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Epigenomic links from metabolism -- methionine and chromatin architecture

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Abstract

Chromatin and associated epigenetic marks provide important platforms for gene regulation in response to metabolic changes associated with environmental exposures, including physiological stress, nutritional deprivation, and starvation. Numerous studies have shown that fluctuations of key metabolites can influence chromatin modifications, but their effects on chromatin structure (e.g. chromatin compaction, nucleosome arrangement, and chromatin loops) and how they appropriately deposit specific chemical modification on chromatin are largely unknown. Here, focusing on methionine metabolism, we discuss recent developments of metabolic effects on chromatin modifications and structure, as well as consequences on gene regulation.

Keywords

Metabolism; Chromatin; Epigenetics; Transcription; Methionine

Introduction

Cells metabolize distinctive extracellular nutrients into other products to provide energy and chemical building blocks for their survival. Diverse metabolic pathways are interconnected and tightly regulated to allow cells to respond to changing environmental conditions (e.g. fasting, nutrient deficiency/excess). For example, fasting causes the liver to engage glycogenolysis, gluconeogenesis, and ketogenesis pathways to produce energy [1,2]. Modulation of cellular metabolism (e.g. methionine availability) has been suggested to contribute to mammalian lifespan and to be relevant to cancer pathogenesis [3,4]. How metabolism contributes to transcriptional and other gene regulatory responses is still incompletely known.

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Author contributions

Z.X. and J.W.L.: Conceptualization. Z.X.: Writing-Original draft preparation. J.W.L.: Reviewing and Editing.

Declaration of competing interest

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Genes encoded in DNA are packaged in the nucleus by wrapping around histone octamer complexes to form nucleosomes. The amino-terminal tails of histones are subject to chemical modifications, which can be recognized by specific binding proteins. Adjacent nucleosomes are linked by DNA and progressively fold into higher-order chromatin structures. The rearrangement of nucleosomes can expose or hide DNA binding sites from DNA-binding proteins. These chromatin features provide diversity in the mechanisms through which genes can be activated or suppressed. Emerging studies suggest that metabolism and diets connect with epigenetic modifications, chromatin compaction, nucleosome arrangement, and long-range chromatin interactions via metabolites, intermediates, metabolic enzymes, histone modifiers, and signal-responsive proteins (Fig. 1). Here, we summarize several major advances in understanding the connections between metabolism and chromatin with a focus on methionine, and also discuss their downstream effects on gene transcription.

The selective effect of methionine metabolism on histone methylation

Histones are modified by a plethora of chemical groups (e.g. methyl, acetyl, crotonyl, lactyl, and serotonyl), which represents a key chromatin feature that is often associated with gene regulation. Histone lysine methylation is a particularly important modification that involves both gene activation (e.g. H3K4me3 and H3K79me2) and repression (e.g. H3K27me3 and H3K9me3). The deposition of methyl groups on histone tails is catalyzed by methyltransferases that use S-adenosylmethionine (SAM) from the methionine cycle as the major donor of the methyl group (Fig. 2). Dietary methionine restriction has been used to elucidate its function on histone methylation and gene expression because of its profound impact on SAM production and promising influence on cancer therapeutic outcomes [3,4]. We and others have found that different types of cells respond to this nutritional variation selectively. For the cancer cells and certain types of lymphocytes such as Th cells, methionine restriction significantly impairs SAM synthesis, leading to loss of H3K4me3 and changes in gene expression relevant to one-carbon metabolism [5,6]. While for $CD8^+$ T cells, low methionine selectively reduces H3K79me2 but not other marks, resulting in low expression of *STAT5* and impaired T cell function [7] (Fig. 3a). What causes this disparity of epigenetic response to the same stimulus between different cell types? First, the cellular SAM level is highly dependent on the efficiency of methionine uptake. Two members of the solute carrier family (SLC7A5 and SLC43A2) responsible for methionine transportation are relatively lower expressed in $CD8^+$ T cells than tumor cells, suggesting lower methionine consumption and lower SAM production in $CD8^+$ T cells comparing to tumor cells [7]. Second, adding methyl groups donated by SAM to histone tails is catalyzed by a specific methyltransferase. Both H3K4me3 and H3K79me2 are histone marks of actively transcribed genes but deposited by different methyltransferases. H3K4me3 is catalyzed by the COMPASS-like methyltransferase family which requires a high level of SAM, whereas H3K79me2 is specifically catalyzed by methyltransferase DOT1L [8,9], which has a relatively low Michaelis constant (K_m) thus use small amounts of SAM [10,11]. Therefore, both the deficiency of methionine transporters and low requirement of DOT1L to SAM concentration in $CD8^+$ T cells may explain why H3K79me2 is more sensitive than other histone marks to methionine changes. However, tumor cells take in

