# The evolving metabolic landscape of chromatin biology and epigenetics

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Abstract | Molecular inputs to chromatin via cellular metabolism are modifiers of the epigenome. These inputs — which include both nutrient availability as a result of diet and growth factor signalling — are implicated in linking the environment to the maintenance of cellular homeostasis and cell identity. Recent studies have demonstrated that these inputs are much broader than had previously been known, encompassing metabolism from a wide variety of sources, including alcohol and microbiotal metabolism. These factors modify DNA and histones and exert specific effects on cell biology, systemic physiology and pathology. In this Review, we discuss the nature of these molecular networks, highlight their role in mediating cellular responses and explore their modifiability through dietary and pharmacological interventions.

Nucleosome
The basic structural unit of chromatin. Each nucleosome consists of two copies apiece of the histones H2A, H2B, H3 and H4.

Chromatin remodellers
Protein complexes that regulate gene expression by changing the organization of nucleosomes.

Electrophilic moieties
Molecules that have the tendency to accept an electron pair by reacting with electron-rich nucleophiles.

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The cells comprising a living organism contain near-identical genomic DNA that is processed and expressed differentially, owing to the presence of a molecular scaffold known as the nucleosome. Within a single nucleosome, 147 bp of DNA wraps around an octamer of positively charged proteins called histones, present as two functional copies apiece of histone type H2A, H2B, H3 and H4 proteins. Each nucleosome is then further condensed at increasing levels into a higher-order structure called chromatin, which can form a tightly packed barrier that restricts the access of molecular factors to the genome[1]. Cells contextually circumvent or reinforce this barrier by dynamically modifying DNA and histones at specific nucleotide or amino acid residues, establishing regions of the genome that are differentially exposed to the cellular machinery. These modifications individually or synergistically influence various genome-associated processes — such as transcription or DNA replication and repair — by a variety of mechanisms, including by serving as recognition sites for proteins, such as transcription factors, histone chaperones, chromatin modifiers and chromatin remodellers, and by changing both the local and the global structure of chromatin organization[2–4].

Histones are modified on their free N-terminal tails, or their globular domains that physically interact with DNA, through chemical modifications including acetylation, methylation, phosphorylation, ubiquitylation, acylation, hydroxylation, glycation, serotonylation, glycosylation, sumoylation and ADP-ribosylation[5,6]. DNA is methylated at cytosine as well as adenine residues[7,8]. Chromatin is modified either enzymatically, which we will discuss below, or non-enzymatically. Non-enzymatic chromatin modifications, which occur via the covalent adduction of histones and DNA to electrophilic moieties derived from metabolism, are characteristic features of certain cellular abnormalities, but their functions are still poorly understood[9]. Finally, RNA can be methylated and acetylated[10,11], referred to as epitranscriptomic modifications, which regulate RNA processing, mRNA half-life and translation, among other processes. These modifications, which for simplicity we refer to as epigenetic modifications, together form the epigenome and are linked to gene regulation and thus to many physiological and pathological processes. Each modification is derived from intermediates from metabolism.

Metabolism is the result of networks of biochemical reactions that take in nutrients in order to process them to serve cellular demands, including energy generation and biosynthesis[12]. Intermediates of these reactions are used as substrates and cofactors for a variety of epigenome-modifying enzymes[13], allowing metabolism to directly communicate environmental changes to the chromatin state[14]. The aberrant regulation of these molecular networks, due to genomic mutations or environmental perturbations, is associated with changes across the life cycle, to embryonic development[15], cellular identity[16], immune cell function[17], tumorigenesis[18], tumour progression[19] and microbiome–host commensalism[20]. These networks can be manipulated, both pharmacologically and through diet and nutrition, to have varying effects on altering physiology and disease.

Elucidating the ways in which chromatin can be modified by metabolism and their functional importance remains an active and growing area of research that is helping uncover fundamental cellular mechanisms that underlie both normal and disease states. In this Review, we discuss the principles underlying the regulation of metabolism and epigenetics, as well as

the multifaceted ways in which chromatin can be modified by metabolic reactions. We describe a growing appreciation for the diverse types of metabolite-derived chromatin modifications beyond the 'canonical' methylation and acetylation marks[13,21–23], such as histone acylation, homocysteinylation, monoaminylation and many other modifications. Furthermore, we explore the functional molecular consequences of these modifications for different aspects of chromatin biology — including chromatin structure, accessibility and transcription — as well as the resultant cellular and organismal effects, driving processes such as cell fate determination, immune function and cancer. We also discuss emerging areas of metabolic influence on chromatin status and epigenetics, including diet, nutrition and microbiota.

## Principles of the metabolic link to epigenetics

Despite the challenges of completely understanding the context-dependent roles of the metabolism–epigenetics axis and the complexity of metabolic pathways and the chromatin modifications regulated by them, several universal principles underlie this crosstalk, demonstrating the evolutionary emergence of specific molecular mechanisms that facilitate epigenomic dynamics under metabolic alterations.

The ability of epigenetic modifications to respond to fluctuations in metabolic activities is a consequence of the intrinsic thermodynamic and kinetic parameters of different chromatin-modifying enzymes (BOX 1). The addition and removal of most of these modifications are catalysed by enzymes (that is, 'writers' and 'erasers') that utilize metabolites as substrates or cofactors (that is, chromatin-modifying metabolites) (FIG. 1). Chromatin-modifying enzymes that use metabolite substrates whose physiological concentrations are close to or lower than the enzymes' intrinsic $K_m$ and $K_d$ values are more susceptible to metabolic pathway alterations than those whose substrates are present in excess amounts[13]. This property thus enables metabolic fluctuations to influence the activities of certain chromatin-modifying enzymes and to modulate the levels of specific epigenetic modifications, and the differences in substrate availabilities and $K_m$ values may determine the relative sensitivities of epigenetic modifications to metabolic alterations[24,25] (BOX 1). On the other hand, chromatin modifications can also be added non-enzymatically; in this case, the detailed kinetic and thermodynamic properties are less well characterized, but they are influenced to some extent by the law of mass action.

There are several additional mechanisms that enable the efficient and precise regulation of enzyme-catalysed chromatin modifications by metabolic activity. Metabolic enzymes involved in the synthesis of chromatin-modifying metabolites, such as acetyl-CoA and *S*-adenosylmethionine (SAM), may be able to localize in the nucleus and interact with nucleosomes and chromatin-modifying enzymes in order to efficiently produce metabolites at specific genomic loci[26–32]. Levels of chromatin-modifying metabolites such as SAM are controlled by multiple mechanisms, including both environmental inputs such as nutrient availability and intracellular methyl group sinks that consume SAM[33–35]. Methyl group sinks are mediated by enzymes that metabolize SAM, allowing them to divert methyl groups away from enzymes such as histone methyltransferases, thus affecting the activity of these enzymes. These mechanisms provide avenues for the control of metabolite levels and thus for chromatin to sense intracellular metabolic status.

Epigenetic modifications influence transcriptional programmes through various mechanisms (BOX 2). All of these outcomes can potentially be influenced by metabolic regulation of the epigenome. Additionally, recent studies have shown that chromatin compartments with differing transcriptional activity can segregate into membraneless organelles through liquid–liquid phase separation in response to chromatin modifications, establishing distinct chromatin domains with distinct patterns of regulation. Transcriptionally inactive heterochromatin can form phase-separated liquid droplets by interacting with heterochromatin protein 1 (HP1), which recognizes and binds to the histone modification H3 methylation at K9 (H3K9me), allowing chromatin to stably condense inside these droplets[36–38]. On the other hand, active chromatin regions, such as those containing histone acetylation, enhancers and superenhancers, are also able to phase-separate through interacting with binding proteins such as bromodomain-containing proteins[39–41]. Similar effects that promote phase separation have also been found to be mediated by the interaction between $N^6$-methyladenosine ($m^6A$) in mRNA and the $m^6A$-binding YTHDF proteins[42]. Although it is an open question whether chromatin phase separation is regulated by metabolism, these findings suggest that the ability of chromatin to phase-separate within cells may be regulated by epigenetic modifications derived from metabolites and thus may be sensitive to cellular metabolism. Furthermore, phase separation of other biomolecules has been shown to concentrate molecules in a certain phase in order to activate biochemical signalling processes[43]. Whether chromatin phase separation also results in the localization of metabolites and the activation or inhibition of chromatin-modifying reactions in a specific phase remains unknown, but it potentially serves as an additional mechanism for the precise control of local metabolite levels and chromatin modifications.

