revealed that DNA methylation can inhibit the expression of prostate antigen presentation genes, thus inducing early prostate immune escape.[39] Similarly, a transgenic mouse model that can induce breast cancer was used to collect extremely early and late tumors for comprehensive single-cell transcriptome sequencing (scRNA seq). The results showed that early tumor editing significantly affected the preferential silencing of key innate and adaptive immune pathways in tumors, the differentiation and function of tumor infiltrating lymphocytes (TILs), and tumor immune cell communication. Inhibition of DNA methylation by the low-dose DNA methyltransferase inhibitor decitabine (DAC) can enhance the activity of key innate immune pathways in tumors and promote the transition from "cold" to "hot" tumors, thereby improvement of anti-tumor immunity.[40] This further indicates that DNA methylation mediates tumor immune escape and participates in carcinogenesis.

RNA methylation accounts for more than 60% of all RNA modifications, with 6mA being the most common post-transcriptional modification in eukaryotic mRNA.[41,42] 6mA post-transcriptional modification is involved in cancer progression by regulating RNA transcription,[43,44] processing,[45,46] splicing,[47–49] stability,[50] and translation.[51,52] For example, studies have shown that 6mA methylated mRNA can remove DNA methylation and promote chromatin opening, thus activating oncogene expression in esophageal cancer and mediating carcinogenesis.[53] Interestingly, the RNA produced by the super-enhancer (seRNA) is an important chromatin-associated RNA that can also be methylated. In pancreatic cancer cells, seRNA-m6A levels were significantly higher than in normal cells, which was attributed to the high expression of cofilin 1 (CFL1), a cofactor of m6A methyltransferase (METTL3), in pancreatic cancer cells. The high level of expression of the latter allows seRNA to be modified by m6A as soon as it is transcribed, leading to increased trimethylation of histone H3K4 in neighboring chromatin regions,

resulting in local chromatin opening to upregulate oncogene expression.[54] This study revealed for the first time the regulation of histone modifications and oncogene expression by seRNA methylation modifications in pancreatic cancer, expanding new insights into the function of super-enhancers and their transcripts. Furthermore, studies have shown that 6mA methylated mRNA can remove DNA methylation and promote chromatin opening, thus activating oncogene expression in esophageal cancer and mediating carcinogenesis.[53] Furthermore, some enzymes involved in RNA methylation are also involved in cancer progression. For example, downregulation of demethylase FTO leads to increased 6mA and changes in the Wnt signaling cascade at the 3′ end of key mRNAs, inducing epithelial-mesenchymal transition (EMT) processes, making tumor cells in mice sensitive to inhibitors the Wnt inhibitor iCRT3.[55] This suggests that RNA methylation also plays an important role in mediating DNA demethylation and regulating chromatin and transcriptional states. At the same time, RNA methylation is involved in the development of cancer by interfering with genomic stability or gene expression.

Notably, aberrant transcriptional initiation of protein-coding genes mediated by activation at the epigenetic level frequently affects related genes and is involved in the process of cancer development. DNA methylation or enzymes involved in DNA methylation may participate in carcinogenesis through gene mutations or the promotion of cryptic antisense transcription. Indeed, in some mutants or under stress, genes begin to transcribe from the downstream "promoter-like" regions that should have been suppressed, producing short transcripts that are inconsistent with or meaningless to the original function of the gene. This phenomenon, known as cryptic transcription, has been linked to the activation of oncogenic transcripts. Earlier studies comparing genome-wide DNA methylation (5mC) and DNA 5-hydroxymethylcytosine methylation (5hmC) in young vs. old cells, using a variety of transcriptome and epigenome sequencing technologies, found that while overall DNA methylation levels were reduced in cryptic transcriptional start regions, 5hmC, an intermediate product of the demethylation process, did not decrease, and the average content was higher than other genomic regions.[56] This implies that altered chromatin status may be one of the triggers for cryptic transcription of genes. Similarly, interactions between DNA methylation and cryptic transcription have been observed in cancer. In a recent study, we used a powerful computational pipeline to analyze transcriptome and epigenome datasets and identified hundreds of previously unannotated cryptic antisense polyadenylated transcript (CAPT) enriched in tumor samples. We found that the activation of these transcripts is associated with chromatin accessibility and histone markers. The chromatin accessibility of the transcription initiation region of CAPT expression was significantly higher. Meanwhile, the expression of some CAPTs was accompanied by decreased DNA methylation in the transcription initiation region and enrichment of histone H3K27ac and K3K4me3, which are related to transcription. Consequently, inhibition of DNA methyltransferase and histone deacetylase can promote cryptic antisense transcription. The abnormal expression of the reverse strand-transcribed CAPT of the protein-coding gene *LRRK1* promotes lung cancer cell growth, whereas knockdown or inhibition of CAPT reduces the proliferation of lung cancer cells.[57] In addition, by mapping global transcription start sites (TSSs) and chromatin dynamics, the researchers found that inhibition of DNA methyltransferases and histone deacetylase induced cryptic transcription start sites, which produced transcripts that were frequently spliced into protein-coding exons and encoded truncations or chimeric open reading frames (ORFs) that were translated into products with predicted aberrant or immunogenic functions.[58] These studies suggest that DNA methylation and chromatin accessibility participate in cellular carcinogenesis by regulating cryptic transcription. Although there are fewer studies on how epigenetic changes, including DNA methylation, regulate cryptic transcription, some of the transcripts regulated by epigenetic modifications may be harmful RNAs or truncated proteins, the latter of which interferes with the cellular process of carcinogenesis.

Histone modification

Histone are structural protein of chromosomes, forming nucleosomes with DNA. Histone variants and modifications are involved in chromatin epigenetic inheritance. Histones are evolutionarily conserved proteins with flexible N-and C-terminal domains and conserved globular domains. The N-terminal of histones can undergo various modifications, including acetylation, methylation, phosphorylation, ubiquitination and SUMOylation. Histone methylation occurs on lysine (K) or arginine (R) residues of H3 and H4 histones. This process is mainly catalyzed by histone methyltransferases (HMTs). HMT can be divided into histone lysine methyltransferases (HKMTs) and protein arginine methyltransferases (PRMTs). Histone demethylases can be divided into two families: lysine-specific demethylases (LSDs) and Jumonji C domain-containing (JMJD) demethylases. Notably, positions 4, 9, 27, 36, and 79 of histone H3lysine (H3K) and position 20 of histone H4 lysine (H4K) can be methylated.[59] H3K27me3 accumulates near the promoter regions of normally expressed genes to repress gene expression. The H3K27me3 enzymes enhancer of zeste homolog 1 (EZH1) and enhancer of zeste homolog 2 (EZH2) have been targeted for cancer therapy. In experiments with the targeted EZH1/2 dual inhibitor (Valemetostat), high levels of H3K27me3 were found in invasive adult T cell leukemia/lymphoma (ATL). One week after Valemetostat treatment, the number of abnormal lymphocytes decreased dramatically, this was accompanied by a rapid decrease in H3K27me3 levels across the genome, especially in tumor suppressor genes (TSGs). This implies that Valemetostat causes epigenetic reprogramming in cancer by eliminating H3K27me3, providing sustained clinical benefit.[60] This suggests that restoring histone Hypermethylation is a fundamental cause of drug resistance in cancer cells. Similarly, a model of impaired histone inheritance was constructed by introducing the MCM2-2A mutation, a parental histone-binding defect, into MCF-7 breast cancer cells. In this model, impaired histone inheritance leads to significant epigenetic reprogramming, especially in the repressive histone mark H3K27me3 pattern, and promotes tumor growth and metastasis *in vivo*. This further suggests that genetic impairment of histones can drive tumor progression.[61] Although there are many modification sites on histones, histone H3 lysine 4 (H3K4) and histone H3 lysine 9 (H3K9) are the two most frequently modified sites. Among them, the state of gene

activation markers on H3K4me3 is one of the most widely studied post-translational modifications (PTMs); it can be catalytically generated by six different COMPASS complexes in mammalian cells.[62] H3K4me3 has long been known to promote gene transcription initiation because its enrichment level near gene promoters positively correlates with gene expression levels. However, a recent study revealed that H3K4me3 inside the cell regulates gene expression through the transcription pause-release process rather than by promoting transcription initiation.[63] These studies suggest that H3K4me3 plays an important role in regulating gene expression, and dysregulation of H3K4me3 may mediate cancer by affecting the expression of downstream genes. In addition, aberrant expression of histone methylation enzymes or modifying enzymes can lead to cell apoptosis and genomic instability, which are closely related to the occurrence and development of various cancers. For example, abnormal expression of histone methyltransferases and histone demethylases can not only cause changes in H3K4me3, H4K20me3, H3K9me, and H3K27me3 but also mediate carcinogenesis.[64] They also participate in cancer occurrence by affecting the transduction of signaling pathways in cancer cells. Studies found that the histone methyltransferase KMT2D specifically mediates histone H3 lysine 4 methylation (H3K4me) and is frequently mutated in various cancers. Transcriptome (RNA-seq) analysis of KMT2D knockout (KMT2D-cKO) and KMT2D wild-type (KMT2D WT) lung squamous cell carcinoma cells revealed that the KRAS signaling pathway was one of the significantly enriched pathways in KMT2D-cKO cells. Phospho-ERK (pERK), downstream of KRAS signaling, was also significantly increased in KMT2D-cKO cells. Further studies revealed that receptor tyrosine kinases (RTKs) upstream of KRAS, including epidermal growth factor receptor (EGFR) and ERBB, were also activated in KMT2D-cKO cells. Thus, KMT2D deletion upregulated RTK-RAS signaling in lung squamous cell carcinoma.[65] Similarly, mutations in the *KRAS* oncogene in male patients with colorectal cancer upregulate Y chromosome histone lysine-specific demethylase 5D (KDM5D) expression, leading to the disruption of tight junctions between cancer epithelial cells and increasing the risk of cancer metastasis. KDM5D also inhibited major histocompatibility complex (MHC I) antigen presentation in cancer cells, promoting cancer cell evasion of CD8(+) T cell immune surveillance.[66] These studies reveal that histone methylation is crucial for regulating gene expression and signaling pathway transmission in cancer cells.

In addition to histone methylation, histone acetylation and ubiquitination also play vital roles in cancer development. Histone acetylation sites are widely distributed, with common modification sites including H3K9, histone H3 lysine 14 (H3K14), histone H3 lysine 18 (H3K18), histone H3 lysine 23(H3K23), histone H3 lysine 27 (H3K27), histone H3 lysine 5 (H3K5), etc.[67,68] Lysine acetylation in histone tails is highly dynamic and essential for regulating chromatin structure, transcription, and DNA repair.[69] In charge of histone acetylation of enzymes are two competing family of enzymes, including histone lysine acetyltransferase (HATs) and histone acetylation enzyme (HDACs). Aberrant histone acetylation may lead to dysregulated gene expression and mediate cancer development. Many studies have pointed out that HDAC overexpression and enhanced activity have been identified to mediate cancer initiation and metastasis by altering histone acetylation levels.[70] Additionally, most ubiquitination involves the addition of a single ubiquitin protein. The study found that the proteasome component PSMD14 acts as an enzyme, interacting with histone H2AK119 ubiquitination and histone H3 lysine 36 (H3K36) dimethyltransferase NSD2 in chromatin, promoting H3K36 dimethylation, leading to higher chromatin accessibility and activation of oncogenic transcription. PSMD14 can increase the for patients with multiple myeloma and potentially overcome bortezomib resistance as a target for intervention.[71] Similarly, RNA demethylase ALKBH5 promotes osteosarcoma (OS) progression by upregulating USP22 and RNF40 to inhibit histone H2A ubiquitination and induce the expression of crucial DNA replication and DNA damage repair-related genes.[72] As mentioned earlier, excessive DNA damage and insufficient repair within cells can lead to genomic instability, further promoting cancer development. Our previous study found that position 119 of histone H2A depends on crotonylation and ubiquitin modification; SIRT1/BMI1 can dynamically convert the latter to manage DNA replication stress.[73] These studies show that abnormal histone modifications can mediate cell carcinogenesis (Figure 1).