more methionine and generate more SAM for H3K4me3 deposition (Fig. 3a). According to Michaelis-Menten kinetic theory, each of these histone methylations may be highly sensitive to SAM accumulation when SAM concentration is close to the K_m value of the corresponding methyltransferase [12]. A recent study reports that hepatocyte nuclear factor 4α (HNF4α) and key metabolic enzymes which mediate sulfur amino acid metabolism dictate the sensitivity of liver cancer to methionine restriction, but the underlying molecular mechanisms and their impacts on histone methylation warrant further investigation [13]. Interestingly, the breadth or length of the H3K4me3 domain, which has previously been suggested to be associated with transcription activity [14] and cell identity [15–18], can also respond to methionine restriction and shows a positive correlation with the differential gene expression [19]. Different methyltransferases are reported to specifically establish broad or narrow H3K4me3 domains [20]. Overall, both SAM availability and highly specific methyltransferases with different susceptibility to the fluctuation of its substrate determine the selective effects of methionine metabolism on histone modification and its breadth.

Histone methylation connects metabolism to chromatin compaction

Chromatin exists in two broadly distinct states: densely arranged heterochromatin and less condensed euchromatin. Compared with euchromatin, heterochromatin is transcriptionally inactivated or silenced because its tightly packaged conformation precludes regulatory elements and transcription factors (TFs) to access the chromatin. It is further categorized into facultative and constitutive heterochromatin based on their histone marks. Facultative heterochromatin is marked by H3 lysine 27 tri-methylation (H3K27me3) and can switch to more open, transcriptionally active conformation at a specific cell differential phase [21–23], whereas the constitutive heterochromatin is enriched with H3K9 methylation and is generally associated with the stable maintenance of gene silencing [24,25]. These modifications can be recognized by chromatin “readers” containing specific domains (e.g. HP1) and regulate chromatin compaction [26]. Glutamine deficiency, isocitrate dehydrogenase 1 mutation, and inhibition of H3K27 demethylases can regulate H3K27me3/H3K9me3 and contribute to gene regulation by affecting the production of α-ketoglutarate (α-KG), a key cofactor for the Jumonji-domain-containing histone demethylases (JHDMs) and 2-hydroxyglutarate (2HG), an inhibitor of α-KG [27–30]. Decondensation of heterochromatin in the absence of H3K27me2/3 is found to become more interactive with other euchromatin regions [31,32]. H3K9me3-decorated heterochromatin loss at protein-coding genes is concomitant with cell type-specific gene expression [33]. Therefore, these studies suggest the critical role of histone methylation in maintaining the compact chromatin structure. Heterochromatin also represents a compensatory system to maintain genome stability and suppress the activity of transposable elements to prevent their potentially harmful effects [34]. Recently, two studies reveal that the reconfiguration of epigenetic modifications compensates for the losses of histone/DNA methylation due to the insufficiency of the methyl-group donor SAM, allowing cells to preserve a compacted state and maintain the repressed state of repetitive DNA elements that enriched in heterochromatic regions (Fig. 3b). Haws et al. demonstrate that cells prefer mono methylation of H3K9 at the expense of broad losses in histone di- and tri-methylation at repetitive and transposable loci under SAM-depleted conditions [35]. Deblois et al. report