## Metabolism-derived chromatin modifications

***DNA and histone methylation.*** One of the most well-studied chromatin modifications is the addition of a methyl ($-CH_3$) group to the ε-amino group of lysine or arginine residues on histones and CpG islands of DNA[44]. This modification is derived from the metabolism of the essential amino acid methionine (Met), which in mammals is almost exclusively obtained from the diet[45]. Met uptake is followed by its conversion into the methyl-donor metabolite SAM[46], which is then used as a substrate for DNA and histone methyltransferases (FIG. 2), producing *S*-adenosylhomocysteine (SAH), which competitively inhibits DNA and histone methyltransferases. Disruptions in Met metabolism and one-carbon metabolism, such as changes to threonine or methionine intake and the activation or inhibition of metabolic enzymes in these pathways, have been shown in a variety of cellular systems to affect

$K_m$ and $K_d$ values
Quantities that describe the affinity of the substrate ($K_m$) and an inhibitor ($K_d$) to an enzyme. Smaller values for $K_m$ and $K_d$ indicate higher binding affinity.

Methyl group sinks
Molecular pathways that regulate intracellular methyl group availability by consuming *S*-adenosylmethionine (SAM).

Liquid–liquid phase separation
Demixing of fluid into two or more distinct phases, which can help compartmentalize molecules within a cell by forming membraneless organelles.

Enhancers
Gene-regulatory elements that can be coding or non-coding sequences and that potentiate the transcription of genes proximal or distal to them.

Superenhancers
Large clusters of enhancers that are bound by multiple master transcription factors in order to activate the transcription of cell-identity-related genes.

Bromodomain
A protein domain that recognizes and binds to acetylated lysine residues.

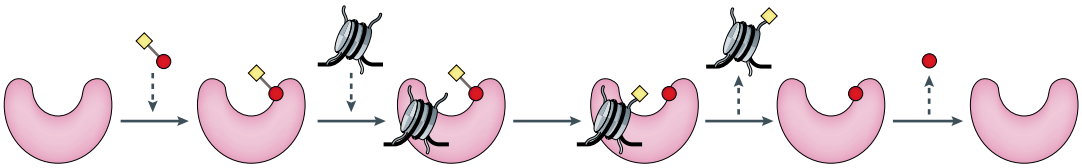
One-carbon metabolism
A metabolic network for transferring one-carbon units from nutrients to metabolites that support multiple physiological processes, including nucleotide synthesis.

Box 1 | **Kinetic and thermodynamic properties of chromatin-modifying enzymes**

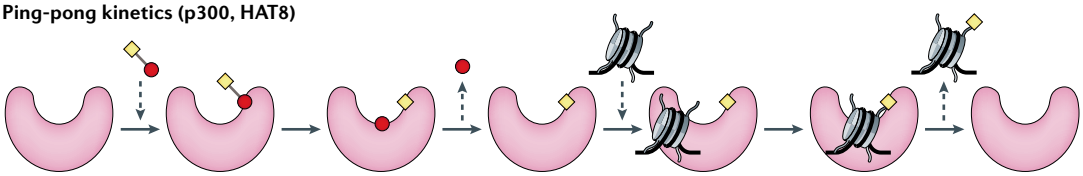
Rates of enzyme reactions depend on many factors, including intrinsic enzymatic parameters, such as turnover number, Michaelis–Menten constant ($K_m$) values, enzyme abundance, substrates, cofactors and allosteric activators or inhibitors, and other environmental factors, such as pH, temperature and local viscosity. These variables together determine the overall reaction rate through a quantitative relationship that depends on the molecular mechanism of the enzymatic reaction[236]. Studies describing the biochemistry and structural biology of chromatin-modifying enzymes have provided crucial insights into their catalytic mechanisms and regulators. The kinetic mechanisms of the enzymes involved in DNA methylation, histone acetylation and histone methylation have been extensively investigated, particularly when issues related to drug development have been concerned, showing that the exact catalytic mechanisms of different chromatin-modifying enzymes are diverse and largely context-dependent (see the figure). For example, the histone acetyltransferases (HATs) PCAF and GCN5 exhibit an ordered ternary catalytic mechanism in which acetyl-CoA binds to the enzyme before the histone peptide, which is followed by release of the acetylated histone and, finally, of the CoA molecule (CoA-SH)[237–239]. By contrast, p300 and HAT8 function through a ping-pong mechanism that starts with the binding of acetyl-CoA and ends with release of the acetylated histone[240,241]. Finally, random ternary kinetics have been observed in the yeast histone acetyltransferase Rtt109 (REF.[242]).

Given the diversity in the catalytic mechanisms of chromatin-modifying enzymes and the variability in the specific enzymatic kinetic parameters, epigenetic modifications are likely to exhibit specificity due to these different mechanisms. The thermodynamic and kinetic properties of epigenetic modifications depend on the type of modification, the corresponding chromatin-modifying enzyme, the specific genomic locus and the abundance of allosteric regulators and cofactors. This variability results in distinct dynamics of deposition and turnover in response to perturbations of metabolism. Directly targeting these epigenetic modifications has shown that the dynamics of histone acetylation are in general faster than those of DNA and histone methylation[243] and that acetylation and deacetylation occur on a timescale of minutes in vivo[244,245]. Histone and DNA methylation, on the other hand, are more stable than acetylation, which might constitute a type of epigenetic memory in response to stronger but transient perturbations[243]. An additional layer of complexity arises from the heterogeneous affinity and activity of chromatin modifiers with regard to different chromatin modifications[246] and different genomic loci[247,248]. Variation in the abundances of chromatin-modifying metabolites and in the apparent $K_m$ values in different cells and tissues might therefore lead to heterogeneity in the sensitivity of epigenetic marks to metabolic alterations in different contexts.

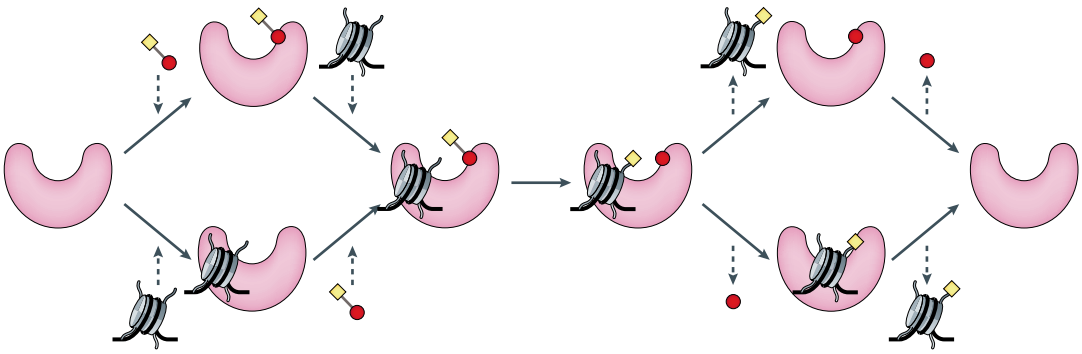
**Ordered ternary kinetics (PCAF, GCN5)**



**Ping-pong kinetics (p300, HAT8)**



**Random ternary kinetics (Rtt109)**



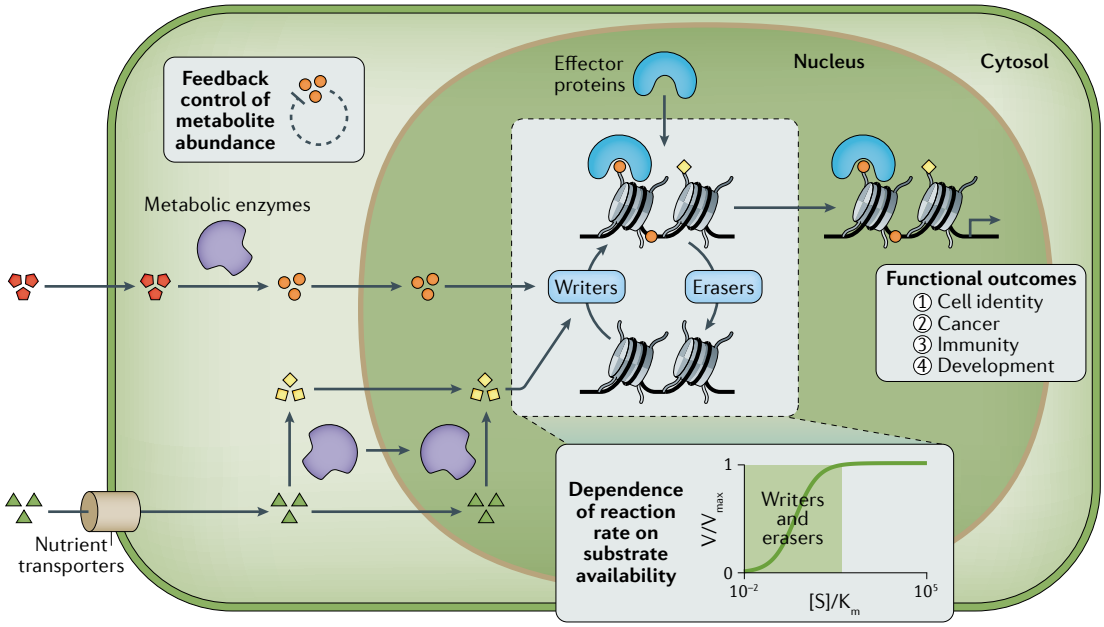



Fig. 1 | **Overview of the mechanisms involved in the metabolic regulation of epigenetics.** The abundance of chromatin-modifying metabolites is intracellularly regulated by several mechanisms. Metabolites that are taken up by cells can passively or actively diffuse through the plasma and nuclear membrane in order to modify chromatin. Alternatively, metabolites can be processed internally by the activity of metabolic enzymes that convert them into the substrates or cofactors for chromatin-remodelling enzymes. The metabolic enzymes can also translocate to the nucleus, where they can locally produce substrates for chromatin modification. The resultant consequences of metabolite abundance for the rate of chromatin modification are dependent on the kinetic and thermodynamic parameters of the particular enzyme. Enzymes with initial [S]/$K_m$ ratios on the highlighted part of the displayed curve are more susceptible to perturbations in substrate concentrations; these enzymes include methyltransferases and acetyltransferases, among others. Finally, once the modifications have been deposited, effector proteins can recognize and bind to them using specific protein-binding modules, through which the markings determine a variety of intracellular fates, involving processes such as development, immune regulation and tumorigenesis.