Nucleosome localization

DNA, which stores genetic information, is approximately 2 m long. This lengthy DNA must be packaged within a nucleus about 10 microns in diameter. Nucleosomes are disc-shaped structures formed by DNA wrapped around an octamer of histone proteins, protects the DNA. The stability and localization of nucleosomes are closely related to cellular activities. Since cells undergo different cycles and life activities, nucleosome positioning changes accordingly. Thus, nucleosome positioning and spacing are dynamic in regulating active and repressed genes.[74] *Cis*-acting DNA sequences and *trans*-acting chromatin remodeling complexes primarily regulate nucleosome positioning. The study found that in different types of prostate cancer in circulating tumor DNA (ctDNA), transcriptional start sites (TSS) and transcription factor (TF)-binding site (TFBS) can be used to infer gene expression and TF activity, and further predict different types of advanced prostate cancer.[75] Interestingly, when genetic DNA information is read, the chromatin remodeling complex SWItch/Sucrose Nonfermentable (SWI/SNF) reorients the nucleosome near the read start site, altering the chromatin structure to make the DNA easier to read. Subsequently, RNA polymerase transcribes the gene by reading the DNA from the newly positioned nucleosome. This repositioning process is called nucleosome remodeling. During nucleosome remodeling, the repositioned nucleosome collides with nearby nucleosomes to form a chromatin structural unit, the overlapping dinucleosome (a histone octamer nucleosome bound to a histone Hexamer nucleosome). This suggests that the incomplete formation of overlapping binucleosomes may trigger genetic switch abnormalities, allowing normal cells to transform into cancer cells.[76] Nucleosomes are the basic building blocks of DNA genetic information and epigenetic information carriers, and they carry a variety of histone posttranslational modifications (PTMs) that are key components of epigenetic marks. These markers are passed from parent to offspring during cell division and play a role in maintaining epigenetic memory and in rewriting epigenetic

information.[77] Unassembling the parental nucleosome and ensuring that the replicon contacts the DNA is an important step in opening double-stranded DNA and ensuring that the DNA replication fork advances. Recent studies have found that histone hexamers are likely to be an important recycling unit in the nucleosome disassembly and histone recycling process of DNA replication coupling. Disturbances in the mechanism of inheritance of epigenetic information coupled to DNA replication can lead to alterations in chromatin structure and nuclear gene expression profiles and trigger the development of cancer.[78] Indeed, during processes such as DNA replication, transcription, and repair processes, the position and arrangement of nucleosomes in terms of their denseness are adjusted accordingly. In general, regions with sparsely arranged nucleosomes are transcriptionally active, while regions with dense nucleosomes are transcriptionally repressed. It has been found that histone modifications regulate gene transcription processes by affecting the location and tightness of nucleosome arrangement, thereby affecting the expression of specific genes. For example, the epigenetically modified histones H2AK119 and H2BK119 with mono-ubiquitinated modifications (H2AK119ub1, H2BK120ub1) and variant H2A.Z are precisely recovered and recycled after DNA replication, symmetrically assigning them to the lagging strand and facilitating the rapid recovery of epigenetically modified landscapes, and the rapid transient memory of H2A-H2B during replication Helping to maintain chromatin accessibility status.[79] Interestingly, the structure of the nucleosome is not static, but undergoes spontaneous structural transformations, including DNA respiration (spontaneous opening of DNA ends on the nucleosome) and the open state (opening of the interface between histone subcomplexes), to form the unwrapped nucleosome, and this dynamic change of the nucleosome is called nucleosome unwrapping.[80] Indeed, intracellular nucleosomes become more dynamic and unfold in a greater variety of forms when they are subjected to biological processes such as epigenetics, transcription and DNA replication. Accordingly, unfolded nucleosomes may also play a regulatory role in DNA metabolic processes such as DNA replication, transcription and damage repair. It was found that histone variant (H2A.Z) nucleosomes unfolded to a greater extent than conventional nucleosomes and that unfolded H2A.Z nucleosomes were widely distributed in the promoter- and CTCF-binding regions. On the first nucleosome downstream of the promoter (+1 nucleosome), H2A.Z nucleosomes unfolded to 120–140 bp were associated with active promoters, whereas H2A.Z nucleosomes unfolded to 30–80 bp were associated with inactive promoters.[81] This suggests that nucleosome unfolding *in vivo* is ubiquitous and regulated by epistatic factors; at the same time, nucleosome unfolding *in vivo* can itself serve as a regulatory factor involved in biological processes such as the modulation of transcription and the organization of high-level chromatin structure. More interestingly, it was found that nucleosomes containing the histone variant H2A.Z were able to promote dimethylation modification of the H4 histone lysine at position 20 on the nucleosome (H4K20me2) through direct binding to the methylase SUV420H1. H2A.Z nucleosomes with the H4K20me2 modification are able to recruit origin recognition protein 1 (ORC1) in the replication precursor complex, thereby aiding in the selection of replication initiation sites on chromatin. In cancer cells, H2A.Z co-localizes with H4K20me2, ORC1, and replication initiation sites activated for use in a very high proportion genome-wide, and replication initiation sites regulated by H2A.Z have higher replication signals than others and are biased toward activation for use early in the replication phase.[82] These studies suggest that nucleosome assembly and unfolding are regulated by epigenetic modifications, and that regulated nucleosomes, in turn, regulate DNA metabolic processes such as DNA replication, transcription, and damage repair in cancer cells.

Epigenetic modifications also play an important regulatory role in the localization of nucleosomes. Other studies have found that nucleosome localization plays a role in DNA damage repair, where depletion induces replication stress and lead to genomic instability. BRG1 promotes DNA repair at double-strand breaks through nucleosome localization and the recruitment of repair factors.[83] This indicates that nucleosome positioning plays a regulatory role in the cancer genome. Additionally, DNA-binding proteins, such as transcription factors, can bind to exposed DNA to regulate gene transcription. However, in tightly structured heterochromatin, transcription factors usually have less affinity for nucleosomal DNA, resulting in permanent gene silencing. Pioneer transcription factors (e.g., Yamanaka factors OCT4, SOX2) can induce cell reprogramming. Recent studies have found that pioneer factors PU.1 and CCAAT/enhancer-binding protein α (C/EBPα) significantly reduce heterochromatin stability and change nucleosome structure in heterochromatin through two pathways: histone H1 dissociation and nucleosome terminal DNA opening.[84] Similarly, cGAS in the nucleus encounters a large amount of genomic double-stranded DNA (dsDNA). Under normal physiological conditions, its activity is inhibited by the DNA-binding protein barrier-to-autointegration factor 1 (BAF) and bound to chromatin. Structural biology studies have shown that cGAS can be tethered to the acidic patch (AP) on histones, blocking its binding to chromatin DNA and inhibiting its activity. Interestingly, the MRE11 protein of the MRE11-Rad50-NBN complex, which plays a vital role in DNA damage repair, can bind to nucleosomes and help the cGAS protein escape from the nucleosome, allowing damaged dsDNA to activate cGAS. Activated cGAS further suppresses tumors through a Z-DNA-binding protein 1 (ZBP1) -dependent cellular necrosis program.[85] These studies suggest that nucleosome positioning and remodeling can affect gene expression or genome stability and may mediate cancer development.

Remodeling of chromatin

In eukaryotic cells, chromatin exists in the three-dimensional nucleus, efficiently folding into chromosomes to facilitate precise gene expression and replication. Three-dimensional chromatin folding is a complex process associated with genome stability, transcriptional signaling, cell proliferation, and function. Point mutations can impair the spatial organization of chromatin, resulting in structural alterations to the three-dimensional (3D) genome.[86] Chromatin remodeling, a key epigenetic modification, involves changes in nucleosome positioning mediated by chromatin remodeling complexes. The effects of chromatin remodeling differ across tissue types and influence gene expression specificity.[87,88] Chromatin remodeling complexes like SWI/SNF, ISWI, CHD, and INO80 are commonly found at

specific nucleosome sites, such as those involved in transcription and replication initiation. SWI/SNF is the most common ATP-dependent chromatin remodeling complex. Mutations in chromatin remodeling complexes are notably linked to cancer. About 20% of human cancers exhibit mutations in SWI/SNF complex subunits,[89,90] SWI/SNF influences DNA positioning on nucleosomes, affecting chromatin accessibility, transcription, and DNA repair. The most commonly mutated SWI/SNF complexes are the BAF and polybromo-associated BAF (PBAF) complexes, which feature unique subunits like ARID1A, ARID1B, and DPF2. These complexes manage chromatin structural changes that impact gene expression.

Mutations in BAF/PBAF complexes have been found to cause many cancers and other diseases. Loss of ARID1A leads to the generation of R-loops in the nucleus during DNA replication and transcription, which enrich single-stranded DNA and RNA. Interestingly, these hybrids can be detected by the cGAS-STING pathway in cancer cells, leading to the expression of type I interferons, activating antitumor immunity.[91] Similar studies have also identified DPF3 as a component of the SWI/SNF chromatin remodeling complex, which has been associated with clear cell renal cell carcinoma (ccRCC) in genome-wide association studies.DPF3a specifically interacts with SNIP1, through which it forms a complex with SMAD4 and p300 histone acetyltransferase. The binding of DPF3a releases the inhibitory effect of SNIP1 on p300 histone acetyltransferase activity, leading to increased local histone acetylation and activation of cell motility-related genes, which promotes renal cell carcinoma migration.[92] Similarly, the chromatin remodeling factor chromodomain helicase DNA-binding protein 6 (CHD6) can regulate TMEM65-mediated mitochondrial dynamics through the EGF and Wnt signaling pathways, promoting colorectal cancer development. Knockdown of CHD6 decreases cancer cell proliferation, migration, invasion, and tumorigenesis.[93] These studies suggest that the three-dimensional structure of chromatin is essential for genome stability and proper cellular function and that mutations in genes involved in chromatin remodeling can lead to cancer.

Non-coding RNA

Proteins in the human body are produced through the transcription and translation of RNA, but only 2–3% of genes can encode proteins. The rest are non-coding RNAs (ncRNAs) that do not encode proteins.[94] Non-coding RNA includes long noncoding RNAs (lncRNAs), small nuclear RNAs (snRNA), transfer RNAs (tRNAs), and microRNAs (miRNAs). ncRNAs can be divided into two subclasses based on size: RNAs less than 200 nucleotides are called small or short noncoding RNAs, and RNAs longer than 200 nucleotides are called lncRNAs, which are essential for gene expression. Although the length of these ncRNAs varies, their common feature is that they are transcribed from the genome without being translated into proteins, exercising their respective biological functions at the RNA level. In the process of cancer development, ncRNA usually act on the target or signaling pathways and plays the role of inhibiting or promoting cancer.[95]

miRNAs are a class of short single-stranded ncRNA molecules, approximately 22 nucleotides in length. Abnormal expression of miRNAs has been shown to affect various biological processes in cancer, including cell proliferation, apoptosis, and metabolism.[65] miRNA regulate through three primary modes: direct miRNA, where a mature miRNA directly complements another miRNA to influence its activity and expression; indirect miRNA, where an miRNA targets the non-coding region of a target gene; and global miRNA, where an miRNA can regulate the expression of multiple other miRNAs or an entire miRNA family.[96] The most studied miRNAs regulate gene expression by binding to the 3′ untranslated region (3’ UTR) and 5′ untranslated region (5’ UTR) of target gene mRNAs. Notably, miRNA genes are transcribed from the genome into primary miRNA transcripts (pri-miRNAs) with hairpin structures, which are then processed by the Microprocessor complex (Drosha/DGCR8) into precursor microRNAs (pre-miRNAs) within the nucleus. These pre-miRNAs are then transported out of the nucleus for further processing. In the cytoplasm, Dicer processes pre-miRNAs, allowing them to play regulatory roles on the downstream target genes.[97] Research shows that only RNA hairpins with specific structures and sequence characteristics become efficiently processed miRNA precursors.[98] Additionally, when miRNA clusters are located within the same transcript gene, optimal miRNAs compete for protein factors during processing and maturation. Thus, their expression exhibits mutual inhibition result.[99] It is important to note that during cancer development, the loss or reduction of tumor suppressor miRNAs may increase oncogene translation, resulting in an excess of carcinogenic proteins and promoting cancer formation. Conversely, upregulated oncogenic miRNAs may block tumor suppressor genes, leading to tumor formation. For example, miR-103, miR-25, and miR-92a in liver-cell-derived extracellular vesicles (EVs) in fatty liver enhance oncogenic Yes-associated protein (YAP) signaling and the immunosuppressive microenvironment, promoting liver metastasis of colorectal cancer.[100] Additionally, many studies have shown that miRNAs can be used as cancer markers and can participate in the cancer process by affecting gene expression or abnormally activating signaling pathways.[101]