that impairment of methionine metabolism significantly reduces the SAM level in breast cancer cells, leading to a global decrease in DNA methylation and accompanying with the reallocation of H3K27me3 modifications into regions enriched in transposable elements [36]. As we described in preceding paragraph, these different epigenetic changes may reflect the kinetic properties of various methylation-modifying enzymes and their sensitivities to fluctuations of cellular SAM. However, the detailed mechanisms of how heterochromatin organization is established and maintained remains a mystery. Thus, how methionine metabolism affects chromatin structure remains an emerging area of inquiry. Recent studies suggest that the formation of heterochromatin is mediated by phase separation [37,38], whereas the role of epigenetic modifications or in this process is still not answered.

Metabolic influences on DNA accessibility through nucleosome remodeling

The accessibility of DNA at promoters and enhancers to regulatory factors and transcriptional machinery is an important parameter of regulating transcription initiation. Both the chromatin compactness (as described in the preceding paragraph) and the nucleosome arrangement are thought to determine DNA accessibility. ATP-dependent chromatin remodeling complexes, such as INO80 and SWI/SNF, alter nucleosome position and occupancy (e.g. nucleosome sliding or eviction) to adjust the space between adjacent nucleosomes and contribute to nucleosome-free region that required for TFs binding [39,40]. Interestingly, recent studies suggest that these complexes regulate metabolic gene expression in response to changing nutrient environments [41–46]. A study by Gowans et al. reveals that INO80 complex rapidly and reversibly changes DNA accessibility of periodical genes crucial for coordinating cell division with cellular respiration in the yeast metabolic cycle [45]. Each remodeling complex possesses the same core ATPase subunit but different bromodomains that can read specific histone modifications [47]. For example, the mammalian SWI/SNF complex preferentially targets to specific enhancers and interact with p300 (acetyltransferase) to modulate H3K27ac [48]. The modifications, such as acetylation and succinylation, may reduce the affinity between DNA and histone core by altering the charge of histone tail [49,50]. H3K27ac is well recognized as a marker for active promoters and enhancers, and its distribution on chromatin is tied to metabolism because the substrate of histone acetyltransferase (i.e. acetyl-CoA) is produced from metabolic processes (e.g. glucose, fatty acid, and amino acid catabolism) that are highly dependent on nutrient availability. Recent studies show that under stress conditions, for example, glucose restriction, hypoxia, and mitochondrial stress, cells regulate the histone acetylation and DNA accessibility by controlling the pool of acetyl-CoA generated from available nutrients [51–53]. Nutritional supplements can increase the accumulation of cytoplasmic acetyl-CoA and facilitates the transportation of acetyl-CoA into the nucleus for histone acetylation, where significant changes in DNA accessibility could be detected by ATAC-seq at the activated genes along with the increasing of H3K27ac. Non-enzymatic covalent modifications (e.g. glycation) also connect the metabolic state with DNA accessibility by disrupting the assembly and stability of nucleosomes [54]. These and other studies suggest that regulation of gene transcription by rapidly altering DNA accessibility promotes metabolic homeostasis and affects cell differentiation [55–58]. How methionine and histone methylation might influence DNA accessibility warrants future study. Further investigation

is required to investigate the precise mechanism of how metabolic status regulates nucleosome organization.