intracellular concentrations of SAM and SAH, thereby changing levels of both DNA methylation[47,48] and histone methylation. These metabolism-linked histone methylation alterations include H3K4me3 in mouse and human embryonic stem cells (mESCs and hESCs)[49,50], human colon cancer cells, mouse liver[51,52] and *Caenorhabditis elegans*[53]; H3K9me1/2/3 in human colon cancer cells and mouse liver[24]; H3K27me3 in mESCs[33]; H3K36me3 in immune-activated macrophages[54] and T cells[55]; and multiple trimethylation marks in yeast[34,35]. These changes correlate with changes in gene expression to varying degrees.

Metabolism can also influence the activity of enzymes responsible for the turnover of chromatin methylation. Active removal of histone and DNA methylation is catalysed by the TET family of DNA demethylases (TETs)[56] and histone demethylases, including JmjC-domain-containing demethylases (JHDMs) and amine oxidases (LSDs)[57]. TETs and JHDMs belong to the class of α-ketoglutarate (αKG)-dependent dioxygenases that use αKG and oxygen as substrates. These enzymes are inhibited by metabolism-derived structural analogues of αKG, including succinate, fumarate and the oncometabolite 2-hydroxyglutarate (2-HG), produced by gain-of-function mutations of the metabolic enzyme isocitrate dehydrogenase 1 (IDH1) or IDH2. Catalysis by TETs and JHDMs is activated by ascorbate[58] and also requires ferrous iron, Fe(II), as a cofactor, whereas LSD histone demethylases rely on flavin adenine dinucleotide (FAD) (FIG. 2). Conditions that involve alterations in the metabolic pathways producing or consuming any of these molecules — such as glutamine deficiency[59,60], iron deficiency[61] or mutation of mitochondrial enzymes including IDH1/2 (REF.[62]), succinate dehydrogenase (SDH)[63] and fumarate hydratase (FH)[64] — are thus able to shape the methylation landscape by modulating the activity of histone and DNA demethylases by affecting the activity of each of these aforementioned cofactors.

Another axis for the metabolic regulation of chromatin methylation is through the regulation of redox balance. Redox balance ensures the maintenance of healthy levels of reactive oxygen species (ROS), which is crucial for cell survival. ROS generation during early development in *C. elegans* was recently shown to modulate transcription of the genes required for long-term survival, by inhibiting the H3K4 methyltransferases MLL1–4 and reducing global levels of H3K4me3 (REF.[65]). Whether ROS generation as a result of metabolic reprogramming during this time involves the oxidation and depletion of SAM remains to be seen, but several potential mechanisms exist, including the redox-responsiveness of the vitamin-$B_{12}$-utilizing enzyme methionine synthase. Additionally, hypoxia can inhibit TETs as well as JHDMs such as KDM5A, KDM6A and KDM6B by limiting oxygen, resulting in global DNA[66] and histone[67,68] hypermethylation.

α-Ketoglutarate
(αKG). A metabolic intermediate of the tricarboxylic acid (TCA) cycle, which is derived from isocitrate and is further processed into succinyl-CoA. It can also be derived from glutamine metabolism.

Redox balance
Reaction systems that help maintain healthy levels of reactive oxygen species in intracellular compartments.

Metabolic fasting
An intentional abstinence from food and drink during a period of time.

***Histone acetylation.*** Another 'canonical' chromatin modification is the acetylation of histones, which involves the transfer of an acetyl group derived from the high-energy metabolite acetyl-CoA to the ε-amino group of a histone lysine, catalysed by acetyltransferases[44]. Acetyl-CoA in mammalian cells is derived primarily from carbon units provided by extracellular glucose, which feeds into mitochondrial metabolism in order to generate citrate. Citrate is then exported to and lysed within the cytosol by the enzyme ATP-citrate lyase (ACLY) to generate acetyl-CoA[69] (FIG. 2). The availability of glucose and glycolytic activity subsequently influences global levels of histone acetylation through the generation of acetyl-CoA[69,70]. The short-chain fatty acid (SCFA) acetate is an additional source of acetyl-CoA for histone acetylation, through the function of the enzyme acetyl-CoA synthetase 2 (ACSS2). Acetate has recently been shown to be produced de novo from pyruvate, providing another pathway from glucose to histone acetylation[71]. Both acetate and acetyl-CoA can also be generated from ethanol metabolism in the liver, which supports histone acetylation in the brain[72] and other organs, or by the oxidative catabolism of lipids, which may contribute up to 90% of the acetylation of certain histone lysines[73–75].

Like histone methylation, histone acetylation is actively turned over, in this case by a class of enzymes called histone deacetylases (HDACs), which are inhibited by metabolites, including butyrate and β-hydroxybutyrate (β-OHB), that are produced during fatty acid oxidation or ketogenesis, or are derived from the commensal microbiota[76]. Sirtuins, another class of HDACs, utilize $NAD^+$ to deacetylate histones and are sensitive to intracellular $NAD^+$ levels[77].

***Histone acylation.*** Perhaps less well understood, but encompassing a broad landscape of emerging metabolic precursors, are histone acylation modifications[78], which are similar to their acetyl counterparts in terms of their functionality and enzymatic regulation. These modifications are derived from short-chain acyl-group-containing molecules, such as SCFAs, by enzymes that produce their respective acyl-CoA molecules, called acyl-CoA synthetases[79,80] (FIG. 2). If they are added non-enzymatically, assuming the law of mass action, the relative abundance of acyl histone modifications is proportional to the concentration of corresponding acyl-CoA metabolites[81]. The acyl-CoA metabolites may also be used by histone acetyltransferases such as p300 and KAT2A to catalyse histone acylation reactions with a reduced binding affinity, compared with the canonical substrate acetyl-CoA[25,82], or they may react with histones in a non-enzymatic fashion[83], especially for certain acyl-CoA metabolites, such as succinyl-CoA and malonyl-CoA, that are particularly reactive towards protein lysine residues[84].

The concentration of acyl-CoA molecules can be dynamically modulated in diverse ways in response to perturbations in the cellular environment. A recent study showed that lactate, the end product of glycolysis, can be used for histone lactylation, an emerging modification that correlates with transcriptional activation and is a functional output of metabolic reprogramming during macrophage polarization[85]. Histone succinylation has been shown to occur at least in part because of the nuclear localization of αKG dehydrogenase, which locally generates succinyl-CoA used by the acetyltransferase KAT2A to succinylate H3K79 around transcriptional start sites[82]. Histone benzoylation has been shown to dynamically respond to levels of sodium benzoate, a chemical food preservative, through the generation of benzoyl-CoA and to correlate with gene expression[86]. Histone crotonylation is derived from crotonyl-CoA produced from the SCFA crotonate and is used by the histone acetyltransferases p300/CBP to crotonylate histones and activate transcription[20,25]. The production of ketone bodies, such as butyrate and β-OHB during metabolic fasting, can be used to butyrylate[87] and β-hydroxybutyrylate histones[88,89], which turns on genes involved in the starvation response. As β-OHB is also an inhibitor of HDACs[76], and as histone butyrylation and crotonylation have additionally been shown to compete with acetylation[87,90], the overall effect of β-OHB on gene expression and biological functions is determined by changes in both histone β-hydroxybutyrylation and acetylation, although acetylation could be more important, given the multifaceted roles of histone acetylation in regulating chromatin state, genome structure and gene expression. Further research will be needed to uncover ways in which the levels of these acyl-CoA metabolites dynamically respond to metabolic reprogramming and compete with histone acetylation to modify chromatin.

