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Permalink

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Journal

Clinical Cancer Research, 23(15)

ISSN

1078-0432

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Publication Date

2017-08-01

DOI

10.1158/1078-0432.ccr-16-2506

Peer reviewed



Published in final edited form as:

Clin Cancer Res. 2017 August 01; 23(15): 4004–4009. doi:10.1158/1078-0432.CCR-16-2506.

Molecular Pathways: Metabolic control of histone methylation and gene expression in cancer

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Abstract

Epigenetic alterations contribute to tumor development, progression, and therapeutic response. Many epigenetic enzymes use metabolic intermediates as cofactors to modify chromatin structure. Emerging evidence suggests that fluctuation in metabolite levels may regulate activities of these chromatin-modifying enzymes. Here we summarize recent progress in understanding the crosstalk between metabolism and epigenetic control of gene expression in cancer. We focus on how metabolic changes, due to diet, genetic mutations, or tumor microenvironment, regulate histone methylation status and consequently affect gene expression profiles to promote tumorigenesis. Importantly, we also suggest some potential therapeutic approaches to target the oncogenic role of metabolic alterations and epigenetic modifications in cancer.

Keywords

metabolism; epigenetic; methionine; glutamine; hypoxia; gene expression

Background

Genetic alterations play a prominent role in tumorigenesis. DNA mutations or chromosomal translocation in cancer cells trigger aberrant gene expression that contributes to chronic proliferation, resistance to cell death, and metastasis (1, 2). Emerging evidence reveals many tumors also exhibit distinct epigenetic patterns (3, 4). These epigenetic modifications dictate chromatin accessibility, adding another means by which gene transcription is intricately regulated throughout tumor development (5).

Histone modifications are post translational modifications made on core histone proteins (6). Histone acetylation results in more accessible DNA contributing to active transcription. Histone methyltransferase (HMT) facilitates histone methylation on specific histone residues which can recruit different transcription associated proteins to regulate transcription (7). In particular, trimethylation of histone at lysine 9, 27 and 20 (H3K9, H3K27, H3K20) is often associated with repressed transcription, while methylation of H3K4, H3K36, and H3K79

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Conflict of interest: The authors have no conflicts of interest.

correlates with active transcription (8). Interestingly, a variety of chromatin modifying enzymes including histone methyltransferases MLL2, EZH2 and histone demethylase UTX are mutated in cancer, leading to abnormal histone methylation and altered gene expression (9–11).

Many chromatin modifying enzymes often require a specific metabolite cofactor to function (12, 13). For example, HMT requires S-adenosylmethionine (SAM), an intermediate metabolite in one-carbon metabolism, to methylate histone (14). Similarly, Jumonji-domain containing histone demethylase (JmjC-KDM) use a TCA-cycle intermediate alpha-ketoglutarate (α KG) to remove methyl groups from histones (15). Interestingly, the availability of a given metabolite may fluctuate in response to metabolic rewiring caused by genetic alterations or the result of a dynamic tumor microenvironment. Cell metabolism is comprised of dynamic reactions induced by *de novo* synthesis, but also heavily influenced by exogenous sources like diet. In cancer cells, metabolic networks are further complicated by oncogenic stimuli, genetic alterations of metabolic enzymes, and the tumor microenvironment, such as hypoxia and nutrient depletion (16). Emerging evidence suggests that changing metabolite levels can regulate enzymatic activity of chromatin modifying proteins, indicating potential crosstalk between cellular metabolism and epigenetics (12, 13). Therefore, besides mutation of epigenetic enzymes, modulation of metabolite levels provides an additional layer of epigenetic control and transcriptional regulation in cancer cells.