LncRNAs are transcriptions longer than 200 nucleotides that do not encode proteins. Although lncRNAs in the nucleus and cytoplasm have poor sequence conservation, they experience little evolutionary pressure. However, compared to small RNAs, lncRNAs have longer sequences, more complex spatial structures, and more diverse and complex mechanisms involved in expression regulation.[102] Under different stimulus conditions and signaling pathways, lncRNAs are specifically transcribed and participate in the signal transduction. For example, the lncRNA GAS5 is positioned in the mitochondria and lysosomes, dynamically regulating cholesterol induction and mTORC1 activation.[103] Moreover, the interaction between lipid-bound lncRNA (LINK-A) and PtdIns (3,4,5) over-activates AKT, conferring resistance to AKT inhibitors in cancer cells.[104] Furthermore, lncRNA BREA2 interacts with the Notch receptor intracellular structural domain (NICD) by inhibiting the E3 ubiquitination ligase WWP2, thereby causing transcriptional activation events downstream of Notch that ultimately leads to the development of malignant lung metastases from breast cancer.[105] These studies suggest that lncRNAs can act as novel regulatory elements in signal transduction and tumorigenesis. LncRNAs can also function as molecular chaperones that regulate the transcription of

downstream molecules by binding proteins, usually transcription factors, to localize protein complexes to specific DNA sequences. For example, hypoxia-induced LncRNABX111 promotes metastasis and progression of pancreatic cancer by regulating ZEB1 transcription.[106] Similarly, lncPSCA can interact with oncoprotein DDX5 to promote ubiquitination and degradation of DDX5, thereby reducing DDX5 binding RNA Pol II and activating Pol II transcription of multiple tumor suppressor genes in the p53 signaling pathway, driving cancer development.[107] LncRNAs can also act as "central platform" through scaffolding mechanisms and participate in cancer processes. For example, LncRNA GClnc1can function as a molecular scaffold for WDR5, affecting histone modification and the combination and adjustment of KAT2A, thereby activating downstream genes such as SOD2 and promoting tumorigenesis.[108] In addition, lncRNAs can not only influence the level of phosphorylation modification of protein kinases and splicing factors by mediating their interaction with the latter, which in turn regulates variable splicing of downstream genes. It can also interact with chromatin and then recruit protein complexes to remodel the chromatin state and regulate gene expression.[109] For example, c-Myc upregulates PTB, hnRNPA1, and hnRNPA2 transcription, adjusting the splicing of the pyruvate kinase PKM2 subtype, which is involved in cancer progression.[110]

Occurrence of metabolic reprogramming

Cancer cells frequently meet their energy requirements for abnormal proliferation through metabolic reprogramming, which helps them resist external stress and gain new functions. Therefore, metabolic reprogramming is considered a hallmark of carcinogenesis.[7] The Warburg effect reveals that cancer cells prioritize glycolysis to produce ATP, even when sufficient oxygen is available. This effect paves the way for studying cancer mechanisms from the perspective of tumor metabolic reprogramming.[111] The metabolic pathways of cancer cells primarily include carbohydrate, amino acid, nucleotide, fatty acid, and lipid metabolism. Glucose is one of the primary energy sources in cancer cell metabolism. Extracellular glucose is first absorbed into the cell by the glucose transporter (GLUT), then metabolized to provide energy for cancer cells through various metabolic pathways, accelerating the proliferation and growth of tumor cells. Compared to normal tissues, the expression levels of these transporters in cancer cells are higher, leading to an increased uptake or transport rate of glucose by tumor cells, which is much higher than that of normal tissues. This enables tumor cells to obtain large amounts of glucose and metabolize it to produce ATP, providing energy for their proliferation. Numerous studies have shown that high GLUT expression is closely correlated with the occurrence and progression of breast, gastric, and colorectal cancers.[112–114] After entering the cells, tumor cells undergo complete oxidative metabolism through three main pathways: glycolysis, the pentose phosphate pathway (PPP), and the trichloroacetic acid (TCA) cycle. Studies have shown that PFKL, a subtype of phosphofructokinase 1 (PFK1), a metabolic enzyme of glycolysis, and glucose-6-phosphate dehydrogenase (G6PD) in the PPP pathway often upregulate their expression levels and enhance the proliferation and growth of cancer cells.[115,116] When cancer cells use glycolysis to supply energy, they produce several acidic byproducts, such as lactic acid. High levels of lactic acid can act as donors for protein lactylation, regulating tumor signaling pathways. Sodium lactate treatment can promote the level of pan-lactylation and homologous recombination repair in cancer cells without increasing the level of intracellular lactic acid. Lactate dehydrogenase A (LDHA) inhibitors can significantly inhibit homologous recombination repair and enhance the efficacy of chemotherapeutic drugs on tumor cells. This is because MRE11, a nuclease that plays an important role in regulating DNA terminal cleavage and homologous recombination repair, has the highest level of lactylation. Lactylation of the MRE11 lysine K673 site promotes MRE11 binding to DNA, enhancing DNA terminal cleavage and homologous recombination repair, thereby increasing the resistance of colorectal cancer cells to chemotherapeutic drugs.[117] This further indicates that the high concentration of lactic acid produced by cancer cell glycolysis mediates protein post-translational modifications and participates in cancer progression. Interestingly, recent studies have discovered that cancer cells possess a unique metabolic behavior. When glucose intake is restricted, these cells can metabolize and transport most of the glucose to the mitochondria more efficiently. However, when they ingest excess glucose, the "extra" glucose operates in a less efficient metabolic mode, resulting in its conversion into lactic acid. This indicates that cancer cells can efficiently use glucose until this highly efficient metabolic pathway is saturated.[118] Similarly, recent research has shown that cancer cells can accurately sense changes in glucose levels. Specifically, after the decrease of 3-phosphoglycerate (3-PGA), an intermediate product of low-level glucose metabolism, phosphoglycerate dehydrogenase (PHGDH) can sense the depletion of 3-PGA on its enzyme molecules and then form a large complex with the structural protein AXIN, thereby phosphorylating the serine 46 site of p53 and promoting cancer cell apoptosis.[119] These studies not only confirm the importance of glucose uptake for tumor cell proliferation but also reveal the adaptability and control of cancer cells over glucose metabolism.

Besides serving as substrates for protein synthesis, numerous studies have shown that amino acids act as metabolites and metabolic regulators supporting cancer cell growth. Amino acids in cancer cells can be divided into two categories: non-essential (glutamic acid, glutamine, serine, glycine, and proline) and essential (arginine, leucine, and methionine). Among these, glutamine and arginine have received significant attention. An in-depth study of tumor metabolic reprogramming indicated that some tumor cells tend to be highly dependent on glutamine and less dependent on glucose during rapid proliferation.[120] Glutamine is transported into cancer cells via plasma membrane glutamine transporters such as SLC1A5, SLC38A1, and SLC38A2, and its catabolism is mediated by glutaminase (GLS). GLS expression and glutamine metabolism are activated by the oncogenic transcription factor MYC (c-MYC) in cancer cells.[121] MYC-induced metabolic reprogramming can trigger cancer cell dependence on exogenous glutamine, which serves as a carbon source to maintain mitochondrial membrane potential and macromolecular synthesis. Notably, glutamine consumption can inhibit the proliferation or transformation of tumor cells in an MYC-dependent manner.[122] In addition to glutamine,

arginine metabolism is crucial for the growth of cancer cells. Argininosuccinate synthetase 1 (ASS1) is often overexpressed in tumors. Significant differences in metabolite content and metabolic pathways were observed between hepatocellular carcinoma and normal liver tissues, with hepatocellular carcinoma cells showing increased demand and dependence on arginine. Recent studies have uncovered that a large amount of arginine and its binding protein RNA-binding motif protein 39 (RBM39) can promote arginine absorption through positive feedback, thereby promoting the proliferation and growth of liver cancer cells.[123] Additionally, the metabolism of branched-chain amino acids (BCAAs) regulates the growth of cancer cells. Analyzing mutation data of key metabolic enzymes in the BCAA metabolic pathway revealed high-frequency mutations of glutamate and alanine in BCAT1, including the glutamic acid to alanine mutation at codon 61 ($BCAT1^{E61A}$) in some gastric cancer cells and leukemia. This mutation can increase BCAA metabolic enzyme activity and enhance cancer cell proliferation and migration.[124] These studies have revealed that cancer cells choose different metabolic modes to produce ATP and biological macromolecules for their own use according to the concentration of external nutrients and different stress conditions. These nutrients included glucose, glutamine, serine, arginine, fatty acids, and lipids.

Dysregulation of tumor immunity

The growth and metastasis of cancer cells are closely linked to the internal and external environments of tumor cells. The TME affects tumor immunity through signal transduction and changes in metabolites. The TME consists of various immune cells (macrophages, dendritic cell (DC), neutrophils, B cells, T cells, CAF cells, etc.) and the extracellular matrix (ECM). As mentioned earlier, a large amount of lactic acid produced by glycolysis in cancer cells can cause an acidic microenvironment in the tumor and affect the immune cells in the tumor and its microrings for a prolonged time. For example, when tumor cells are in hypoxia, the Warburg effect is enhanced, a large amount of lactic acid is produced, and tumor cells resist excessive acidification by enhancing the synthesis of carnosine, a mobile buffer. This maintains intracellular pH homeostasis, regulates the location and function of lysosomes in cells, and further regulates the expression of the immune checkpoint protein Galectin-9, ultimately promoting tumor immune escape and hepatocellular carcinoma progression.[125] In addition to promoting immune escape, among many components of TME, immune cells and their secreted cytokines (interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-10 (IL-10), transforming growth factor β (TGF-β), matrix metalloproteinase 9 (MMP9), and vascular endothelial-derived growth factor (VEGF)) promote the immune escape of cancer cells through specific mechanisms. Tumor-specific T cells kill tumors by recognizing MHC-I antigen peptide complexes on the surface of cancer cells via specific T cell receptor (TCR), releasing cytokines, or activating other immune cells. With cancer development, due to constant antigen stimulation and immunosuppressive signal interference, some T cells enter the weak phase and differentiate into a state of loss of function, specifically, exhausted T cells (Tex), which promotes the immune escape of cancer cells.[126] In addition to the existence of direct killing of cancer cells by CD8(+) T cells, other mechanisms of clearance of cancer cells also exist. For example, CD4(+) T cells inhibit immune escape by inducing inflammatory cell death and play a role in cancer immunotherapy independent of CD8(+) T cells.[127] Besides, cancer-related fibroblasts (CAFs) are the most common cells in the TME and can promote cancer progression through cancer stem cell renewal, immunotherapy, and chemotherapy resistance. Single-cell sequencing has revealed that CAFs with high lysyl oxidase (LOX) expression show increased infiltration in recurrent osteosarcoma. Beta-aminopropionitrile (BAPN), an LOX inhibitor, can induce macrophages to promote M1-type polarization by regulating CAF function, thereby inhibiting osteosarcoma occurrence.[128] Interestingly, cancer cells adapt to and resist immune attacks through various strategies, including adaptive immune resistance (AIR). Programmed cell death protein 1 (PD-1)/programmed cell death ligand-1 (PD-L1) in cancer cells induces T cell death or dysfunction, making tumor cells more resistant to T cells and promoting immune escape.[129] Notably, in some TMEs, key immune response components, such as T cells, are very low or absent, preventing immune response activation. These "cold tumors" do not respond to immune checkpoint inhibitors. Therefore, advanced cancers may use various AIR mechanisms to escape immune system attacks.