Box 2 | **Epigenetic modifications, chromatin structure and gene expression**

The earliest clues suggesting the functional consequences of particular epigenetic modifications are their locus-specific enrichment and association with gene expression levels and gene regulation. Although these findings do not conclusively imply causality, they have been used to theorize on the existence of a 'histone code', which postulates that the presence and combination of specific DNA and histone modifications link to the regulation of transcriptional programmes and gene expression events[249]. Studies over the past few decades have revealed two major ways for epigenetic modifications to regulate gene expression: by changing the local chromatin structure or by influencing the recruitment of non-histone protein effectors to chromatin[250]. Chromatin can be roughly classified into two categories based on their structural and biochemical properties: condensed, transcriptionally silenced heterochromatin, and decondensed, actively transcribed euchromatin. The formation of heterochromatin and euchromatin is dependent on the existence of epigenetic modifications. Histone acetylation, typically enriched in euchromatin, is able to neutralize the positive charge of the modified lysine residue, thus disrupting the interaction between histone and DNA and resulting in an open chromatin structure that facilitates active transcription. Heterochromatin is typically enriched in trimethylation of histone 3 lysine 9 (H3K9me3), which is bound by heterochromatin protein 1 (HP1), which promotes the compaction and spreading of heterochromatin[251] and triggers liquid–liquid phase separation by forming oligomers[38].

The chromatin-binding affinities of a plethora of proteins — including transcription factors, chromatin remodellers and components of the transcription machinery — can be modulated by these modifications. This is best demonstrated by the presence of chromatin-binding 'reader' modules in these proteins, such as the chromodomains and PHD fingers, which recognize and bind to methylated histones, and the bromodomains and YEATS domains, which bind to acetylated histones[252,253]. It has been hypothesized that the association between H3K4me3 and active transcription is largely mediated by the binding of H3K4me3 by the PHD finger of the TAF3 subunit of TFIID, a component of the RNA polymerase pre-initiation complex[254]. DNA methylation has recently been shown to reduce the binding affinity of most transcription factors while promoting the binding of PHD-containing proteins through hydrophobic interactions with the methylated cytosine[255]. Readers of some of the emerging noncanonical histone modifications, such as succinylation[116] and crotonylation[256,257], have also been identified recently[258].

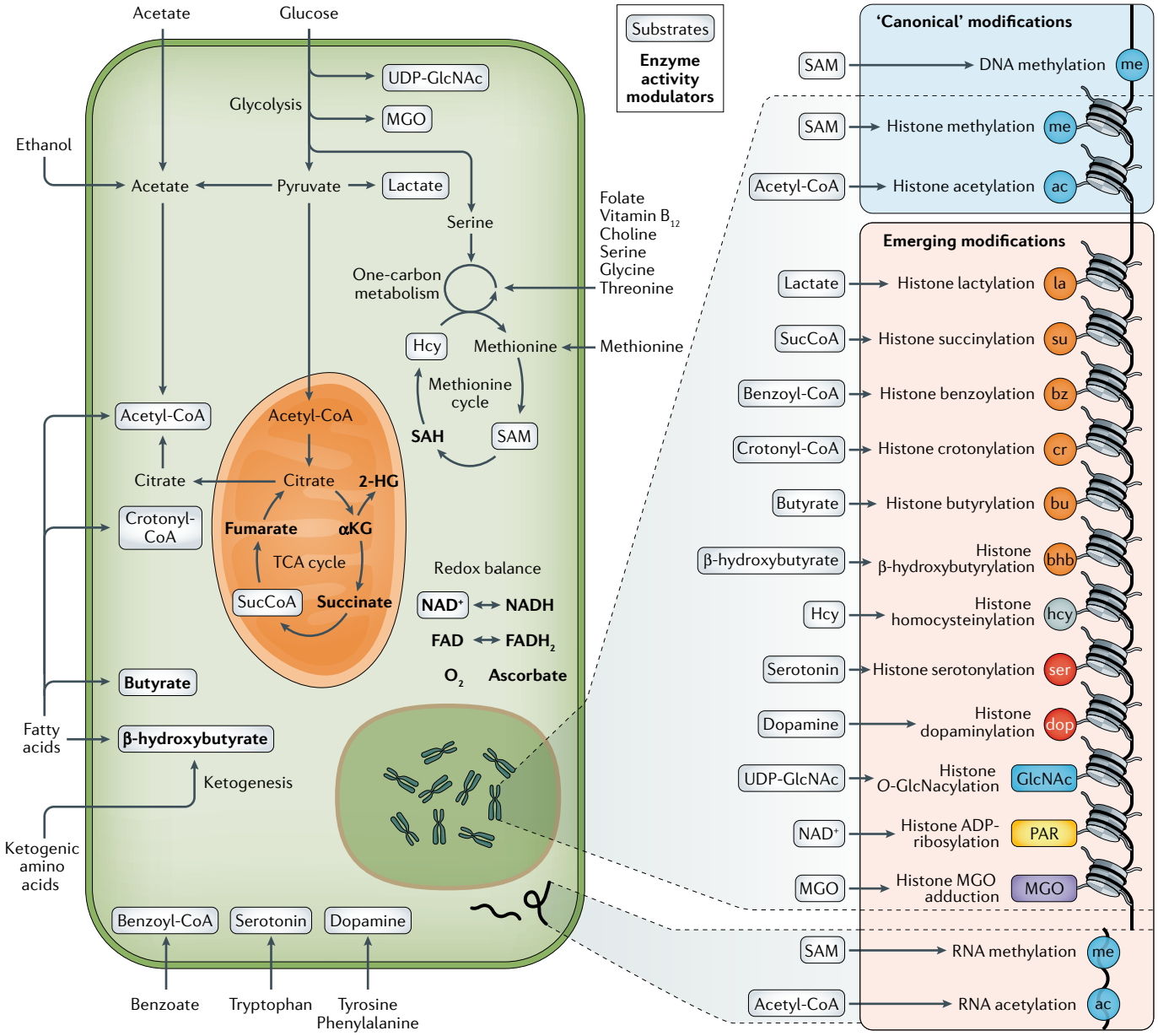



Fig. 2 | **Metabolic pathways producing chromatin-modifying metabolites.** Nutrients such as glucose, fatty acids, amino acids and vitamins are utilized by cellular metabolic pathways to produce metabolites that are used as substrates or activity modulators of chromatin-modifying enzymes. These molecules are included in regulation of the abundance of a plethora of both 'canonical' modifications, including histone acetylation, histone methylation and DNA methylation, and 'emerging' modifications, including acylation, homocysteinylation, serotonylation and so forth. Pathways related to central-carbon, one-carbon and methionine metabolism, acetate metabolism, ketogenesis, and redox balance feed the pools of several of these metabolites and thus help regulate the epigenomic landscape, in concert with chromatin modifiers, remodellers and transcription factors. 2-HG, 2-hydroxyglutarate; αKG, α-ketoglutarate; GlcNAc, β-*N*-acetylglucosamine; FAD, flavin adenine dinucleotide; Hcy, homocysteine (hcy as a histone modification); MGO, methylglyoxal; PAR, poly(ADP-ribose); SAH, S-adenosylhomocysteine; SAM, S-adenosylmethionine; SucCoA, succinyl-CoA; TCA, tricarboxylic acid.

***Histone homocysteinylation.*** Histone homocysteinylation is an emerging modification that has been observed in response to increased cellular homocysteine (Hcy) levels in human fetal brains during pregnancy (FIG. 2). A study revealed 39 sites of histone lysine homocysteinylation in the four major histone variants, among which H3K79-Hcy negatively correlated with the expression of genes associated with neural tube closure, thus potentially contributing to the acquisition of neural tube defects[91]. Although it remains to be seen whether perturbations to methionine and one-carbon metabolism contribute to changes in histone homocysteinylation, this finding, together with the long-known association between maternal folate deficiency and neural tube defects in infants, suggests that the effects of folate deficiency on neural development may have some connection to dysregulated histone homocysteinylation.

***Histone monoaminylation.*** Another newly emerging histone modification is histone monoaminylation, which was recently shown to have roles in regulating neural functions and behaviours. Histones can be modified at

glutamine residues by reacting with monoamine neural transmitters, including serotonin and dopamine, which can sequentially influence chromatin biology, gene expression, neural function and behaviours.

The uptake of the essential amino acid tryptophan is limiting for the generation of the neurotransmitter serotonin[92,93] (FIG. 2). Serotonin is involved in the maintenance of neuronal circuits. In tissues that produce the bulk of serotonin in humans, serotonin has been found to serotonylate H3K4me3-modified histones at glutamine residues, forming H3K4me3Q5ser. This modification is catalysed by the enzyme transglutaminase 2 (TGM2) and is associated with transcriptional initiation and euchromatin, contributing to neuronal differentiation and signalling[94].

Dopamine is a neurotransmitter with functions in the reward circuit of the brain. In neurons, dopamine is synthesized from tyrosine and phenylalanine[95], and its release in the human brain is reduced by dietary depletion of these two amino acids[96]. In a brain region rich in dopaminergic neurons, dopamine has been associated with an emerging epigenetic modification, histone 3 glutamine 5 dopaminylation (H3Q5dop). H3Q5dop was decreased upon cocaine exposure but increased after drug withdrawal, and reduction in its level reversed changes in gene expression and drug-seeking behaviours upon drug withdrawal, indicating a causal relationship between H3Q5dop and addictive behaviours[97].