Diet and metabolism contribute to chromatin looping

The human genome contains hundreds of thousands of regulatory elements, such as enhancers that contain binding sites for TFs, allowing them to act together to control gene activation. Enhancer-associated histone marks (e.g. H3K4me1 and H3K27ac) can be regulated by methyltransferases and concentration of metabolites (e.g. glucose), then consequently influence the enhancer activity [59–61]. Enhancer elements can be located as much as a million base pairs away from target promoters, where the chromatin looping can bring them into very close spatial proximity (<200 nm) by “looping factors” (e.g. CTCF and cohesin), thereby facilitating enhancer-promoter interactions [62,63]. This mechanism allows for gene regulation. The DNA and histone methylation states can regulate the CTCF binding and recruitment of the cohesin, which, in turn, control chromatin loops at specific DNA sites and thus impact transcriptome diversity [64,65]. In such a way, T cells translate αKG-sensitive metabolic changes into context-dependent gene expression [65]. Studies have suggested that several proteins induced by chronic metabolic stress contribute to chromatin looping. Manuel et. al [66] have reported that during fasting, elevated glucocorticoids can regulate lipid metabolism through the glucocorticoid receptor (GR). Once stimulated by glucocorticoid, GR is translocated into the nucleus and interacts with SETDB2 which works as a signal responsive protein other than methyltransferase to facilitate long-range chromatin looping. The formation of chromatin loops consequently activates the target genes relevant to the metabolic stress of fasting in the liver, such as *INSIG2*. INSIG2 protein suppresses SREBP (sterol regulatory-element binding proteins) accumulation in the liver and inhibits lipogenesis. Another study shows that during β-adrenergic stimulation, phosphorylated JMJD1A, an H3K9 demethylase, can function as a cAMP-responsive protein that interacts with the SWI/SNF chromatin remodeling complex and DNA-bound PPARγ to induce long-range chromatin interactions which influence metabolic gene expression in brown adipocytes [67]. These cases highlight the diverse roles of histone modification proteins in response to environmental signals. With the development of chromatin conformation assays [68,69], more chromatin interactions involved in gene regulation to respond to nutrient availability are beginning to be identified. Using promoter capture Hi-C, Qin et. al. have detected more long-range enhancer-promoter interactions in the liver cells during metabolic adaptation to lipid-rich and carbohydrate-rich diets [70]. Depending on the given diet, the chromatin interactions are regulated either by activating pre-established chromatin loops or by forming new loops. Hnf4α is suggested to be activated by its ligand and can bind with other regulatory factors to activate chromatin loops under a lipid-rich diet. These chromatin loops upregulate genes involved in fatty acid oxidation and downregulate genes associated with de novo lipogenesis. Further studies are required to determine how such systemic effects on chromatin are induced, and which proteins are required to form new chromatin loops to adapt to the carbohydrate-rich diet. The extent to which metabolism itself such as methionine metabolism, aside from hormonal regulation influences three-dimensional structure is currently unclear. Nevertheless, these early studies support a model describing that the regulation of chromatin loops can be mediated by the cooperative action of stimulus-

responsive molecules and proteins, which ensures gene activation during chronic metabolic stress. Chromatin looping often drives interactions between distal regulatory elements and target gene promoters in a cell-type-specific manner [71], it is thus interesting to investigate whether the chromatin interactions vary across different cell types under different metabolic stresses, and what metabolic consequences are associated with this variation.

Conclusions

We have discussed that various nutrients or metabolic stimuli elicit diverse changes in epigenetic modifications and chromatin structure, which enable cells to alter their gene expression programs. The selective impact of methionine metabolism on epigenetics is involved in cell proliferation and anti-tumor immunity, thus which have implications for tumor therapy. Because both tumor cells and T cells existing in the same tumor microenvironments compete for the limited nutrients, disrupting the entry of methionine to tumor cells while allowing T cell to take in more methionine may suppress the proliferation of tumor cells and restore T cell immunity [7]. The reconfiguration of histone methylation makes chromatin robust to tolerate metabolic alterations although the role of these modifications in organizing the compact chromatin structure needs to be clarified. Metabolism can also influence chromatin remodelers and histone modifications to affect DNA accessibility by altering nucleosome mobility, allowing a rapid and reversible way to control gene transcription. Finally, we highlight that chromatin loops induced by diets enable gene activation by promoting enhancer-promoter communications. Such mechanisms may allow for adaptation to long-term dietary changes as they might directly influence chromatin by metabolism through diet itself. Much remains to be discovered about how metabolites, metabolic enzymes, chromatin remodelers, and chromatin modifiers coordinately translate environmental cues into chromatin architecture.