During cancer progression, the TME is characterized by nutritional competition, low pH, hypoxia, and metabolite accumulation. This environment can lead to immunosuppression or tolerance in immune cells, promoting cancer cell immune escape.[130] Metabolites of cancer cells contribute not only to energy and biosynthesis but also act as signaling molecules in tumor immunity. For example, hypoxia in the TME leads to the accumulation of S-2-hydroxyglutarate (S-2-HG) in cells, altering CD8(+) T cell activation and differentiation, and inhibiting cytokine secretion and cytolysis.[131] The increase in extracellular lactic acid and H^+ can also inhibit T cell proliferation, survival, cytotoxicity, and cytokine production, further mediating cancer cell immune escape.[132] Aconitate decarboxylase (ACOD1) is a metabolic enzyme that catalyzes the conversion of *cis*-aconitonic acid to itaconic acid in cancer cells. It is an important regulator of tumor-associated macrophages (TAMs). TAMs lacking ACOD1 can reshape the TME and transform cold tumors into hot tumors, enhancing tumor immune efficacy.[133] Moreover, itaconic acid, a metabolite, plays an important role in tumor immunity. Studies have shown that large amounts of itaconic acid secreted by myeloid-derived suppressor cells (MDSCs) are absorbed by CD8(+) T cells, blocking the synthesis of aspartic acid, serine, and glycine in CD8(+) T cells, thus inhibiting their anti-tumor effects.[134] Similar studies have found that ACOD1/itaconic acid can promote the immune escape of hepatoma cells by inducing the depletion of CD8(+) T cells in the TME.[135] These studies reveal that metabolites produced by cancer cell metabolism not only promote tumorigenesis and development as energy sources but also regulate tumor signaling pathways as signal molecules.

METABOLIC REPROGRAMMING OF CANCER CELLS MEDIATES EPIGENETIC MODIFICATION AND REMODELING

Cancer cells achieve the necessary macromolecules and energy for their abnormal proliferation through metabolic reprogramming,

which involves the abnormal accumulation of metabolites or excessive activity of metabolic enzymes.[136] This occurs because mutations in oncogenes or tumor suppressor genes drive the remodeling of metabolic and epigenetic modifications. When the oncogenic signaling pathway is overactive, various genes regulate the expression of metabolic enzymes or the activation of metabolic pathways, causing metabolic reprogramming. The metabolites generated by this accumulation mediate epigenetic remodeling, forming a bidirectional interaction between cell metabolism and epigenome, creating favorable conditions for cancer cell proliferation. Previous studies have found that epigenetic abnormalities regulate the expression of many metabolic genes, playing a crucial role in the metabolic reprogramming and redox homeostasis of cancer cells.[137] Recent research suggests that metabolism is a main participant in epigenetic modifications and context-dependent adjustment factors. A growing body of evidence indicates that intermediate metabolites drive chromatin dynamics by altering the chromatin structure and function through chemical posttranslational modifications (PTMs).[138] Notably, epigenetic modifications of histones, including acetylation and crotonylation, require enzymatic or non-enzymatic covalent binding of specific groups to specific amino acids, such as lysine. Therefore, substrates or cofactors such as acetyl-CoA, nicotinamide adenine dinucleotide (NAD+), S-Adenosylmethionine (SAM), α-ketoglutarate (α-KG), flavin adenine dinucleotide (FAD), ATP and succinic acid salts are required for these events and reactions (Figure 1). Most of these substrates or cofactors originate from cancer cell metabolism.[139] Understanding cancer cell metabolism, and how essential metabolites control the reprogramming process through dynamic adjustments of DNA, histones, and other proteins to control the epigenome, is crucial for cancer treatment.

Lactate-mediated modification of lactylation

Studies have shown that the most significant metabolic change in cancer cells is enhanced glycolysis. As early as the 1920s, Warburg and others proposed that compared with normal cells, most cancer cells significantly increase glucose uptake and lactic acid production.[111] Although glycolysis is less efficient than mitochondrial oxidative phosphorylation, it produces more ATP at a faster rate in the presence of excess glucose, with the concomitant production of large amounts of lactate.[140] Additionally, glycolysis generates metabolic intermediates and precursors for the biosynthesis of macromolecules, which are crucial for the rapid proliferation of tumor cells. Lactic acid accumulated from cancer cell metabolism has long been considered a waste product of glycolytic. However, studies have gradually revealed that lactate plays an important role in regulating cancer cell proliferation and immune escape. First, lactate can serve as a major carbon source for the mitochondrial TCA cycle in both normal tissues and tumors.[141] Second, lactate can act as an HDAC inhibitor to promote histone acetylation and regulate gene expression.[142] Recent studies have found that lactate can modify histone lysine residues through a new epigenetic modification called lactylation. This modification leads to the lactylation of histone lysine, thereby regulating gene expression.[143] For example, in ocular melanoma, elevated levels of histone lactylation have been observed. Inhibiting histone lactylation can suppress melanoma development.[144] Similarly, lactylation of histone H3 lysine 18 (H3K18la) promotes RUBCNL expression, contributing to bevacizumab resistance in colorectal cancer cells.[145] Additionally, H3K18la is highly expressed in pancreatic ductal adenocarcinoma and is negatively correlated with survival time. *In vivo* and *in vitro* experiments found that glycolysis inhibitor intervention or knockdown of lactate dehydrogenase A could inhibit lactate production and down-regulate H3K18la levels. The decrease in histone lactylation can inhibit not only the proliferation and migration of pancreatic ductal adenocarcinoma cell lines *in vitro* but also the growth and metastasis of pancreatic ductal adenocarcinoma *in vivo*.[146] DNA damage greatly affects genome stability and is closely related to cancer. Recent studies have found that the homologous recombination (HR) protein MRE11, as the core component of the MRN complex (MRE11/RAD50/NBS1), plays a key role in the sensing, processing and repairing double-strand breaks (DSBs). Lactylation of MRE11 at the K673 locus enhances its DNA binding ability, promotes DNA end resection, and homologous recombination repair, leading to chemotherapy drug resistance in colorectal cancer cells.[117] These studies suggest that histone modifications in cells are critical for DNA replication and damage response, and may mediate cancer development. Surprisingly, glycolysis in cancer cells produces a large amount of lactic acid, forming a lactate-rich tumor microenvironment. This inhibits the energy metabolism, proliferation, and production of pro-inflammatory factors in effector T cells. Conversely, tumor-resident regulatory T cells can efficiently utilize lactate, and high lactate levels promote the proliferation of regulatory T cells and enhance their immunosuppressive function.[147] This implies that lactate accumulation is an important mechanism of tumor immunosuppression. Additionally, recent studies have revealed a new mechanism of histone lactylation -mediated tumor immune escape. The study found that pERK-driven glucose metabolism promotes the immunosuppressive activity of monocyte-derived macrophages (MDM) through histone lactylation.[148] It is worth considering whether the effect of lactate on tumor immunity or immune cell production is related to the lactylation modification of histones in immune cells. Therefore, understanding how lactate affects other cell types and solving the mystery of the Warburg effect are particularly important for cancer prevention and treatment.

Succinyl-coenzyme A-mediated succinylation modification

Succinyl-CoA, derived from the TCA cycle, is the primary substrate for succinylation. It can be produced through the TCA cycle as well as lipid and amino acid metabolism.[149] Researchers have found that succinylation affects tumors through histone and non-histone modifications. Succinylation of non-histone proteins mainly involves vital metabolic enzymes or proteins in the metabolic reprogramming of cancer cells. Succinylation of these proteins can change enzyme activity or localization, affecting normal metabolic pathways and contributing to cancer progression. For example, SIRT5-mediated desuccinylation enhances tumorigenesis by inactivating succinate dehydrogenase subunit A (SDHA) in renal cell carcinoma, malic enzyme 2 (ME2) in CRC, stabilizing glutaminase (GLS) in breast cancer, and activating serine hydroxymethyltransferase-2 (SHMT2) in colon cancer.[150–153] Histone acetyltransferase 1 (HAT1) is a type B histone

acetyltransferase that regulates histones and histone acetylation. HAT1 succinylates histone H3 on K122, contributing to epigenetic regulation and gene expression in cancer cells.

Additionally, HAT1 catalyzes the succinylation of PGAM1 on K99, increasing its enzymatic activity and stimulating glycolytic flux in cancer cells. HAT1 succinyltransferase activity and PGAM1 succinylation by HAT1 play a key role in liver cancer progression *in vitro* and *in vivo*. Thus, HAT1 acts as a succinyltransferase for histone and non-histone proteins in hepatocarcinogenesis.[154] Histone succinylation is highly conserved among species with widespread distribution in HeLa cells, mouse embryonic fibroblasts (MEFs), Drosophila S2 cells, and Saccharomyces cerevisiae cells.[155] Common succinylation sites include H2AK95, H2BK116, H2AK95, and H2BK120. Histone succinylation can facilitate the unencumbering of DNA from the histone surface, allowing transcription factors easy access to buried regions of nucleosome DNA. This indicates that metabolite-mediated histone succinylation will affect the interaction between transcription factors and DNA, gene transcription regulation, and intervention.

Acetylation modification mediated by Acetyl-CoA

As mentioned earlier, histone acetylation is a chemical reaction catalyzed by HATs. Three central families of KATs have been identified: general control non-repressible 5 (GCN5)-related N-acetyltransferases (GNAT), MYST (Moz Ybf2/Sas3 Sas2 and Tip60), and p300/CBP (e1 binding protein p300/CBP).[156] Meanwhile, zinc-dependent HDACs and NAD+-dependent sirtuins are two significant families of lysine deacetylases.[157] Class III HDACs, also called sirtuins, depend on NAD+ concentration. During histone acetylation, acetyl groups provided by acetyl-CoA are added to lysine residues of histones. Acetyl-CoA is the sole donor of acetyl groups in eukaryotic cells.[158] Acetyl-CoA is a central metabolite produced primarily from glucose-derived pyruvate via the pyruvate dehydrogenase complex (PDC) in mitochondria. Because acetyl-CoA does not penetrate cell membranes, it must either be present in the compartment where it functions or be transported to other compartments. Thus, compartmental acetyl-CoA is found mainly in mitochondria and nucleo-cytoplasm. It can be roughly divided into mitochondrial, cytoplasmic, and nuclear acetyl-CoA. During the rapid proliferation of cancer cells, mitochondria produce acetyl-CoA and oxaloacetate (OAA) which condense to form citric acid. Citric acid is quickly transported into the cytoplasm via the SLC25A1 carrier, where it is converted into acetyl-CoA and OAA.[159] Cytosolic acetyl-CoA is irreversibly converted to malonyl-CoA by acetyl-CoA carboxylase 1 (ACC1) and acetyl-CoA carboxylase 2 (ACC2). The use of acetyl-CoA as a substrate for the acetylation of histones and other proteins is emerging as an essential factor in tumorigenesis. Carcinogenic metabolic reprogramming can influence the expression or activity of metabolic enzymes to increase the use of acetyl-CoA in chromatin regulation. Histone acetylation plays an important role in this process. For example, acetyl-CoA metabolism has been found to drive epigenomic alterations and increase cancer risk in patients with fatty liver disease.[160] This may imply a mechanistic link between acetyl-CoA metabolism, epigenetics, and cancer. Additionally, numerous studies have found that the pyruvate kinase activity of pyruvate kinase M2 (PKM2) controls the production of pyruvate from PEP and that nuclear PDC catalyzes the production of local acetyl-CoA from pyruvate at pP300-controlled gene enhancers, which can mediate histone acetylation.[161] Additionally, a novel oncogene with a kinase-domain (NOK) can induce PDC translocation from the mitochondria to the nucleus, promoting histone acetylation and leading to tumorigenesis and metastasis.[162] It is important to note that acetyl-CoA, which mediates histone acetylation, is produced by two main enzymes: ACSS2 and ACL. ACL is particularly significant for acetyl-CoA metabolism and histone modification in cancer cells. For example, CAFs can regulate the metabolism in cancer cells. The specific molecular mechanism is that ACSS2 catalyzes acetic acid to synthesize acetyl-CoA, which increases the acetylation level of histone H3 on the one hand and also acetylates the transcription factor SP1 on the other hand and enhances its stability and transcriptional activity and further enhanced the expression of STA1. These conditions enhance the survival of pancreatic cancer cells in the tumor microenvironment.[163] These studies suggest that changes in the utilization of acetyl-CoA by cancer cells are closely related to gene expression regulation. However, how cancer cells regulate specific genes by altering acetyl-CoA availability may involve two main mechanisms: the regulation of transcription factors through acetylation and the generation of compartmental acetyl-CoA in the nucleus to regulate histone acetylation at specific genomic sites.