***Histone O-GlcNacylation.*** Like cytosolic proteins, histones can be reversibly modified with β-*N*-acetylglucosamine (GlcNAc) at the hydroxyl group of serine or threonine residues, using UDP-GlcNAc as a substrate. UDP-GlcNAc is a by-product of the hexosamine biosynthetic pathway[98], which requires metabolic precursors generated during central-carbon metabolism, nitrogen metabolism and fatty acid metabolism[99] (FIG. 2). *O*-GlcNAcylation is catalysed by the canonical *O*-linked GlcNAc transferase (OGT) and turned over by *O*-linked GlcNAc hydrolase (OGA)[100]. In mammalian cells, OGT appears to associate with TET proteins TET2 and TET3, which facilitate the transfer of the GlcNAc moiety to histones and help localize the modification towards transcriptional start sites. The modification helps regulate gene expression[101] and might influence chromatin structure during DNA replication[100].

***Histone ADP-ribosylation.*** Histones can be reversibly mono- or poly-ADP-ribosylated (PARylated), which involves the oligomeric addition of an ADP-ribose (PAR) moiety derived from $NAD^+$ with the help of the poly(ADP-ribose) polymerase (PARP) family of enzymes[102] (FIG. 2). PAR modifications have been found to occur on histone lysines, where they can influence the placement of other modifications, and to bind a variety of molecular effectors that regulate gene expression, chromatin structure and DNA replication and repair[103]. PARP enzymes can be activated in response to various physiological perturbations, including a high-fat diet, oxidative stress, ageing and DNA damage[104].

***Non-enzymatic chromatin modifications.*** In certain circumstances, chromatin modifications are added without the participation of enzymes. These non-enzymatic chromatin modifications involve both canonical chromatin marks, such as acetylation and methylation, and modifications generated through adduction with electrophilic compounds[105]. Although histone acetylation and acylation occur through both enzyme-catalysed and non-enzymatic mechanisms[83], histone acylation has relatively lower rate constants[106]. The reactivity towards non-enzymatic acetylation varies greatly across lysine residues and is largely determined by their biophysical properties, such as surface exposure and local electrostatic interactions[107]. Non-enzymatic methylation of histones and DNA by SAM has also been reported[108,109].

A poorly understood class of chromatin modifications are those enabled by electrophilic metabolites generated during glycolysis, lipid peroxidation[110] or exposure to environmental toxicants[9,111,112], which form covalent adducts with nucleophilic functional groups on both histones and DNA. One example is methylglyoxal (MGO), a by-product of glycolysis, amino acid metabolism and lipid metabolism[113] (FIG. 2). The formation of MGO adducts, termed advanced glycation end products (AGEs), is closely related to ageing and to chronic diseases including diabetes and cancer. MGO glycation of histones is upregulated upon enhanced glycolytic flux[114] and is able to destabilize the nucleosome structure and disrupt the landscape of chromatin modifications by competing with acetylation and methylation for the same residues[115].

The functions of non-enzymatic chromatin modifications are still poorly understood. Paradoxically, several enzymes have been discovered that actively catalyse their removal from chromatin, offering clues as to their potential functions. Non-enzymatically added histone acetyl and acyl groups are removed by sirtuins, which can lead to disease states when their activities are disrupted[83], and are recognized by their specific readers, such as the YEATS domain[116], suggesting that the maintenance of their genomic distribution can be enzymatically regulated and can be important in transcriptional control. Conversely, several intracellular detoxification systems, including the activity of the enzymes DJ-1 and GLO-I/II[115,117,118] and non-enzymatic buffering by the ketone body acetoacetate[119], are required in order to detoxify MGO and suppress the formation of MGO adducts. These findings suggest that non-enzymatic histone adducts represent cellular stress events that may require appropriate buffering in order to ensure proper cellular function.

***RNA methylation and acetylation.*** As with DNA and histones, RNA undergoes a variety of covalent modifications[120], among which methylation and acetylation of mRNA are the best understood. Both modifications regulate mRNA degradation, splicing and translation through 'readers' that recognize and bind to the modified RNA molecules, as well as regulating other functions[10,121,122]. The landscape of these chemical groups on mRNA molecules is sometimes termed the 'epitranscriptome', which can also be edited by enzymes that rely

Hexosamine biosynthetic pathway
A branch of glycolysis that utilizes substrates from amino acid, fatty acid and nucleotide metabolism to generate substrates that participate in *N*-linked and *O*-linked protein glycosylation.

Central-carbon metabolism
Metabolic pathways involved in the catabolism of carbohydrates, lipids and amino acids for the production of ATP and biomass precursors, as well as for signalling and redox status maintenance.

Rate constants
Quantities that relate the speed of a chemical reaction to the concentrations of its substrates.

Lipid peroxidation
A process by which lipids are endogenously rendered electrophilic by a degradative chemical reaction with free radicals.

Nucleophilic functional groups
Chemical groups that have the tendency of donating an electron pair in reactions with electron-poor groups.

Advanced glycation end products
(AGEs). Covalent adducts formed through the chemical crosslinking of glycolytic by-products to macromolecules such as DNA and protein.

on metabolite substrates or cofactors. The formation of $m^6A$, the most abundant form of mRNA methylation, is catalysed by the METTL3–METTL14 complex and by METTL16, which are SAM-dependent RNA methyltransferases. SAM depletion has been shown to reduce METTL16-dependent $m^6A$ of the *MAT2A* mRNA, thus promoting its stability and enhancing MAT2A expression. As *MAT2A* encodes SAM synthetase, this mechanism appears to function as a negative feedback loop to increase SAM levels under SAM-deficient conditions[123,124].

Removal of $m^6A$ is catalysed by the RNA demethylases FTO and ALKBH5, both of which are αKG-dependent dioxygenases that are inhibited by succinate, fumarate, citrate and 2-HG[125,126]. Interestingly, the oncometabolite 2-HG and expression of mutant IDH1 were shown to exhibit tumour-suppressive activity by inhibiting FTO in leukaemia cells, resulting in enhanced global $m^6A$ and decreased stability of transcripts of the *MYC* oncogene and of the gene *CEBPA*, which positively regulates FTO expression[127]. The inhibition of FTO by 2-HG also increases the methylation of small nuclear RNAs (snRNAs) and regulates mRNA splicing[128]. Perhaps in contrast to what we currently know about many of the noncanonical histone modifications, at this stage, an abundance of evidence illustrates the importance of RNA methylation for gene regulation.

Acetylation of mRNA is catalysed by the acetyltransferase NAT10, whose activity depends on acetyl-CoA abundance and ATP[129], generating $N^4$-acetylcytidine ($ac^4C$) that enhances translation efficiency[10]. Whether RNA deacetylation is enzyme-regulated and the molecular mechanism by which it occurs are currently unknown. Its role in gene regulation, although interesting to speculate about, remains lesser known than the role of $m^6A$.

## Metabolism–epigenetics in cell fate specification

The metabolic reprogramming of chromatin modifications is associated with several functional outcomes that include cell fate specification and, by extension, processes such as development, ageing, immunology and the aetiology of diseases such as cancer (FIG. 3). It is essential to understand whether or in what contexts metabolism per se drives cell fate transitions, or whether metabolic changes during cellular transitions occur independently of the driving events. Accumulating evidence has begun to demonstrate that metabolically driven chromatin dynamics directly affect the expression of genes related to cellular functions, and that their functional outcomes can be at least partially reversed by interfering with the metabolic changes or metabolically driven epigenomic changes, indicating that, in many circumstances, metabolism drives cell fate transitions through regulation of the epigenome.

***Differentiation.*** The regulation of pluripotency and lineage specification involves the participation of a variety of metabolic pathways in a context-dependent manner; the pathways have been reported to fulfil bioenergetic demands during these transitions and to aid in cellular signalling pathways[130]. Metabolic pathway activity and nutrient availability have been associated with cell-fate-related outcomes, such as induced pluripotency[131,132], maintenance of stemness[133–136] and differentiation towards specific lineages[137–140]. Notably, these changes in fluxes through metabolic pathways can also modify the epigenome in response to differentiation cues or nutrient availability.

Disruption to one-carbon metabolism has been shown to regulate embryonic stem cell (ESC) differentiation through changes in SAM levels, both in culture[49,50] and in mice[15], along with changes to histone methylation and DNA methylation. Maintenance of the intracellular αKG/succinate ratio in mouse ESCs[141], epiblast stem cells and primed human pluripotent stem cells[142] can regulate differentiation by modulating DNA methylation and histone methylation through their dependence on TET and JHDM proteins, respectively. Modulating acetyl-CoA levels can affect the differentiation of ESCs and muscle stem cells, with concurrently occurring changes in histone acetylation[16,143] and chromatin accessibility[16]. Emerging metabolically regulated modifications, including histone serotonylation (H3K4me3Q5ser) and histone homocysteinylation, recently have also been shown to play some role in cell fate specification. As we mentioned above, histone serotonylation at a particular site (H3K4me3Q5ser) can potentiate the differentiation of serotonergic neurons in cell culture and during mouse development[94]. As we also mentioned above, histone homocysteinylation has been shown to associate with increased Hcy levels in human fetal brains and with the decreased expression of genes important for neural tube closure during development[91].