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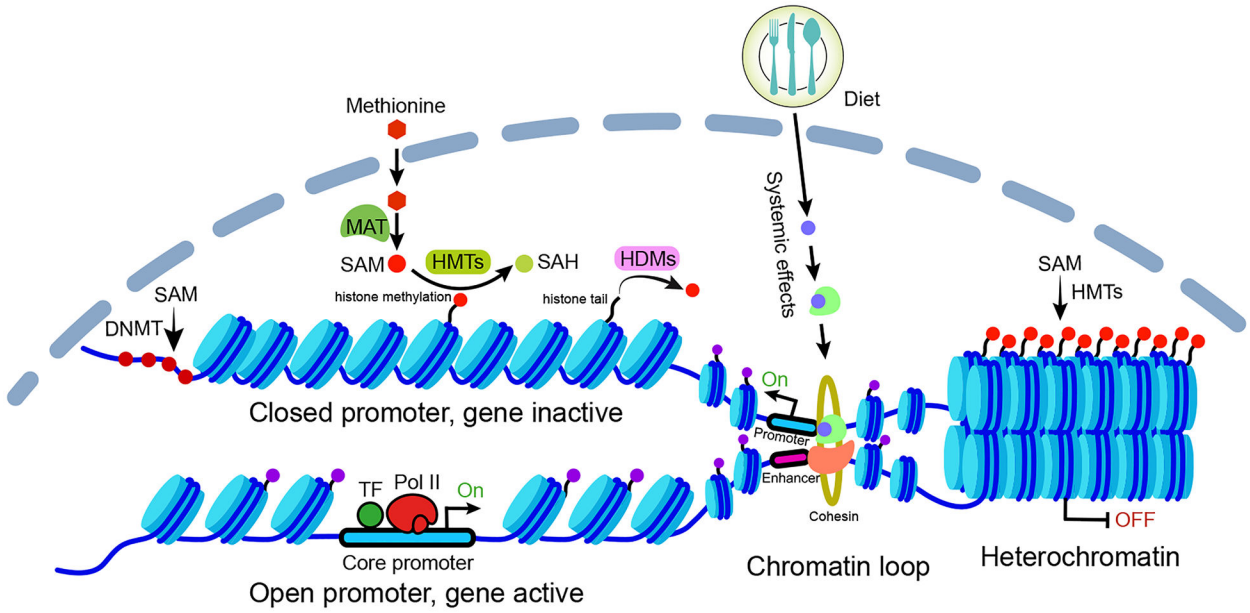

Figure 1. Overview of how metabolism influences gene activation via chromatin regulations.

The gene activation and repression are mediated by chromatin structure and modifications, which can be regulated by metabolism through several mechanisms. Metabolic intermediates (e.g. S-adenosylmethionine [SAM]), catalyzed from the primary metabolites (e.g. methionine) by various enzymes (e.g. methionine adenosyltransferase [MAT]), are transported into the nucleus and serve as the substrates for histone and DNA modifications. Enzymes, such as methyltransferases and demethylases, are responsible for the deposition and removal of these modifications. Various modifications can either activate or repress gene transcription by altering DNA accessibility, for example, forming compact heterochromatin structure, exposing DNA regulatory elements to transcription factors (TFs) as well as transcription machinery (Pol II complex) by nucleosome remodeling. Moreover, the systemic effects of diets (e.g. activation of the nuclear receptor) can mediate chromatin looping and drive gene expression by promoting the interactions between enhancers and promoters. SAH: S-adenosylhomocysteine, is a product of methylation reaction involving SAM. DNMT, DNA methyltransferases; HMT, histone methyltransferase; HDM, histone demethylase.