Methionine metabolism in cancer and histone methylation

SAM serves as a major methyl donor for the methylation of DNA and histone. SAM is primarily generated from methionine in the one-carbon metabolism pathway. Under normal conditions, cells acquire endogenous methionine from either the methionine salvage cycle or the folate cycle (17). Interestingly, a key enzyme in the methionine salvage cycle, methylthioadenosine phosphorylase (MTAP), is deleted across a wide range of cancers (18). Loss of MTAP expression impairs methionine biosynthesis and may render cancer cells dependent on exogenous methionine (18). Moreover, defects in folate metabolism also promote methionine dependence in cancer cells (19). Methionine is shown to be highly consumed in tumor cells compared to normal cells, and some cancer cells are not able to grow in the absence of methionine (19, 20). Recent studies have demonstrated that defects in methionine metabolism reduce intracellular SAM levels, affecting histone methylation dynamics (21–23). Deficiency in methionine or folate leads to reduced SAM levels and reduced H3K4 methylation in both yeast and human cells (21). Knockdown of SAM synthase SAMS-1 in *C. Elegans* inhibits H3K4 methylation and suppresses the expression of H3K4-associated genes during *Pseudomonas* infection (24). In addition, methionine metabolism also plays an important role in cellular differentiation of mouse embryonic stem cells. Depletion of methionine in stem cells diminishes H3K4 levels and reduces the expression of the pluripotent marker, NANOG, leading to enhanced differentiation potency (23). This evidence suggests that H3K4-specific HMT activity is sensitive to fluctuating intracellular SAM levels. In fact, a methionine restriction diet in mice triggers a rapid decrease in H3K4 methylation by modulating intracellular SAM levels. Importantly, ChIP-sequencing analysis of H3K4me3 reveals that methionine restriction decreases H3K4

methylation, affecting cell fate genes and cancer-associated genes including *AKT1*, *MYC*, and *MAPK* (22) (Figure 1). Therefore, it is speculated that elevated methionine metabolism through the induction of H3K4 methylation drives the expression of many cancer-associated genes and contributes to tumor progression.

Genetic mutation of metabolic enzymes and histone methylation

Histone demethylase enzymes use α KG as the co-substrate to remove methyl groups on histones and to release succinate and formaldehyde. While histone α KG is essential for histone demethylation, increased succinate or fumarate levels inside the cell can antagonize the activity of the histone demethylases. In fact, accumulation of succinate or depletion of α KG promotes cellular differentiation in both mouse embryonic stem cells and human pluripotent stem cells (25, 26). In contrast, the elevated intracellular α KG in naive stem cells through the modulation of histone methylation induces the expression of pluripotency-associated genes (e.g. *NANOG*) and favors self-renewal (25). Thus, genetic mutations that lead to alteration of succinate, fumarate or α KG levels often result in changes in histone methylation and gene expression. For example, loss of function mutations in the succinate dehydrogenase (SDH) gene and the fumarate hydratase (FH) gene are found in a number of human cancers that lead to rapid accumulation of succinate or fumarate (27, 28). In SDH and FH deficient cancer cells, the accumulation of succinate and fumarate respectively inhibits various KDM enzymes leading to histone hypermethylation and altered gene expression (29) (Figure 1). Recent studies also demonstrate that fumarate accumulation in FH deficient cells, through epigenetic modulation, activates the expression of EMT-related transcription factors and vimentin to promote epithelial-to-mesenchymal-transition (30).

In normal cells, the isocitrate dehydrogenase (IDH) converts isocitrate to α KG in the TCA cycle. Multiple whole-genome sequencing experiments reveal heterogeneous mutations on the IDH gene in different cancers including, glioblastoma, acute myeloid leukemia and T cell lymphoma (31). The mutated IDH1 and IDH2 not only fail to synthesize α KG, but also gain additional function to produce 2-hydroxyglutarate (2HG). 2HG, a structural analog of α KG, competitively inhibits many α KG-dependent enzymes including histone demethylases, leading to histone hypermethylation and inhibition of cellular differentiation (32, 33). In fact, 2HG treatment in 3T3-L1 cells inhibits H3K9-specific demethylase KDM4C activity and represses the expression of adipogenesis-associated factors *CEBPA*, *PPARG* and *ADIPOQ*, ultimately blocking adipocyte differentiation (34) (Figure 1). A recent study also demonstrates that IDH1 mutation promotes H3K9 hypermethylation and downregulates ATM expression, resulting in increased DNA damage and impaired cell renewal in hematopoietic stem cells (35).