In addition to acetyl coenzyme A, NAD is an essential coenzyme in redox processes reactions. It carries high-energy electrons and mediates redox phosphorylation through reversible redox.[164] NAD+ acts as a cofactor for sirtuins during lysine residue deacetylation and plays a vital role in enhancing mitochondrial function and protecting liver and kidney tissues from damage. Mammalian cells synthesize NAD through three pathways: one, the *de novo* pathway from tryptophan; two, the Preiss-Handler pathway using nicotinic acid as the raw material; and three, the salvage pathway using nicotinamide (NAM) or nicotinamide riboside as raw materials.[165] The dependence and selectivity of the NAD pathway during tumorigenesis are determined by tissue lineage-based gene amplification and epigenetic remodeling.[166] The NAD+/NADH ratio is closely related to acetylation status and energy state. Interestingly, highly glycolytic cells generally produce a lower NAD+/NADH ratio, inhibiting sirtuin activity.[167] Additionally, it has been reported that NAD can participate in the regulation of the TUBBY-nicotinamide phosphoribosyltransferase (NAMPT)-NAD+ signal pathway in tumor-infiltrating T cells and promote the synergistic effect of tumor immunotherapy by increasing NAD+ levels.[168] Similar studies have found that NAD+ metabolism drives tumor immune escape by regulating the expression of the immune checkpoint PD-L1. Supplementation of NAD+ precursors can enhance the sensitivity of immunotherapy-resistant tumors to anti-PD-1/PD-L1 antibodies.[169] This indicates that cancer cell metabolism of NAD can mediate the occurrence of cancer and the tumor immune process by affecting NAD+-dependent sirtuin histone acetylation levels.

Crotonic acid CoA-Mediated crotonylation

Amino acid metabolism provides raw materials for synthesizing biological macromolecules such as nucleotides, essential for

the proliferation, invasion, and immune escape of tumor cells. Additionally, amino acid metabolism is crucial for activating immune cells and the anti-tumor effect in the tumor microenvironment.[170] Lysine metabolism produces crotonyl-CoA, a precursor of acyltransferase-catalyzed histone lysine crotonylation (Kcr) reshaping the chromatin environment and affecting gene expression. The enzyme that catalyzes crotonylation is known as a "Writer". P300 was the first identified histone crotonyl transferase. P300 functions as both a histone acetyltransferase (HAT) and a histone crotonyltransferase (HCT).[171] Enzymes that remove modifications from specific residues in proteins are known as "Erasers." The first identified histone decrotonacylase belongs to the class III histone deacetylases of the Sirtuin family (Sirt1, Sirt2, and Sirt3). Additionally, class I histone deacetylases (HDAC1, HDAC2, and HDAC3) also mediate histone decrotonylation.[172] In the highly synchronized yeast metabolic cycle (YMC), it was found that the periodic expression of fatty acid β-oxidation genes synchronized with histone Crotonylation, a by-product of β-oxidation. When nutrients are limited, H3K9 acetylation decreases while H3K9 crotonylation increases, repressing the expression of growth-promoting genes. The Taf14 protein, which contains a specific structural domain, recognizes H3K9 crotonylation and is necessary for this inhibition process. Exogenously added crotonic acid increases histone crotonylation, repressing the expression of growth-promoting genes and disrupting YMC cyclical fluctuations. This suggests that histone crotonylation modifications play an important regulatory role between metabolic states and gene transcription.[173] Kcr levels decrease in liver, stomach, and kidney cancers but increased in thyroid, esophageal, pancreatic, and lung cancers. Elevated levels of Kcr, in particular, impede the motility and proliferation of hepatocellular carcinoma (HCC) cells.[174] In liver cancer cells, knocking down crotonylation enzymes HDAC1 and HDAC3 or using HDAC inhibitors can increase the overall level of crotonylation. This increase in crotonylation can inhibit the proliferation and invasive ability of HCC cells. This suggests that crotonylation can act as an inhibitory factor in the progression of HCC.[174] LINC00922 interacts with SIRT3 by up-regulating H3K27cr in the EST1 promoter region. Glioblastoma stem cells (GSCs) in glioblastoma (GBM) can up-regulate the expression of lysine transporter SLC7A2 and glutaryl-CoA dehydrogenase (GCDH), which produce crotonyl-CoA. Meanwhile, reducing the activity of hydrolytic enzyme enoyl-CoA hydratase short-chain 1 (ECHS1) leads to the accumulation of crotonyl-CoA and histone H4 crotonylation, reducing the tumorigenic ability of GSCs.[175] These studies suggest that histone crotonylation, mediated by the metabolic reprogramming of cancer cells, is essential for regulating gene expression.

Post-translational modifications mediated by other metabolites

Metabolic reprogramming in cancer cells produces metabolites that participate in various post-translational modifications. Methylation can occur on histone lysine and arginine residues, with lysine residues undergoing mono-, di-, and trimethylation, and arginine residues undergoing mono- or dimethylation. Histone methylation primarily occurs on histones H3 and H4. As a universal methyl donor, SAM mediates H3K4me3 and regulates genome structure, chromatin dynamics, and gene expression in cancer cells.[176] Fluctuations in SAM concentration directly affect the rate of histone methylation.[177] A recent study found that dysregulation of the enzyme PCK1 promotes SAM synthesis through serine synthesis. Conversely, the methyltransferase SUV39H1 uses SAM as a methyl donor to support H3K9me3 modification, thereby repressing the oncogene S100A11. SAM supplementation or S100A11 knockdown suppressed PCK1 deficiency-induced HCC progression *in vivo* and *in vitro*.[178] Additionally, nicotinamide N-methyltransferase (NNMT) is an intracellular methyltransferase that catalyzes the formation of 1-methyl nicotinamide (1-MNAM) from NAM using SAM as a methyl donor. Studies found that NNMT regulates SAM and SAM/SAH levels. High NNMT expression alters intracellular SAM levels, affecting DNA and histone methylation.[179] This means that the cancer cells metabolite SAM acts as a bridge between PCK1 dysregulation and H3K9 methylation, participating in cancer progression. Besides SAM, normal IDH catalyzes the conversion of isocitrate to α-KG. The latter is a typical substrate for Jumonji-domain histone demethylases (JHDMs) and the DNA demethylases ten-eleven translocation (TETs). However, mutated IDH continues to convert α-KG into the oncometabolite 2-hydroxyglutarate (2HG), which is absent in normal cells.[180] Due to their highly similar structures, 2HG and α-KG inhibit all enzymes that use α-KG as a cofactor, leading to substantial methylation of histones and DNA.[181] Similarly, deficiency in the metabolic enzyme succinate dehydrogenase (SDH) promotes cancer development by increasing genomic DNA methylation, inhibiting methylation-sensitive protein binding, disrupting existing chromosomal structural boundaries (insulators), and causing proto-oncogenes to interact with distal sites.[182]

Histone phosphorylation involves adding phosphate groups to serine, threonine, or tyrosine residues, regulating tumorigenesis by participating in cellular processes such as DNA damage repair and apoptosis. Mass spectrometry-based proteomics and phosphoproteomics of 30 metastatic colorectal cancer (mCRC) patient-derived xenografts (PDX) revealed differential protein phosphorylation, suggesting a close relationship between protein phosphorylation, cancer occurrence, and drug resistance.[183] Although histones H1, H2A, H2B, H3, and H4 can all be phosphorylated at multiple sites, H3 phosphorylation is the most extensively studied. Recent studies found that phosphorylation of H3.3 at Ser-31 (H3.3S31Ph) promotes SETD2-catalyzed H3K36me3 and antagonizes ZMYND11 binding to H3K36me3, greatly enhancing stimulus-induced gene transcription.[184] This suggests a cross-talk between histone phosphorylation and other epigenetic modifications, enabling rapid response to external stimuli and initiation of specific gene transcription. This may provide a more effective target for cancer therapy than the general transcriptional machinery. It is worth noting that the rapid proliferation of cancer cells requires a large amount of energy derived from ATP, whether from glucose, fat, or amino acid metabolism. Interestingly, AMP-activated protein kinase (AMPK) phosphorylates histone H2B at serine 36 (H2BpS36) in mammalian cells.[185] AMPK plays an essential role in sensing the availability of glucose, glycogen, and fatty acids, as well as pathways that sense lysosomal and nuclear DNA damage.[186] A decrease in energy status or an increase in

the ADP to ATP ratio activates AMPK. This implies that cancer cell energy metabolism is mediated by AMPK activation through histone phosphorylation.[139] Besides the modifications mediated by the above metabolites, lysine β-hydroxybutyrylation (Kbhb) mediated by β-hydroxybutyrate (beta-OHB), O-glycosylation mediated by O-acetylglucosamine, citrullination, and itaconic acid mediated by methylene succinic acid (itaconic acid) all play critical regulatory roles in cancer development.[187,188] It is worth noting that metabolic reprogramming in cancer cells is highly active, with crosstalk between various metabolites. There may also be dialogue or crosstalk between the various modifications mediated by metabolites. Although this aspect of the study is less explored, understanding the crosstalk between various modifiers is particularly important, given the complexity of metabolites, metabolic signals, epigenetic modifications, and gene expression regulation in cancer cells.

REGULATION OF TUMOR IMMUNITY BY EPIGENETIC MODIFICATIONS

As mentioned earlier, aberrant epigenetic alterations contribute to the carcinogenesis of cells during cancer development. Metabolic reprogramming in cancer cells participates in epigenetic remodeling through changes in metabolites or metabolic enzymes, thereby regulating or altering gene expression and creating an environment conducive to cancer cell survival. The coexistence of cancer cells and immune cells in the tumor microenvironment (TME) means that metabolites from cancer cells will enter the TME.[189] Therefore, immune cells in the TME also undergo epigenetic changes, affecting their function. Simultaneously, cancer cells mediate the inhibition of immune cell function in the TME through various oncogene and tumor suppressor gene pathways, by affecting the activation, differentiation, and function of immune cells (such as T cells and NK cells), thus creating favorable conditions for their proliferation.

Immune regulating cell function

The TME is composed of various cell types. Besides tumor cells, the TME includes cells constituting the vasculature (endothelial cells and smooth muscle cells), immune surveillance cells (lymphocytes, macrophages, and mast cells), and stromal cells (fibroblasts), which secrete a range of diffusible growth factors, cytokines, and chemokines into the ECM.[190] Epigenetic mechanisms within the TME play a decisive role in immune cell activation and function (Figure 2).

During ontogeny, B cells differentiate from hematopoietic stem cells and undergo an orderly maturation and selection process in the bone marrow. Many studies have shown that epigenetic modifications (including DNA methylation, histone modifications, and N6-methyladenosine (m6A) mRNA methylation) in bone marrow B cells play an essential role in development.[191] Newly formed immature B cells from the bone marrow migrate and differentiate into various mature functional B cell subgroups (including marginal zone B cells, germinal center B cells, plasma cells, memory B cells, and regulatory B cells). These B cell subsets exhibit multiple functions under different conditions, including antigen presentation, antibody secretion, and cytokine production. Among them, lysine-specific demethylase 1 (LSD1) act as an epigenetic regulator, targeting H3K4me1 and H3K4me2 through flavin adenine dinucleotide-dependent amine oxidation and working with the DNA-binding NF-κB subunit p52 to drive the activation of marginal zone B cells.[192] Compared with naive B cells, germinal center B cells exhibit hypomethylation, significant reorganization of genomic architecture, and massive unpacking of chromosomes.[193] When deficient in methyltransferase-like 3 (METTL3), germinal center B cells (GCBs) show slowed cell cycle progression and proliferation.[194] This suggests that m6A modification of METTL3 is required for germinal center B cell activation. Plasma cells maintain high antibody production, and DNA methylation is crucial for maintaining plasma cell identity. DNA methyltransferase 3 (DNMT3) inhibits key B cell fate and gene expression program to suppress plasma cell differentiation, and DNMT3 gene deletion promotes plasma cell expansion.[195] Similar studies have found that vitamin C can activate ten-eleven translocation enzymes (TETs), regulating GCB epigenetic modification to promote the differentiation of germinal center B cells into plasma cells, thereby enhancing antibody production.[196]

Adaptive immunity is achieved through the initial activation and clonal expansion of antigen-specific T cells, followed by the differentiation of naive CD8(+) T cells into effector T cells or memory T cells through transcriptional regulation, mediating protective immunity in cancer. Increasing studies have shown that T cell differentiation is regulated by epigenetic modifications of histones and changes at the epigenome level, in addition to cytokines and transcription factors.[197] Chimeric antigen receptor T cell (CAR-T) therapy involves bioengineering immune cells to specifically identify and kill tumor cells. Studies have shown that disrupting SUV39H1, a histone methyltransferase gene that trimethylates lysine 9 of histone H3, can enhance the early expansion, long-term persistence, and overall anti-tumor efficacy of human CAR-T cells in leukemia and prostate cancer models. These CAR-T cells show improved expression and accessibility of memory-related transcription factors and reduced expression of inhibitory receptors.[198] This demonstrates the regulatory effect of histone methylation on T cell function.