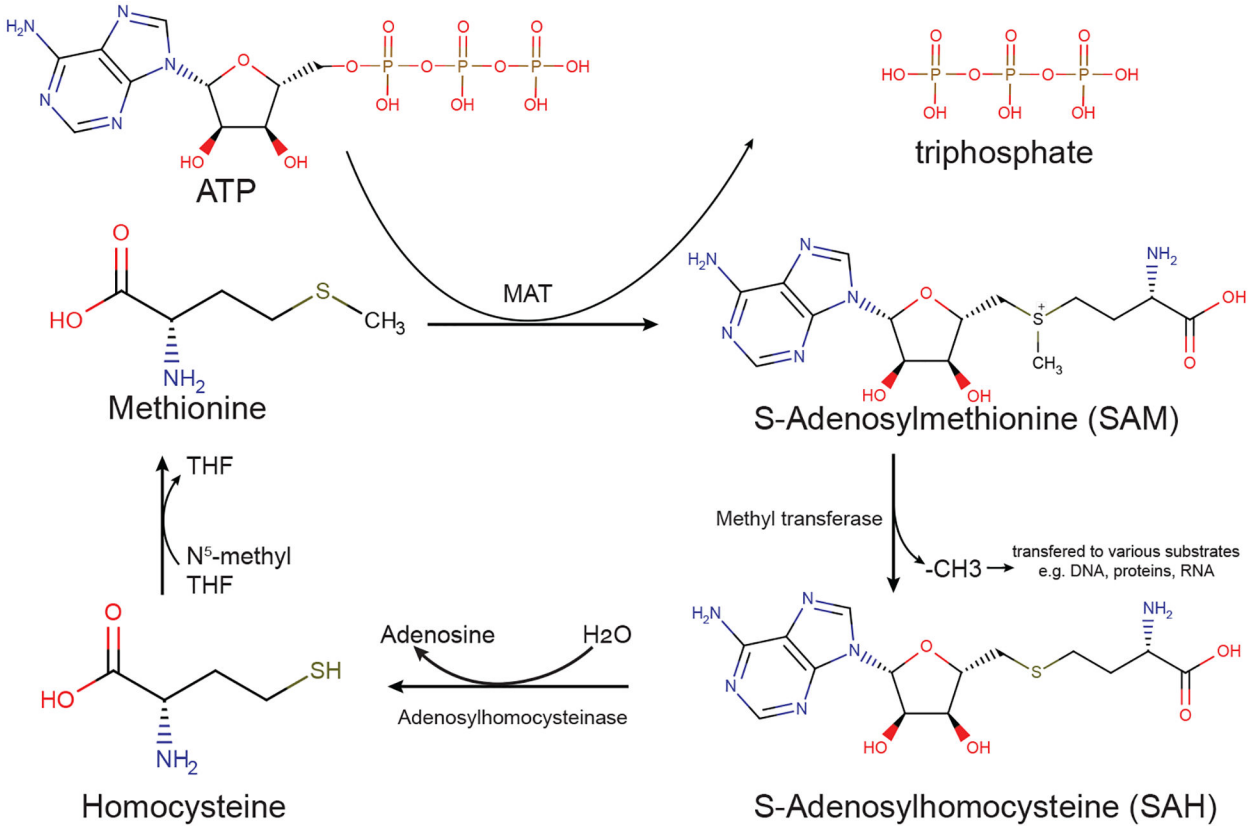

Figure 2. Methionine cycle provides methyl group for methylation.

Methionine is converted into SAM by MAT in an ATP-dependent process. Various methyltransferases use SAM as the methyl donor for DNA, RNA, proteins, etc. and produce SAH. SAH is then catalyzed by adenosylhomocysteinase, forming adenosine and homocysteine. 5-methyl-THF donates its methyl group to homocysteine to synthesize methionine and produce tetrahydrofolate (THF). Chemical structures were obtained from the Human Metabolome Database (www.hmdb.ca).