Glutamine deficiency and histone demethylation

Cancer cells favor aerobic glycolysis to sustain chronic proliferation (36). Because most glucose is often diverted to lactate production, glutamine can be converted to glutamate which is subsequently converted to α KG to replenish the TCA cycle in many cancers. For example, metabolic flux analysis in Ras-transformed cells suggests that glutamine is rapidly converted into α KG in the TCA cycle to support oxidative phosphorylation and ATP

production (37). Therefore, cancer cells also depend on glutamine to make α KG to replenish the TCA cycle (38). Interestingly, oncogenic signaling, including c-Myc and K-Ras, drive excessive uptake and metabolism of glutamine to support cancer cell growth and survival (39, 40). However, glutamine addiction coupled with poor vascularization within the tumor microenvironment depletes the local supply of glutamine. Indeed, metabolomic analyses revealed that glutamine reaches undetectable levels in tumors compared to healthy tissue (41, 42). Interestingly, the tumor also displays differential glutamine levels in intratumoral regions, and glutamine levels are extremely low in the core of tumors compared to peripheral regions (43, 44). The glutamine deficiency in the tumor microenvironment, especially the core region of solid tumors, leads to depletion of α KG levels, which is a critical cofactor for histone demethylases. The low glutamine levels inhibit the JmjC-KDM leading to histone hypermethylation in the tumor core. Specifically, hypermethylation at histone H3K27 represses the expression of melanocyte differentiation genes, such as *PMEL*, *KIT*, and *GJB1*, ultimately resulting in a block to cell differentiation (Figure 1). Importantly, the alteration in histone methylation and gene expression upon glutamine depletion promotes drug resistance of melanoma cancer cells to BRAF inhibitor treatment both *in vitro* and *in vivo* (43).

Hypoxia and histone methylation

In addition to metabolic stress, cancer cells in the microenvironment of solid tumors also experience a profound shortage in oxygen. Hypoxia can contribute to cancer progression, metastasis and drug resistance (45). Recently, different studies have demonstrated that hypoxic conditions in cancer cells induce significant changes in the epigenetic landscape (46, 47). Specifically, hypoxia induces histone dimethylated H3K9 by inducing the activity of methyl transferase G9a, and potentially inhibiting the demethylation activity (48). The hypoxia-mediated H3K9 methylation often leads to repression of tumor suppressors including *BRCA1*, *RUNX3*, *RAD51*, and *MLH1* (35, 49, 50) (Figure 1). Interestingly, oxygen is required by all α KG dependent JmjC-KDM enzymes to facilitate the demethylation process. *In vitro* enzymatic activity assays suggest that JmjC-HDMs have weak binding affinities for oxygen when at levels near the cellular oxygen concentration, leading to the sensitivity of demethylation activities to changes in oxygen availability (51). Earlier reports also indicate that hypoxia inhibits Jumonji histone demethylase activity leading to induction of repressive histone markers, H3K9 and H3K36, and down regulation of chemokines (e.g. Ccl2) and chemokine receptors (e.g. Ccr1 and Ccr5) in macrophages (52). Similarly, hypoxic conditions attenuate the activity of the H3K4-specific demethylase JARID1A, but do not affect protein levels. Hypoxia induced hyper methylation of H3K4 increases the expression of *HMOX1* and *DAF* genes in Beas-2B (53). While indicated evidence suggests that hypoxia inhibits demethylase activity to alter epigenetics, further studies are needed to determine whether the histone demethylase activity depends on oxygen availability, and if oxygen depletion directly impairs demethylase activity *in vivo*. Lastly, lactate dehydrogenase A enzyme, under hypoxic conditions, can produce oncometabolite 2-HG, independent of IDH enzymes (54, 55). Importantly, hypoxia-mediated 2HG also inhibits KDM4C activity to promote H3K9 methylation and alter gene expression (54) (Figure 1).

Clinical-translational advances

Targeting methionine metabolism with dietary restriction

Elevated SAM levels can modulate epigenetic control of gene expression which may contribute to the progression of cancer. Recent studies also suggest that methionine restriction (MR) diets can be an effective approach to lower intracellular SAM levels and reduce histone methylation (20, 22) (Figure 1). MR diets have demonstrated anticancer effects in addition to prolonging life in animal models (56–58). Cumulative evidence demonstrates that a low methionine diet inhibits xenograft tumor growth, prevents metastasis, and enhances the efficacy of chemotherapy drug treatment in different animal models (59–61). Moreover, methionine metabolism may contribute to oncogenesis as MR diets inhibit colonic tumor development in carcinogen-treated rats (62). Data from a phase 1 clinical trial suggests that a MR diet is effective in reducing plasma methionine levels and is safe for 18 weeks (63). However, the effect of an extended MR diet may not be tolerable and remains to be determined. Alternatively, administration of the methioninase enzyme can serve as an alternative approach to reduce methionine levels. Methioninase, originally purified from bacteria, breaks down methionine to α -ketobutyrate, methanethiol and ammonia (64). Treatment with recombinant methioninase enzyme is well-tolerated and displays better anti-cancer properties than a MR diet (65–67). However, the effect of methioninase treatment on SAM levels and histone methylation remains unknown.