Similarly, CD4(+) helper T(Th) cells are critical members of the acquired immune system, with cytokine and gene-specific expression in space and time forming the basis of their function. Naive CD4(+) T cells were isolated and purified from mice for *in vitro* induction of Th1 and Th2 differentiation, with cells harvested at early (24 h) and late (72 h) stages of differentiation for study. A Th2-specific histone modification signature was established by focusing on the Th2 cytokine gene region. Results showed significant refactoring of interactions between regulatory elements in this network during early differentiation. Moreover, through knockout of the histone methyltransferase MLL4 gene, it was found that MLL4-mediated H3K4me1 modification in naive T cells is crucial for reshaping chromatin structure and gene expression programs during early Th differentiation.[199] Additionally, histone H3 N(epsilon)-acetyl-lysine 9 (H3K9ac) in the proximal promoter and first exon region of all three genes was significantly higher in memory CD8(+) T cells than in naive CD8(+) T cells.[200] This suggests that histone acetylation and methylation-mediated epigenetic changes may provide a rapid and

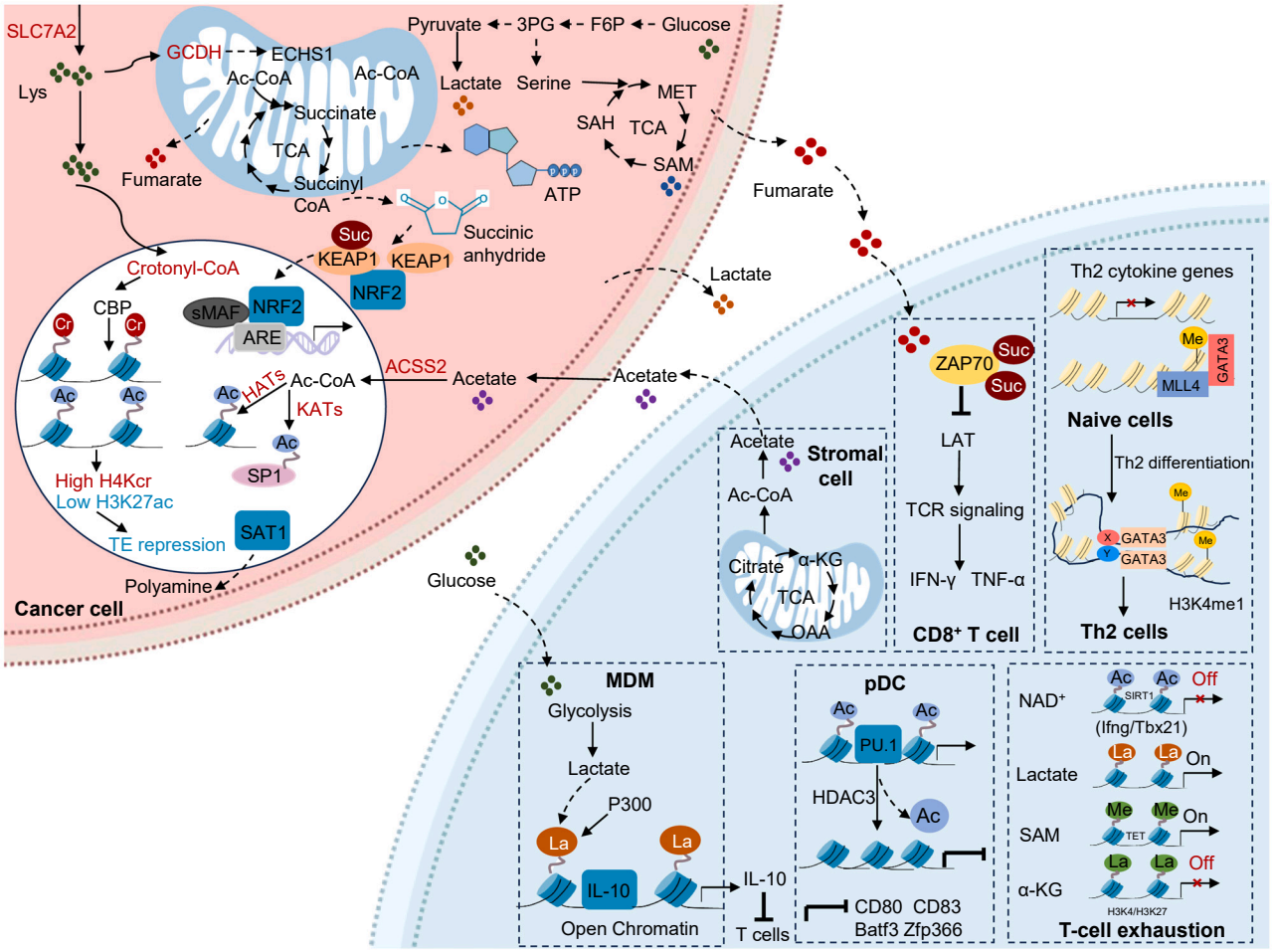

Figure 2. Metabolites produced by cancer cells within TME can mediate epigenetic modifications of immune cells, thereby affecting gene expression or activation of immune cell function

SLC7A2: solute carrier family 7 member 2; Lys: Lysine; GCDH: glutaryl-CoA dehydrogenase; ECHS1: enoyl-CoA hydratase short-chain 1; Ac-CoA: acetyl-coenzyme A; TCA: trichloroacetic acid; 3PG: 3-phosphoglycerate; F6P: fructose-6-phosphate; SAH: subarachnoid hemorrhage; MET: cellular-mesenchymal to epithelial transition factor; SAM: S-adenosylmethionine; ATP: adenosine triphosphate; Keap1: kelch-like ECH-associated protein 1; NRF2: nuclear factor erythroid 2-related factor 2; sMAF: small musculoaponeurotic fibrosarcoma Maf; ARE: antioxidant response element; CBP: CREB binding protein; AC: Acetylation; Low H3K27ac: histone H3 lysine 27 acetylation; HATS: heteromeric amino acid transporters; KATs: lysine acetyltransferases; SP1: specificity protein 1; SAT1: spermidine/spermine N(1)-acetyltransferase 1; TE repression: transposable element repression; ACSS2: Acetyl-CoA Synthases 2; ZAP70: zeta-chain associated protein kinase; LAT: linker for activation of T cells; TCR signaling: T cell receptor signaling; IFN-γ: interferon-γ; TNF-α: tumor necrosis factor-α; α-KG: alpha-ketoglutarate; OAA: oxaloacetate; Th2: type 2 helper T; Me: methylation; MLL4: mixed linked leukemia 4; GATA3: GATA binding protein 3; H3K4me1: histone H3 lysine 4 mono-methylation; MDM: murine double minute; IL-10: interleukin-10; pDC: pre-dendritic cells; Suc: succinylation; Cr: crotonylation; La: Lactylation; HDAC3: histone deacetylases 3; Batf3: basic leucine zipper ATF-like transcription factor 3; Zfp366: the transcription regulator DC-SCRIPT; NAD+: nicotinamide adenine dinucleotide; SIRT1: Situins 1; IFNG: interferon-gamma; TET: ten-eleven translocation enzymes; H3K4:histone H3 lysine 4; H3K27: histone H3 lysine 27.

robust transcriptional "memory" in memory CD8(+) T cells. These studies indicate that epigenetic modifications are critical in regulating T cell activation and function.

DCs are critical regulatory cells in the immune system, mainly divided into classical dendritic cells (cDCs) and plasmacytoid dendritic cells (pDCs). These subsets are widely distributed across major tissues and perform various complex functions under homeostasis and during immune responses. CDCs are professional antigen-presenting cells that initiate antigen-specific immunity and induce immune tolerance, while pDCs are the primary producers of type I interferons during viral infection, promoting antiviral immune responses. DCs rapidly integrate signals from the tissue microenvironment and react accordingly. This rapid response depends on epigenetic changes in DC chromatin structure mediated by various enzymes and their substrates.[201] It has been found that DC activation and maturation are regulated by histone modification. For example, histone deacetylase 3 (HDAC3) inhibits the expression of cDC1-related genes through its deacetylation ability, promotes the expression of pDC-dependent genes, and thus promotes the differentiation

of precursor cells into pDCS.[202] Similarly, the transcription factor FOXM1 is epigenetically regulated by demethylation of lysine 79 of histone H3 (H3K79me2). Inhibition of H3K79 methyltransferase disruptor of telomeric silencing 1-like (DOT1L) not only reduces H3K79me2 enrichment but also decreases FOXM1 expression, partially reversing DOT1L's immunosuppressive effect on bone marrow-derived dendritic cells (BMDCs).[203] This implies that FOXOM1-mediated histone lysine demethylation regulates DC function. In addition to histone modification, long non-coding RNA Dpf3 (lnc-Dpf3) plays a critical role in DC migration and mediates inflammatory diseases.lnc-Dpf3 expression is upregulated during CCR7-mediated DC migration and can inhibit DC migration to stimulated lymphoid tissues under inflammatory conditions. lnc-Dpf3 gene deletion enhances CCR7-mediated DC migration, leading to excessive activation of T cell-mediated adaptive immunity and aggravating tissue inflammatory damage during contact hypersensitivity in mice.[204] This explains the mechanism of inflammatory diseases associated with DC migration and reveals that epigenetic modifications cross-regulate the innate immune response of DC cells.

Epigenetic-mediated immune escape

Besides cancer cells, immune cells, and stromal cells, various metabolites are secreted by these cells in the TME, causing the accumulation of lactic acid or other metabolites.[130] As mentioned earlier, the interaction between the metabolites produced by the metabolic reprogramming of cancer cells and epigenetics can mediate the inhibition of immune cell function by affecting the epigenetics of immune cells, leading to immune escape. Monocyte-derived macrophages are the central immunosuppressive cells in GBM. Protein kinase R-like ER kinase (PERK) upregulates GLUT1 expression and promotes macrophage glycolysis, increasing IL-10 expression mediated by lactic acid modification.[148] This means that lactic acid-modified macrophages may affect the anti-tumor immune process. RNA m6A modification, the most abundant modification in mRNA, is mainly catalyzed by the methyltransferase complex (MTC), with METTL3 as the catalytic core. The accumulated lactic acid in the TME can upregulate RNA methyltransferase METTL3 expression in tumor-infiltrating myeloid cells (TIMs) by inducing histone lactic acid modification, increasing its m6A modification level, and promoting its immunosuppressive function, leading to tumor immune escape.[205] Similarly, histone H3 N-methyl lysine demethylases PHF8 (KDM7B) has also been reported as a new epigenetic checkpoint regulator of tumor immune escape. Interference with PHF8 causes the degradation of methyltransferase SET domain bifurcated 1 (SETDB1) in the nucleus, transcriptional activation of H3K9me3-modified retrotransposons, and induces antiviral and anti-tumor immune response in the tumor, thereby blocking tumor growth.[206] Furthermore, the TME significantly induces high expression of histone demethylase JMJD1C in tumor regulatory T cells (Tregs). The expression level of JMJD1C gradually increases along with the trajectory of cell development and differentiation during the process of Treg infiltration into tumor tissues. Although the conditional deletion of JMJD1C in Treg cells does not affect the development and function of peripheral Tregs, it specifically reduces tumor Tregs, enhances the anti-tumor T cell immune response, and significantly reduces tumor growth.[207] In addition, fumarate (fumaric acid) is a metabolite widely reported to mediate T cell depletion. However, the mechanism of action of fumarate is relatively simple, and cells need to maintain a low level of fumarate to stay healthy. In patients with fumarate hydratase (FH) mutations, excessive intracellular fumarate disrupts the immune balance and causes a worse prognosis. Fumaric acid, usually undergoing amber acyl modification to a specific protein, regulates the target protein's function and further affects cell function. Investigators found that fumarate secreted by cancer cells promoted the succinylation of ZAP70 protein in CD8(+) T cells, leading to T cell exhaustion and reduced antitumor effect.[208]

Interestingly, cancer cells prefer "vinegar" more than normal cells. Acetic acid, or acetate, is an essential component of short-chain fatty acids. Acetate uptake by cancer cells leads to acetyl-CoA formation catalyzed by acetyl-CoA synthases 1/2 (ACSS1/2), contributing to ATP and lipid synthesis and histone acetylation. However, it is unknown whether the metabolism of acetic acid by tumors alters the acetylation level of non-histone proteins. Recent studies have found that acetic acid uptake by cancer cells reprograms tumor cell metabolism and promotes immune evasion by up-regulating c-Myc levels.