***Immunology.*** The immune system is composed of a diverse milieu of specialized cells that are activated or repressed in response to environmental inputs such as the presence of a pathogen and that undergo dynamic changes in gene expression that regulate their function[144]. Metabolic reprogramming has been reported to drive the proliferation and differentiation of a myriad of immune cell populations, which also show concurrently occurring changes in chromatin state. Antigen receptor engagement in T cells, for example, has been shown to increase metabolic flux through the methionine cycle, which upregulates DNA and histone methylation[54]. Methionine uptake has also been shown to maintain SAM synthesis and H3K4me3 levels in $CD4^+$ T helper ($T_H$) cells in culture, which regulates T cell-mediated immune responses in vivo in a mouse model of multiple sclerosis[55]. The upregulation of SAM synthesis and levels of H3K36me3 are observed during lipopolysaccharide (LPS)-induced macrophage activation, which corresponds to increased IL-1β expression and production[17]. The metabolic regulation of TETs and JHDMs also regulates several aspects of immune cell biology. αKG production via glutaminolysis and other metabolic pathways, for example, is important for the activation of M2 macrophages and for endotoxin clearance and involves the demethylation of repressive histone modifications at activating loci[145]. Conversely, glutamine availability in microenvironments of tumour-bearing mice has been shown to suppress T cell activation and to promote tumorigenesis. Using a glutamine

Humoral immune response
A branch of the immune system that involves the activation and differentiation of B cells into plasma and memory cells, which mount antibody responses to invading pathogens.

antagonist in these mice promoted T cell activation by inducing a variety of changes, including the reduction of αKG levels and hypermethylation of activating histone modifications[60]. Iron availability in humans has recently been shown to correlate strongly with antibody production in response to vaccination. When these findings were further explored in cell culture and in mice, iron(II) deficiency was found to induce defects in the humoral immune response due to impaired activities of iron-dependent JHDMs and H3K9 hypermethylation at the promoter region of cyclin E, an important element for B cell proliferation[61].

The metabolic regulation of histone acetylation and acylation has also been reported during immune

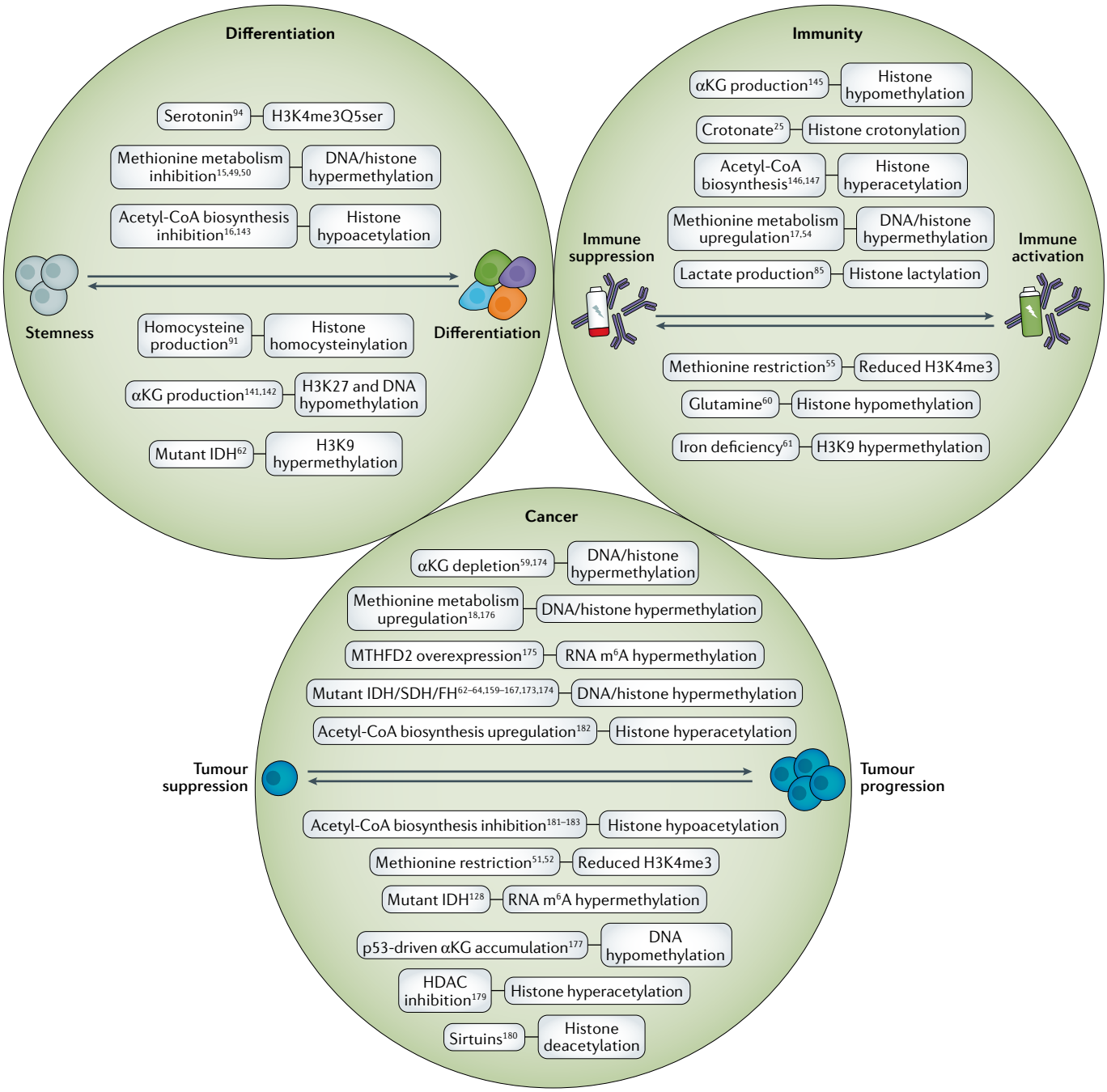



Fig. 3 | **Physiological contexts of the metabolism–epigenetics axis.** The intersection between metabolism and epigenetics is implicated in a variety of physiological contexts, including lineage specification at the embryonic level, immune regulation and the oncogenic transformation of cells. The maintenance of stemness and pluripotency and the process of differentiation are characterized by changes to metabolism and subsequent dynamic changes to epigenetic modifications. This reprogramming is also implicated in the activation or retroactive suppression of a variety of immune cell types, including T cells, B cells and macrophages, and in the ability to mount an immune response to invading pathogens. Finally, the oncogenic transformation of cells can be driven by mutations in metabolic enzymes or by genomic drivers that reprogramme metabolism. These molecular networks offer therapeutic targets in the fields of developmental biology, immunotherapy and oncology. αKG, α-ketoglutarate; FH, fumarate hydratase; HDAC, histone deacetylase; IDH, isocitrate dehydrogenase; m$^6$A, $N^6$-methyladenosine; SDH, succinate dehydrogenase.

Branched-chain amino acids
The amino acids leucine, isoleucine and valine, which each contain a branching aliphatic side chain.

MTHFD2
The enzyme methylenetetrahydrofolate dehydrogenase 2, which couples the folate cycle to the methionine cycle, enabling the transfer of the one-carbon methyl group to homocysteine in order to recycle methionine.

Warburg effect
The phenomenon, first observed by German physiologist Otto Heinrich Warburg, that cancer cells hyperactivate glycolysis, even in the presence of sufficient oxygen.

cell activation. The induction of glycolysis due to the upregulation of lactate dehydrogenase (LDHA) generates acetyl-CoA and histone acetylation in T cells, which regulates production of the cytokine IFNγ[146]. Competition for nutrients such as glucose in tumour microenvironments can also restrict T cell activation, which can be rescued by acetate supplementation. Acetate supplementation rescues histone acetylation, chromatin accessibility and, subsequently, cytokine and IFNγ production[147]. Lactate, the end product of glucose metabolism, can be utilized for histone lactylation and the activation of homeostatic genes during M1 macrophage polarization in response to bacterial infection[85]. Transcriptional responses in LPS-induced macrophage activation are regulated by the SCFA crotonate and its derivative crotonyl-CoA, which crotonylates histones at promoters of the activated genes and stimulates the production of chemokines and cytokines[25]. Each of these metabolic processes is likely to have some epigenetic/chromatin component of its function.

***Cancer biology.*** Metabolic reprogramming can underlie or support the transformation of non-malignant cells into tumour cells. This is driven either by upstream factors, such as aberrations in oncogenes and tumour suppressors, or through direct mutations to metabolic genes; metabolic reprogramming has been hypothesized to support various cellular functions, including the anabolic demands of uncontrolled proliferation[148–151]. Metabolically driven epigenomic conditioning is emerging as a key component of this reprogramming during tumorigenesis.