Targeting epigenetic modifications to reverse deregulation in gene expression

Metabolic alterations in cancer cells affect epigenetic modifications leading to abnormal gene expressions. Thus, the metabolic control of epigenetic also contributes to tumor progression of human cancer. Different from genetic alteration, epigenetic modifications by methylation and acetylation are intrinsically reversible. Therefore, chromatin modifying enzymes can be potential targets to reverse the change in gene expression mediated by epigenetic modifications. Indeed, some inhibitors targeting epigenetic machinery exhibits potent anticancer properties and have been approved by the FDA for the treatment of many cancers (68). Elevated methionine metabolism in cancer is associated with H3K4 hypermethylation which is accountable for the active transcription of many cancer associated genes. Beside MR, targeting the H3K4 histone methyltransferase may provide some therapeutic advantage to reverse abnormal gene expression and block tumor progression. The H3K4 specific inhibitor, MM-401, directly inhibits the MML1 histone methyltransferase, blocking H3K4 methylation and suppressing the expression of *MYC* and dedifferentiation genes (69, 70) (Figure 1). MM-401 treatment can promote cell cycle arrest, cell death and myeloid differentiation in mixed-lineage leukemia cells (69). Thus, it will be of interest to determine whether MM-401 or other H3K4-specific inhibitors can be used to target H3K4 hypermethylation in methionine dependent cells.

Cancer cells in the regions of solid tumors with poorly developed vasculature are subjected to hypoxia and glutamine depletion due to poor tumor vasculature (43, 45). The distinct tumor microenvironment may promote cancer cell dedifferentiation and drug resistance, contributing to poor clinical outcome (71). In particular, glutamine deficiency in melanoma has been shown to promote H3K27 methylation resulting in cell dedifferentiation and drug

resistance (43). While it remains challenging to modulate glutamine levels in the tumors, targeting the H3K27 histone methyltransferase (e.g. EZH2) may underscore a therapeutic advantage. The potent and selective EZH2 inhibitors (i.e. EPZ005687 and GSK126) directly block H3K27 methylation and reactivates transcription of target genes (72, 73) (Figure 1). Importantly, treatment using specific (EPZ005687) or global histone methylation inhibitors suppress the expression of dedifferentiation markers in melanoma cells and reverses the drug resistance phenotype mediated by glutamine deficiency (43). Thus, targeting epigenetic machinery is a promising approach to impair the oncogenic effect of metabolic changes in cancer.

Limited oxygen in the tumor microenvironment facilitates the emergence of cancer stem cells and promotes resistance to chemotherapy (74–76). Moreover, hypoxia-induced H3K9 methylation represses expression of different tumor suppressors, and consequently contributes to tumor progression (77). Therefore, targeting H3K9 methylation in cancer may reverse the change of gene expression and diminish the oncogenic effect of hypoxia in cancer. Chaetocin is an inhibitor that inhibits methyltransferase Suv39h1 and reduces H3K9 repressive markers (78). Chaetocin treatment in human leukemia cells inhibits H3K9 methylation and reactivates the expression of E-cadherin and tumor suppressor p15 (79, 80). Further studies are needed to investigate the effect of H3K9-specific methyltransferase inhibitors on gene expression and the therapeutic response of cancer cells during hypoxia.

Acknowledgments

We thank members of the Kong laboratory for helpful comments on the review. This work was supported by National Institutes of Health (NIH)/R01CA183989 to M.K.