Further studies have found that cancer cells uptake acetic acid via high levels of monocarboxylate transporter MCT1, producing acetyl-CoA catalyzed by ACSS2, which increases lipid synthesis in tumor cells. Moreover, the c-Myc lysine 148 acetylation level increased, affecting CD8(+) T cell infiltration. Both the orthotopic lung cancer model and the subcutaneous lung cancer model showed that drinking water containing acetate inhibited CD8(+) T cell infiltration and promoted tumor growth. Inhibition of acetic acid uptake or its metabolic pathway can inhibit anti-tumor immune escape.[209] Additionally, other studies have found that the intestinal flora can secrete butyrate HDAC3 inhibition activity in the suppression of the cluster of cell proliferation in mice and humans, and the intestinal stem cells specificity knockout HDAC3 will block cluster cell differentiation and downstream II type of immune response.[210] This suggests that metabolites can epigenetically regulate intestinal epithelial cells' steady-state and immune response mechanisms. As mentioned earlier, the methyl donor SAM would be involved in the methylation of histones, and abnormalities in methionine metabolism may lead to specific histone alterations in T cells, resulting in their dysfunction in the tumor microenvironment. Interestingly, cancer cells evade antitumor immunity by expressing high levels of methionine transporter, SLC43A2, and T cells compete for methionine, thereby affecting T cell histone methylation and function.[211] Similar studies have found that GCDH can interact with CBP to promote histone lysine crotonylation in the nucleus. However, the loss of histone lysine crotonylation promotes the production of immunogenic dsRNA and dsDNA through enhanced H3K27ac, which stimulates RNA sensors MDA5 and cGAS to enhance type I interferon signaling, leading to decreased tumorigenic ability of GSC and increased CD8(+) T cell infiltration. However, GSCs can reprogram lysine catabolism by up-regulating SLC7A2 and GCDH and down-regulating ECHS1, leading to intracellular accumulation of Crotonyl-CoA and histone H4 lysine crotonylation, interfering with CD8(+) T cell infiltration and mediating immune escape of cancer cells.

Table 1. Drugs targeting epigenetics

Drug	Target	Mechanism	Adaptation symptoms	Reference
Azacitidine	DNA methyltransferases	Modulate the aberrant DNA methylation	Secondary acute myeloid leukemia	Karantanos et al.[219]
Decitabine	DNA methyltransferases	Modulate the aberrant DNA methylation	Myelodysplastic syndromes	Khan et al.[220]
Belinostat	Pan-HDAC	Enhancing histone acetylation in specific regions of chromatin and inducing apoptosis of cancer cells	Peripheral T cell lymphoma	O'Connor et al.[221]
Panobinostat	Pan-HDAC		Multiple myeloma	Imai et al.[222]
Chidamide	HDAC1/2/3	Enhancing histone acetylation	Peripheral T cell lymphoma	Cao et al.[223]
Mocetinostat	HDAC1/2/3/11	Enhancing histone acetylation	Refractory lymphoma	Batlevi et al.[224]
Valemetostat	E2H1/E2H2	Targeting EZH1/2 to combat epigenetic dysregulation	T cell leukemia	Izutsu et al.[218]
Tazemetostat	E2H2	Targeting EZH2 to reduce histone methylation	Refractory follicular lymphoma	Italiano et al.[225]
Enasidenib	IDH mutation(mIDH)	Reducing 2-HG, inducing histone demethylation	Acute myeloid leukemia	Stein et al.[226]

A lysine-restricted diet combined with MYC inhibition or anti-PD-1 therapy can slow tumor growth.[175]

These results suggest that cancer cells and immune cells, nutrient competition between cancer cells and immune cells within the TME, can influence TME metabolites, thereby mediating epigenetic modifications. This indicates that during the metabolic reprogramming of cancer cells, highly expressed metabolic enzymes can acquire more energy and induce epigenetic modifications in immune cells by competing for nutrients in the TME, allowing cancer cells to evade immune surveillance or immunosuppression.

CANCER TREATMENT BASED ON THE EPIGENETIC

Genome mutations or disorders drive abnormal transcription processes and promote the occurrence and development of cancer. Although most epigenetically mediated gene regulation affects oncogenic and tumor suppressor networks in cancer cells, tumor immunogenicity and immune cells involved in anti-tumor responses may also be affected by epigenomic alterations. Specifically, metabolites or metabolic enzymes resulting from the metabolic reprogramming of cancer cells can affect epigenetic modifications. These modifications, in turn, can activate immune cells or anti-tumor immunity by regulating gene expression or activating intracellular signaling pathways. These complex mutual regulatory processes form a cancer-driven process centered around epigenetic modifications (aberrant epigenetic processes - methylation, and histone post-translational modifications - tumor immunity). By intervening in epigenetics, it is possible to regulate gene expression and the tumor immune process, transforming the tumor immune microenvironment from 'cold' to 'hot'. Increasing research on cancer prevention and treatment through epigenetic intervention has yielded significant results. So far, epigenetic medicine has become a rising field. Unlike traditional drugs, epigenetic drugs are developed to treat cancer at the gene regulation level. These drugs interfere with cancer progression by affecting epigenetic modifications such as DNA methylation and acetylation, thereby blocking the binding of transcription factors to promoters or altering the compactness of chromatin structure.[212]

Epigenetic targeted drugs

Histone acetylation is regulated by HATs and HDACs. Among them, histone Hypoacetylation by HDACs is often associated with chromatin condensation and transcriptional silencing. In clinical practice, histone deacetylase inhibitors (HDACis) have gradually become powerful anticancer agents targeting epigenetic regulation and have been widely used in treating hematological malignancies (Table 1). For example, several HDACis, such as vorinostat (SAHA), romidepsin, belinostat, and panobinostat, have been approved for treating hematological malignancies.[213] However, at present, most HDACis only show mild effects on solid tumors, have toxic side effects, and are prone to drug resistance. Based on the marketed HDACi SAHA, researchers designed and synthesized a series of new thiazole-containing HDACis and found a highly active HDAC1 inhibitor, HR488B, which can significantly inhibit the occurrence and development of CRC *in vitro* and *in vivo*. The research found that HR488B, by inhibiting Rb phosphorylation, slowed E2F1/Rb/HDAC1 complex dissociation to regulate E2F1 protein expression, eventually leading to CRC inhibition.[214] In addition, HDAC inhibitors can also sensitize tumors to CD8(+) T cell killing.[215] Although the therapeutic response to HDAC inhibitors depends on the combination regimen,[216] the underlying mechanisms of HDAC is efficacy in solid tumors remain unclear. However, we still cannot rule out the broad prospect of enhancing the efficacy of HDACi and its application in cancer treatment. Histone methylation of tail residues (single methylation, dimethylation, or trimethylation) can have opposite effects on transcriptional output, primarily catalyzed by HMT. Several HMTs, including the EZH2, SETDB1, and DOT1L, have been used as therapeutic targets. However, only the small molecules EZH2 and DOT1L have entered clinical development.[217] EZH1 and EZH2catalyze H3K27me3, which accumulates near gene promoter regions, repressing gene expression. Therefore, targeting H3K27me3 enzymes (EZH1 and EZH2) has been pursued in cancer therapy. Multiple clinical trials have shown the efficacy of

the EZH1/2 dual inhibitor valemetostat in targeting various lymphomas, including HTLV-1 virus-associated aggressive ATL characterized by high H3K27me3 levels.[218] In addition to histone methylation, targeting histone protein ubiquitination suggests a promising strategy. For example, the proteasome component PSMD14, a novel histone H2AK119 deubiquitinase, interacts with the histone H3K36 dimethyl transferase NSD2 at chromatin and facilitates H3K36 dimethyl initiation. This leads to increased chromatin accessibility and transcriptional activation of oncogenic genes. PSMD14 not only increased the prognosis of patients with multiple myeloma risk stratification but also overcame potential targets for intervention in bortezomib resistance. O-phenanthroline (OPA) and Capzimin, small molecule inhibitors of PSMD14, can inhibit the proliferation of multiple myeloma cells and overcome bortezomib resistance. When combined with anti-myeloma drugs such as lenalidomide and dexamethasone, they can effectively exert synergistic anti-tumor effects.[71]

DNA accessibility is generated by chromatin remodeling agents, such as the mammalian SWI/SNF complex, which uses ATP energy to slide nucleosomes or expel them from DNA. These effects at the promoter and enhancer nucleosome-depleted region (NDR) accelerate the binding of TF and the initiation of transcription. The SWI/SNF chromatin remodeling complexes are highly conserved ATP-dependent chromatin structure regulatory complexes containing multiple subunits. They use the energy obtained by ATPase subunits (BRM and BRG1) to hydrolyze ATP, altering and remodeling the histone and DNA interactions of nucleosomes. This process affects the degree of chromatin openness in specific genome regions and regulates gene expression. Thus, chromatin remodeling by SWI/SNF is essential for establishing appropriate gene expression patterns. However, the mutation frequency of the SWI/SNF chromatin remodeling complex is as high as about 20%. These mutations may affect cancer development by altering the activity of coding subunits and the function of the entire complex. The proteolytic agent (AU-15330) for SWI/SNF chromatin remodeling complex ATPase, developed using proteolysis targeting chimera (PROTAC), can inhibit the chromatin accessibility of the enhancer subregion and effectively and selectively inhibit the growth of androgen receptor-dependent prostate cancer *in vivo* and *in vitro*.[227] This suggests that stopping the SWI/SNF mutant complex from providing access to inappropriate genes can inhibit cancer gene activity, making SWI/SNF therapy feasible. However, the situation is more complex. Recent studies have found that blocking SWI/SNF can only inhibit the activity of a subset of genes. Initially, all genes were turned off when SWI/SNF was suppressed. However, another molecule, EP400, would later restore gene access. Only by blocking both SWI/SNF and EP400 could abnormal gene activity be successfully suppressed. This two-pronged approach has been effective in four cancers: acute myeloid leukemia, diffuse intrinsic pontine glioma (DIPG), prostate cancer, and non-small-cell lung cancer.[228] These studies indicate that drug intervention in epigenetic modification is one of the most effective ways to treat cancer.

Epigenetic-based dietary interventions

Metabolic disorders such as hypertension, hyperlipidemia, hyperammonemia, obesity, and insulin resistance are often associated with the occurrence of cancer. Studies have found that metabolic syndrome (MS) is closely related to various cancers.[229,230] Since metabolites can mediate epigenetic modifications, the strong association between metabolic syndrome and cancer appears to be related to diet. Many studies have found that caloric restriction and fasting can prolong lifespan and have health-promoting effects. Various amino acids (including methionine, serine, and glycine), ketone bodies, arginine, and glutamine have been reported to mediate the progression of different types of cancer.[217,231,232] Recent studies have found that indole-3-acetic acid (3-IAA), produced by intestinal microbial metabolism of tryptophan, is an ''amplifier'' of chemotherapy. It can increase the level of reactive oxygen species in the tumor, weakening cancer cell autophagy and promoting chemotherapy to kill cancer cells. More importantly, short-term dietary intake of tryptophan or direct oral administration of 3-IAA increased the chemotherapeutic efficacy of pancreatic cancer in a humanized mouse model. Moreover, 3-IAA has similar effects when combined with different chemotherapy regimens or when treating different cancers.[233] This study further suggests that dietary interventions mediate cancer development.