Oncogenic mutations exist in genes that encode all classes of the epigenetic machinery, including histones[152], chromatin modifiers[153,154], epigenetic 'readers'[155] and chromatin remodellers[156], indicating a selective pressure favouring epigenomic reprogramming for tumour progression[14,157–160]. Similarly, metabolic genes involved in producing chromatin-modifying metabolites are also frequently mutated in cancers, suggesting that the metabolically regulated epigenomic landscape has critical roles in cancer biology[161,162]. The most well-known example is the mutation of IDH1 or IDH2. According to an analysis of tumour exomes from The Cancer Genome Atlas (TCGA) project, mutant IDH1 serves as an oncogenic driver in at least seven cancer types, including some not typically known to harbour IDH mutations, such as breast cancer[162]. As we discussed previously, mutant IDH1 or IDH2 can lead to DNA and histone hypermethylation through the accumulation of 2-HG, resulting in the downregulation of genes associated with tumour suppression[62,163–167]. These findings have led to the development of inhibitors targeting mutant IDH that have been approved for use in acute myeloid leukaemia (AML) and are being studied in other malignancies[168]. However, in leukaemia cells, mutant IDH and the accumulation of 2-HG have also been shown, interestingly, to suppress cancer cell proliferation by inhibiting the RNA demethylase FTO and destabilizing oncogenic *MYC* transcripts by increasing m$^6$A, suggesting dual roles for 2-HG in cancer biology[127].

Also frequently mutated in cancer are genes encoding the metabolic enzymes FH and SDH[169,170], whose deficiency leads to the accumulation of fumarate and succinate, respectively; both of these metabolites inhibit TETs and JHDMs[171,172], resulting in genome-wide DNA and histone hypermethylation. This has been shown to enable oncogenic promoter–enhancer interactions[63] and to induce epithelial-to-mesenchymal transition (EMT)[64]. A recent study has further shown that histone hypermethylation caused by 2-HG, succinate and fumarate disrupts DNA repair, rendering cancer cells harbouring IDH, FH and SDH mutations vulnerable to PARP inhibition[173]. Similar to IDH, FH and SDH mutations, catabolism of branched-chain amino acids (BCAAs) has recently been shown to induce oncogenic DNA hypermethylation in leukaemia cells by consuming αKG[174]. In renal cell carcinomas, the metabolic enzyme MTHFD2 is overexpressed, contributing to increased global levels of m$^6$A mRNA methylation by promoting the recycling of methionine through the folate cycle. This was shown in these cancers to increase both *HIF2A* mRNA translation and HIF2α-driven tumorigenesis[175].

In addition to mutations in metabolic enzymes, cancer cells often exhibit altered metabolism in response to upstream drivers that can also reprogramme the epigenome. Inactivation of the tumour suppressor LKB1 in a mouse model of KRAS-mutant pancreatic cancer resulted in the upregulation of one-carbon and methionine metabolism and in DNA hypermethylation through the accumulation of SAM[176], whereas expression of the p53 tumour suppressor increased levels of αKG and 5hmC, an intermediate of active DNA demethylation, resulting in premalignant differentiation and tumour suppression[177].

Nearly all aspects of cancer cell metabolism, including the Warburg effect, hypoxia[66,67] and dysregulated amino acid metabolism, result in epigenomic reprogramming to some extent, accompanied by changes in gene expression. Tumour-initiating cells isolated from primary lung tumours have increased methionine cycle activity and histone methylation compared with their non-tumorigenic counterparts, rendering them sensitive to MAT2A inhibition[18]. Methionine uptake by cancer cells regulates global levels of H3K4me3 and the expression of cancer-associated genes, which can be modulated by restricting methionine in culture media[51,52]. This effect of methionine restriction on cancer-related gene expression could be associated with reduced tumour growth in mice[178]. Glutamine deficiency in the core region of melanoma tumours has been shown to result in histone hypermethylation compared with such deficiency in the periphery, due to a decrease in αKG. Reducing glutamine levels was subsequently shown to impair cancer cell differentiation and to lead to therapeutic resistance in these tumours[59]. In addition to histone methylation, histone acetylation can be modulated in cancers by regulating HDACs[179], sirtuins[180] and acetyl-CoA, which has been shown, by titrating glucose or acetate in culture media, to influence the expression of genes associated with cancer growth and metastasis[181–183].

## Diet and microbiota in metabolism–epigenetics

Lifestyle-related factors, such as exercise and nutrition, are important variables that influence health outcomes in humans. Although nutritional epidemiology is

controversial in general, it is widely accepted that diet and nutrition have profound effects on physiology and disease outcomes and that currently there is an urgent need to improve public health through encouraging adherence to healthy, if not as yet precisely defined, eating patterns[184–186]. Human foods and diets are extremely complex mixtures of countless chemical components that exist in varying abundances, but only a small fraction of these have been investigated extensively[187]. Many of these are macro- and micronutrients that feed into metabolism and chromatin biology.

Nutrients also interact with a highly complex and dynamic community of colonizing microorganisms — that is, the microbiota — that further metabolize them and produce a variety of chromatin-modifying compounds. Although the effects of diet and microbiota on metabolism and epigenetics are understood less well than those of cell-autonomous factors such as metabolic enzyme activities, emerging research has started to demonstrate that metabolites derived from diet and microbiota have dynamic interplay with epigenetics and can play an important role in mediating the health-related effects of nutrition and other lifestyle variables (FIG. 4), affecting all biological outcomes that we discussed earlier: differentiation[188–191], immunity[192,193] and cancer[51,52,178,179].

***Dietary profiles and associated epigenetic reprogramming.*** As we discussed earlier, dietary methionine restriction (MR) is able to reduce global histone methylation and influence gene expression by changing intracellular SAM levels[51,52,178].The overall effect of methionine availability on global DNA methylation, however, has been shown to depend on the experimental protocol[194] and tissue type[47], as both global and site-specific hypo- and hypermethylation have