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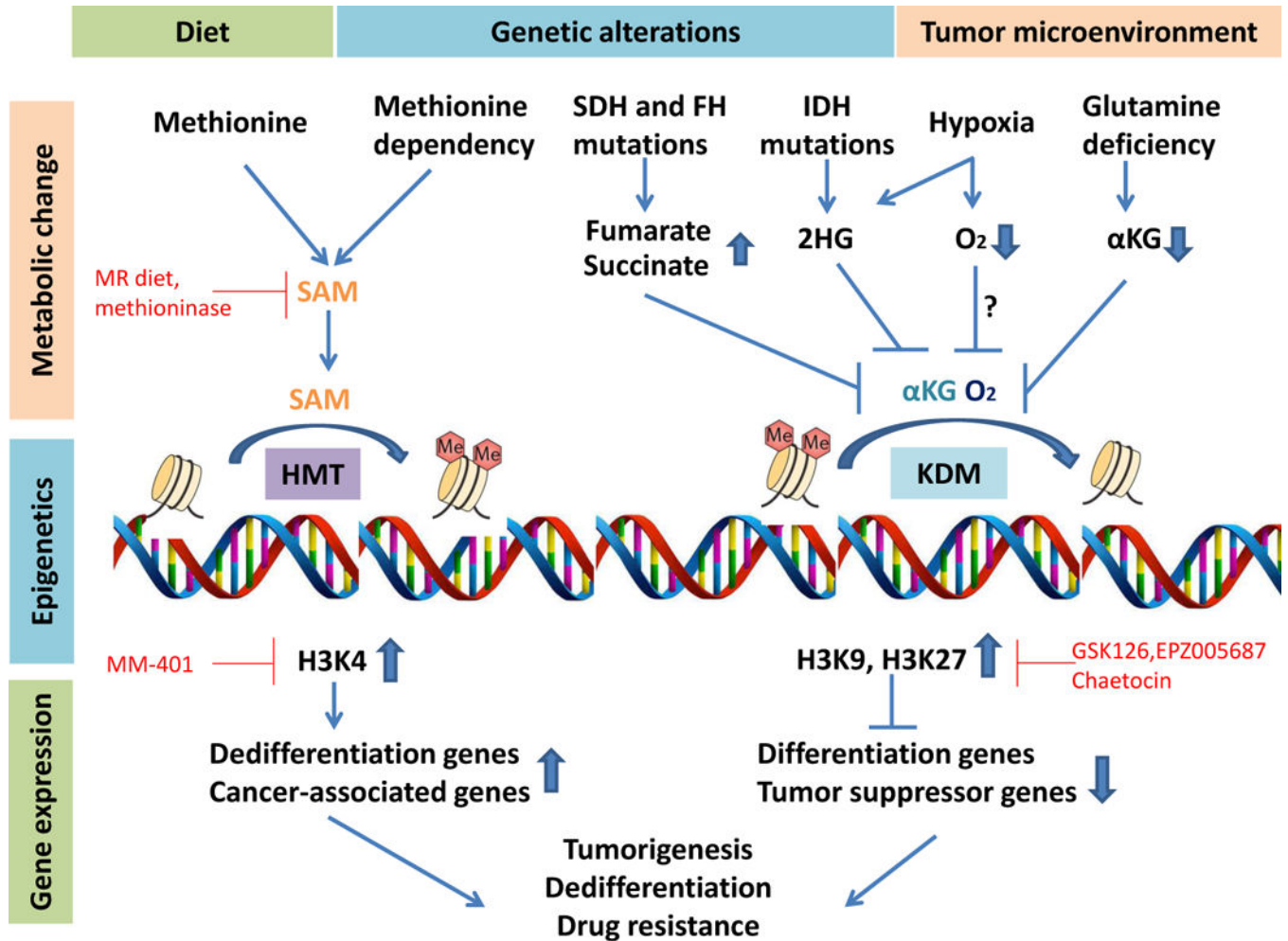


Figure 1. The crosstalk between metabolism and epigenetic control of gene expression in cancer (Left) Methionine dietary intake or methionine dependency leads to increased S-adenosylmethionine (SAM) levels which promote histone methylation catalyzed by histone methyltransferase (HMT). Subsequently, hypermethylation at active marker H3K4 induces transcription of dedifferentiation genes and cancer-associated genes. (Right) Fumarate or succinate accumulation due to the loss-of-function mutant fumarate hydratase (FH) or mutant succinate dehydrogenase (SDH), 2-hydroxyglutarate (2HG) accumulation due to the mutant isocitrate dehydrogenase (IDH) or hypoxia, depletion of α -ketoglutarate (α -KG) due to glutamine deficiency, or low oxygen levels during hypoxia inhibits histone demethylation process catalyzed by histone demethylases (KDM). Subsequently, hypermethylation at suppressive histone markers H3K9 or H3K27 inhibits transcription of differentiation genes and tumor suppressor genes. Together, these metabolic regulations of epigenetics and gene expression may contribute to cell dedifferentiation, tumor progression and drug resistance in cancer. Potential therapeutic approaches to target the intersection of metabolism and gene expression in cancer are highlighted in red.