Glutamine is one of the amino acids cancer cells heavily rely on for proliferation. Most cancer cells have glutamine ''addiction''.[234] Glutamine also plays a regulatory role in immune cell activation and function. Tumor cells and type-1 conventional DCs (cDC1s) compete for glutamine in the tumor microenvironment. When cDC1 cells lack glutamine, their antigen presentation capacity is reduced, preventing efficient activation of anti-tumor T cells.[235] Interestingly, α-KG derived from dietary glutamine supplementation leads to hypomethylation of H3K4me3 and represses epigenetically activated oncogenic pathways in melanoma.[236] This suggests that glutamine dietary intervention can prevent melanoma tumor growth through epigenetic reprogramming. In addition to glutamine, dietary restriction of methionine as a treatment was proposed more than 60 years ago.[237] A methionine-restricted diet not only inhibits cancer invasion and metastasis but also synergistically inhibits cancer progression when combined with single-carbon metabolic inhibitors like 5-Fluorouracil (5-FU).[238,239]

Ketogenic diets (KDs) are characterized by ''ultra-low carbohydrate, high fat, and moderate protein''. KDs can inhibit cancer progression, while high-fat and high-carbohydrate diets can lead to obesity and promote cancer progression.[240] KD forces the body to burn fat instead of carbohydrates, producing ketones such as acetoacetate (AcAc) and β-Hydroxy-butyrate (BHB). Studies have found that BHB produced by KDs can directly inhibit the growth of bifidobacterium in the intestinal tract, reducing the proportion of Th17 cells and regulating the host immune response.[241] Additionally, KDs increase the metabolic effector BHB content, which, through receptor Hcar2 and Hopx expression induced by tumor suppressor factors, inhibits the proliferation of intestinal crypt stem cells and intestinal epithelial turnover, eventually blocking the occurrence and progression of colon cancer.[242] Cancer cells can use ACSS2, acetic acid acetyl coenzyme A, as a power source. This metabolic pathway is essential for cancer cell proliferation under hypoxic and nutrient-deficient conditions. Inhibition of ACSS2 in cancer cells transforms them from consumers of acetic acid to

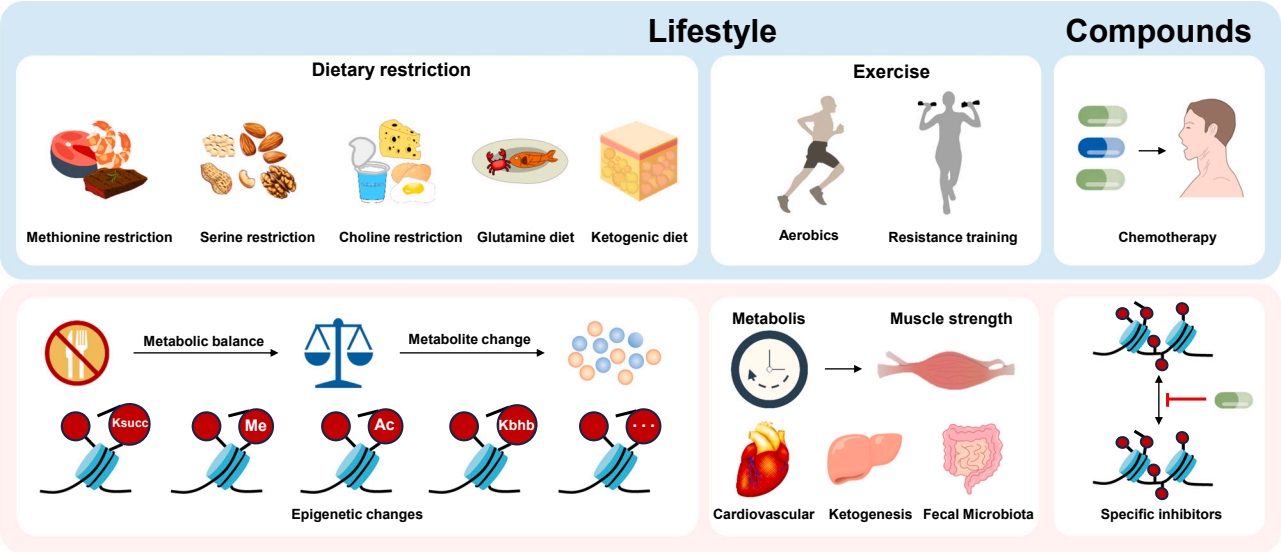

Figure 3. Metabolism-based epigenetic intervention strategies

A range of dietary restrictions including methionine, serine, choline, glutamine and ketogenic diets modulate the levels of metabolites in the body and are involved in regulating epigenetic modifications. At the same time, regular and moderate exercise, including aerobic exercise and resistance training, promotes metabolism and accelerates metabolic rates in the body, thereby protecting normal cardiovascular function. More importantly, exercise can also regulate the gut microflora and participate in the regulation of epigenetic modifications through gut flora metabolites, thereby regulating the expression of specific genes and cancer progression. In addition, in the preventive or therapeutic phase of cancer, certain doses of chemotherapeutic drugs will regulate gene expression by inhibiting some epigenetic modifying enzymes, thus treating cancer. All in all, these strategies are effective regulators of epigenetic modifications in the organism with the help of the external environment, and there are benefits for the health of the organism. Ksucc: Succinylation; Me: Methylation; Ac: Acetylation; Kbhb: β-hydroxybutyrylation.

producers of acetic acid, which T cell-dominated tumor-infiltrating lymphocytes (TILs) will uptake, significantly enhancing their effector function and proliferation activity, thereby effectively enhancing the anti-tumor immune response.[243] This implies that intervention with exogenous acetic acid can mediate anti-tumor immune processes. Other studies have also found that dietary restriction of serine and glycine slows tumor growth and improves survival in mice.[244] However, it is unclear whether the antitumor effects of serine and glycine starvation depend on changes in methylation status. These findings suggest dietary intervention is a practical approach to epigenetic-centered cancer-driven mechanisms (Figure 3).

Epigenetic-based exercise regulation

In the case of cancer, in addition to clinical treatment, care programs are particularly important. Many cancer treatments now incorporate physical activity into the care regimen as well. As mentioned previously, metabolites produced by metabolic reprogramming of tumor cells can serve as enzymes or substrates for a variety of post-translational modifications and are involved in epigenetic remodeling. This suggests, in part, that alterations in metabolic pathways or accumulation of metabolites in cells or organisms are involved in epigenetic regulation in a direct or indirect manner, thereby affecting the process of cancer development and treatment. In fact, cardiorespiratory fitness or muscle strength is strongly associated with health outcomes, including the risk of death from cancer,[245] and moderate to vigorous recreational exercise training reduces cancer risk.[246] Recent studies have found that breast cancer patients who experience a heart attack are 60% more likely to die from cancer than those who do not, and that proper regular exercise boosts metabolism and enhances cardiovascular function, which reduces the risk of cancer.[247] This implies that cardiovascular improvements with exercise will result in survival benefits for cancer patients. On a cellular or molecular level, exercise promotes cellular metabolism and alters the rate of intracellular metabolite accumulation or excretion, thereby modulating the transmission of intracellular signaling pathways or the state of epigenetic modifications (Figure 3). It has been found that hypoxia can cause histone demethylase KDM5A and KDM6A to regulate H3K4me3 and H3K27me3 to regulate chromatin status, which in turn affects the differentiation status of cells.[248,249] Aerobic combined resistance exercise reduces fatigue and improves physical conditioning by affecting the inflammatory response and DNA methylation during active radiotherapy in head and neck cancer (HNC) patients.[250] These studies suggest that hypoxia may cause abnormalities in genes, enzymes, etc. in the body and induce abnormal epigenetic modifications. In contrast, moderate aerobic exercise may promote physical fitness by inducing epigenetics. In addition, changes in metabolite levels appear to be another important reason why exercise modulates epigenetics. Piperidinic acid was found to be a key metabolite for immune health by analyzing serum metabolomics in 4- and 15-month-old mice. Exercise induces enrichment of H3K4me3 in the promoter region of the *crym* gene, a key enzyme that catalyzes piperidinic acid production in the liver, and promotes hepatic *crym* transcription and expression, which leads to the maintenance of piperidinic acid at a high level. The latter can

reduce the production of inflammatory factors in lipopolysaccharide (LPS)-stimulated macrophages by inhibiting mTORC1 signaling, thereby improving immune function and attenuating LPS-induced inflammatory injury in mice.[251] This suggests that exercise may epigenetically modulate liver metabolism, which in turn enhances macrophage function to promote immune health. Other studies have also found that exercise stimulates the biosynthesis of methylation donors in the liver, generates SAM into the prefrontal cortex of the brain, and mediates excitation of m6A levels of transcripts of synapse-associated genes, which enhances neural activity in the brain to reduce anxiety-like phenotypes in response to environmental stressors.[252] This implies that the liver-brain axis and the metabolic-epigenetic regulatory pathways it mediates have a key role in exercise anxiolysis. In fact, aging increases cancer risk.[253] Recent research has also found that regular exercise slows epigenetic aging by delaying immune aging and reducing cardiovascular risk.[254] These studies have shown that exercise can promote metabolic-immune interconnections and regulation by regulating metabolism and mediating epigenetic modifications through metabolites or signaling pathways, ultimately benefiting the health of the organism.

SUMMARY AND OUTLOOK

Genomic instability, metabolic reprogramming, and epigenetic aberrations drive cancer development. In the metabolic reprogramming of cancer cells, highly expressed metabolic enzymes or accumulated metabolites act as various enzymes or substrates for post-translational modification, mediating epigenetic remodeling. This epigenetic remodeling forms abnormal signaling and gene expression pathways in cancer cells, promoting or interfering with cancer progression. Recent decades have seen significant advances in understanding the intersection of tumor metabolism and epigenetics, deepening our knowledge of cancer genesis. Cell proteins, including histones, undergo various modifications such as ubiquitination, acetylation, methylation, butyrylation, crotonylation, 2-hydroxyisobutyrylation, and glutarylation. When these modification pathways target the same amino acid residue, competitive antagonism or dynamic conversion between different modification pathways may occur. For example, under replication stress, SIRT1/BMI1 mediates the dynamic transformation of histone H2A lysine 119 loci crotonic acylation (H2AK119cr) to H2A lysine 119 loci of ubiquitin (H2AK119ub) dynamic transformation.[73] Similarly, there is dynamic competition between histone H4 K5 and K8 acetylation and butyrylation.[255] This suggests that epigenetic modifications cross-switch between complex signaling and metabolic reprogramming, potentially mediating the expression of multiple genes.

The cofactors and substrates for post-translational modifications can be derived from metabolites of cancer cells and immune cells. These metabolites can provide energy for the abnormal proliferation of cancer cells and create favorable conditions for their survival by participating in epigenetic remodeling. Notably, due to the complex crosstalk between metabolic pathways and metabolites, connections may exist between metabolite-mediated epigenetic modifications. Metabolites involved in epigenetic modifications include acetyl-CoA, crotonyl-CoA, succinyl-CoA, and lactate. Theoretically, intervening in the metabolic pathways of cancer cells to reduce metabolite levels can regulate epigenetic modifications. However, given the complexity of transcriptional regulation and chromatin accessibility, epigenetic regulation of target gene expression must be approached holistically. Additionally, metabolites within the tumor microenvironment (TME) can affect the activation and function of immune cells, potentially mediating antitumor immunity. Epigenetic therapy, through the design of drugs targeting epigenetics, can influence the tumor immune process. Therefore, emerging paradigms for cancer treatment increasingly combine epigenetic therapy and immunotherapy. Improving the specificity and affinity of epigenetic therapies and developing small molecules targeting a broader range of epigenetic and immune targets may offer new strategies for cancer treatment.

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DECLARATION OF INTERESTS

The authors declare no competing financial interests.

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