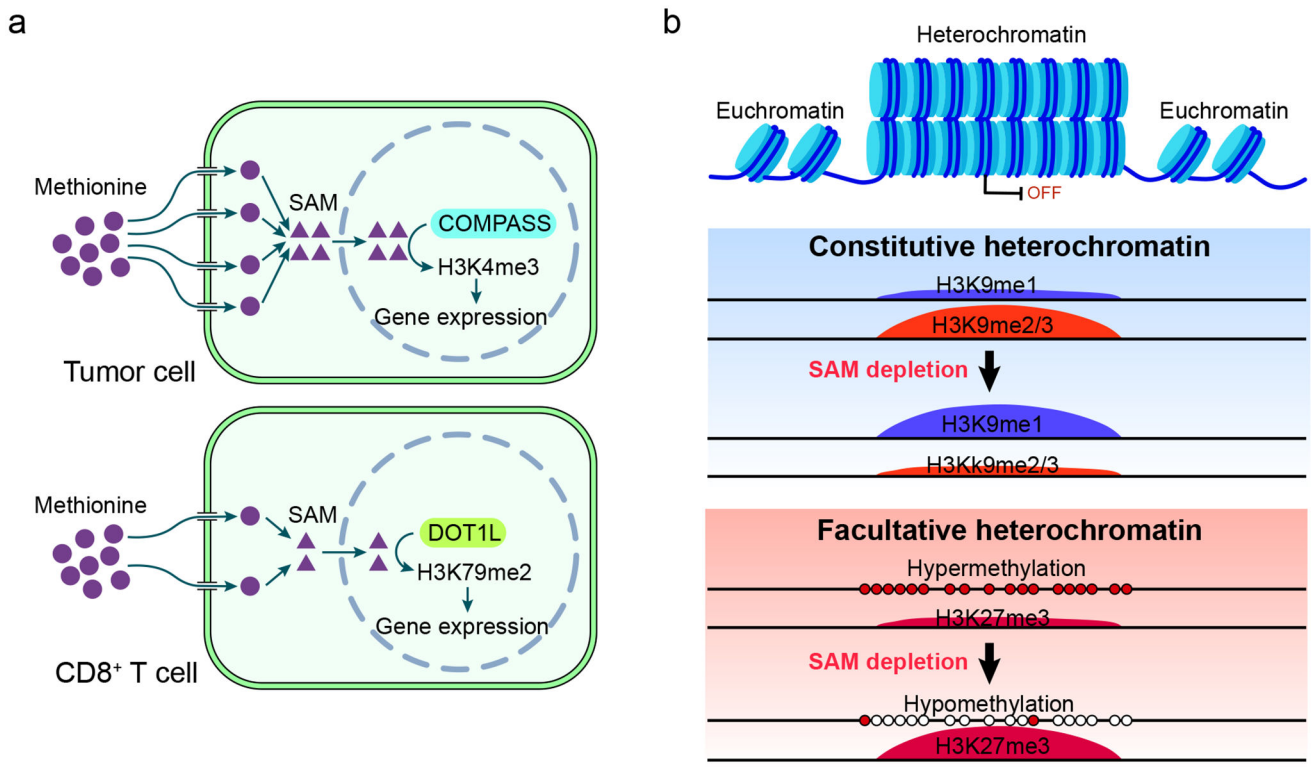

Figure 3. Representative models for methionine metabolism-mediated chromatin regulations

(a) Selective effect of methionine availability on histone methylation in tumor cell and $CD8^+$ T cell. Cells take in methionine through transporters such as SLC7A5 and SLC43A2, which are highly expressed in the tumor cells than in $CD8^+$ T cells. The lack of methionine transporters in $CD8^+$ T cells leads to lower methionine uptake and less SAM production. The methyltransferase DOTL1 is sensitive to a small amount of SAM and specifically deposit H3K79me2. Although the tumor cells consume much more methionine and produce a large amount of SAM, which is used by COMPASS (Complex of Proteins Associated with Set1) to deposit H3K4me3. Both H3K79me2 and H3K4me3 are associated with active gene expression. (b) Reconfiguration of epigenetic modifications keeps genome stable and sustains DNA repetitive elements repression during metabolic stress. Heterochromatin is a highly condensed chromatin structure and is often marked by H3K9 and H3K27 methylation. Under the S-adenosylmethionine (SAM) limitation conditions, epigenetic modifications are regulated to preserves heterochromatin stability.