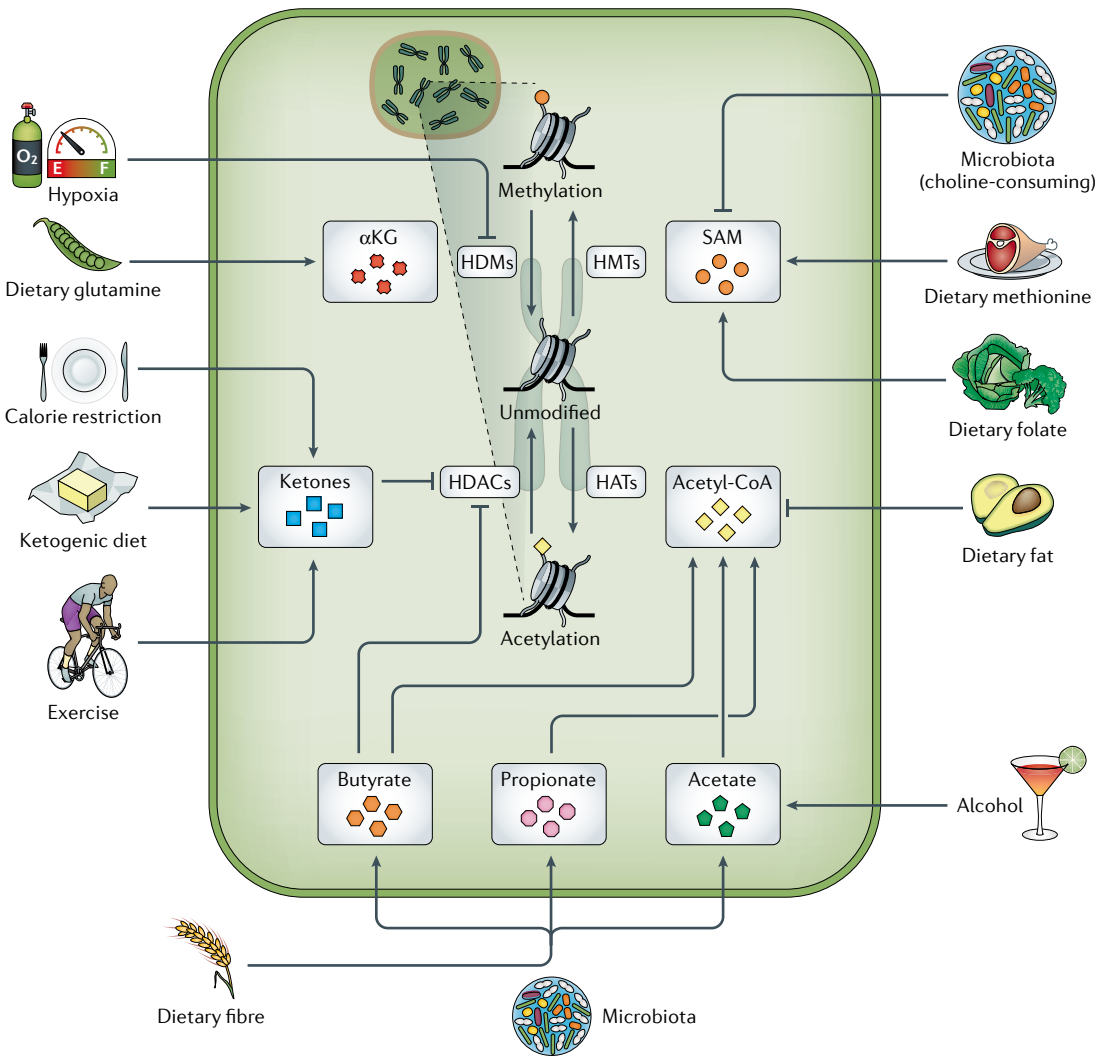



Fig. 4 | **Influences of environmental factors on histone acetylation and methylation.** Environmental factors, including nutrition, exercise and the gut microbiome, regulate histone methylation and acetylation by modulating the intracellular pools of metabolites, including *S*-adenosylmethionine (SAM) and acetyl-CoA, that are used by histone methyltransferases (HMTs) and histone acetyltransferases (HATs), respectively. The activity of histone demethylases (HDMs) is supported by α-ketoglutarate (αKG), which can be derived from dietary glutamine, and is inhibited by the limited oxygen availability during hypoxia. Ketone bodies and short-chain fatty acids (SCFAs) such as acetate, propionate and butyrate can provide acyl-CoA precursors for histone acylation, while also directly inhibiting the activity of histone deacetylases (HDACs).

been observed under MR. Nevertheless, these results together demonstrate that dietary methionine functions as an important regulator of the landscape of DNA and histone methylation through modulating methionine metabolism. As methionine levels differ greatly across human foods and diets (for example, plant-based diets are generally lower in methionine)[46], it is possible that each human diet is associated with a unique methylation signature, which contributes to the differential health outcomes associated with various diets. In addition to methionine, other nutrients that feed into one-carbon and methionine metabolism, including folate, vitamin $B_{12}$ and choline, are also able to modulate the levels of SAM and its downstream metabolite SAH (which competes with SAM to inhibit the activities of DNA and histone methyltransferases) in order to induce epigenomic reprogramming[195]. In micropigs, dietary folate deficiency was shown to synergize with ethanol intake to decrease the SAM/SAH ratio in the liver, resulting in global DNA hypomethylation and increased DNA damage[196].

Calorie restriction (CR), which reduces total daily calorie intake by around 15–40% without causing malnutrition, is the most broadly recognized dietary intervention regimen with potential health benefits[197]. Prolonged CR has been previously shown to extend lifespan and generate positive health outcomes in model organisms such as yeast, fruit flies, mice and monkeys, through a variety of metabolic and physiological effects. In mice, the anti-ageing effects of CR have been associated with protection from the age-related reprogramming of DNA methylation — referred to as the 'epigenetic clock'[198,199] — implying that epigenetic mechanisms could mediate the beneficial health outcomes of CR. It is unclear, however, what the precise mechanisms are that regulate these phenotypes and whether metabolic regulation of the methylation landscape is involved. Generation of the ketone body β-OHB is another consequence of CR that mediates these phenotypes. β-OHB and other ketone bodies are produced through the breakdown of fatty acids and ketogenic amino acids, in a process named ketogenesis, which is a metabolic adaptation to fasting[200–202]. β-OHB has multifaceted roles in regulating chromatin modifications: it can inhibit class I HDACs, causing a global upregulation of histone acetylation[76], and can serve as a substrate for histone β-hydroxybutyrylation, a mark enriched at active promoters and associated with the upregulation of starvation-responsive metabolic pathways[88]. Ketogenesis and histone acetylation have also been observed from exercise[203,204], fasting[197,205] and the intake of a ketogenic diet[206–208]. The ketone body acetoacetate, which detoxifies MGO and potentially suppresses MGO adduction of histones, has also been shown to increase in response to a ketogenic diet[119], implying an additional mechanism through which the ketogenic diet can modulate chromatin state. Conversely, the generation of β-OHB is not observed during the intake of a non-ketogenic high-fat diet (HFD)[209]. HFD intake has additionally been shown to reduce levels of acetyl-CoA and histone acetylation by inhibiting the enzymes ACLY and ACSS2 (REF.[210]), as well as to induce global reprogramming of circadian enhancer activities in mouse liver[211]. The distinct epigenetic responses to a spectrum of different diets suggest that multiple dietary factors may function together to shape the epigenomic landscape and potentially to regulate phenotypic outcomes. This remains an exciting area of future inquiry.

***Interaction between diet and gut microbiota.*** Dietary intake can influence nutrient availability in concert with the activity of numerous microorganisms that colonize the host body[212,213]. The interaction between diet and the intestinal microbiome is bidirectional and complex: the composition of the human gut microbiome can be substantially and rapidly changed by alteration in diet[193,214,215], and nutrients from foods and diets are also metabolized by bacterial species in order to produce a personalized microbiotal metabolome[216] that influences host physiology, including epigenetic programmes. The digestion of dietary fibre by gut bacteria produces SCFAs, including acetate and butyrate[217], which can be oxidized to feed the intracellular acetyl-CoA pool and histone acetylation. Butyrate, which is also an inhibitor of HDACs, can influence levels of histone acetylation[192] and crotonylation[20]. Therefore, a high-fibre diet is likely to enhance circulating levels of SCFAs and histone acetylation due to microbiotal activity. In mice, microbiotal colonization has been shown to result in a diet-dependent increase in H3 and H4 acetylation in different tissues, effects that are partially phenocopied by SCFA supplementation[218]. Colonization of butyrate-producing bacteria in colorectal-tumour-bearing mice fed a high-fibre diet has tumour-suppressive effects through the inhibition of HDACs by butyrate, which upregulates histone H3 acetylation, activates apoptotic genes and suppresses cancer cell proliferation[179].

Another mechanism through which microbiotal species may regulate the host epigenome is by competing with host cells for nutrients. Colonization of choline-consuming strains of *Escherichia coli* in mouse gut was shown to reduce serum levels of methionine-cycle-related metabolites, to induce heritable changes to global DNA methylation and to predispose these animals to HFD-induced metabolic disorder[219].

***Alcohol intake and the epigenome.*** Alcohol consumption is a highly common practice around the world and is considered an important risk factor for a variety of pathologies. Alcohol is metabolized in the liver by alcohol dehydrogenase (ADH), forming acetaldehyde. Acetaldehyde is then further metabolized into acetate by aldehyde dehydrogenase (ALDH)[220]. A recent study showed that alcohol metabolism in mice feeds the acetate pool in circulation, which in turn provides acetyl-CoA for histone acetylation in an ACSS2-dependent manner in the brain. This was shown to affect the activation of transcriptional programmes related to learning and memory, influencing alcohol-related reward behaviour. In utero exposure to alcohol was additionally shown to influence histone acetylation in the developing fetal forebrain and midbrain, a potential mechanism for the incidence of fetal alcohol spectrum disorder[72]. The contribution of alcohol to histone acetylation has also been

Ketogenic diet
A diet low in carbohydrate and high in fat, which precipitates the generation of ketone bodies by fatty acid catabolism.

Fetal alcohol spectrum disorder
In utero exposure to alcohol that can give rise to the postnatal acquisition of developmental disorders.

demonstrated by in vivo $^{13}$C-tracing experiments[221]. These studies identified a molecular network connecting alcohol intake, epigenetics and health outcomes, which can potentially shape future therapeutic strategies to treat alcoholism or alcohol-related developmental disorders[72].

## Concluding remarks and future perspectives

In this Review, we have discussed how metabolism can shape the epigenomic landscape and potentially generate stable, and even transgenerationally heritable, functional consequences in different contexts. It has been particularly exciting for both the epigenetics and metabolism fields to see that metabolically regulated epigenetic modifications include a broad spectrum of enzymatic and non-enzymatic modifications on histone, DNA and RNA molecules beyond the 'canonical' methylation and acetylation marks. Extensive work will be needed to characterize the kinetic and thermodynamic behaviours of these 'noncanonical' marks and their context-specific dynamics in response to metabolism.

All the metabolically regulated chromatin-modifying enzymes mentioned so far have been epigenetic 'writers' and 'erasers' for covalent chromatin modifications. Notably, so far we have not included ATP-dependent chromatin-remodelling complexes[222–224], owing to the high concentration of intracellular ATP, which far exceeds the $K_m$ values of the ATPase domains of chromatin remodellers, or of any enzyme for that matter. Thus, ATP-utilizing enzymes are substrate-saturated and have minimal sensitivity to changes in ATP concentrations. Nevertheless, the ability of chromatin remodellers to recognize and bind to various metabolically driven histone modifications, such as histone methylation and acetylation, is critical for their localization and function; hence, metabolism may regulate the functions of these complexes through these modifications. Metabolites such as methionine, αKG, acetyl-CoA, ketone bodies and redox agents all potentially regulate the function of chromatin remodellers in this way, yet how this may occur remains uncharacterized and requires further investigation.

Despite the exciting progress in discovering new metabolically regulated epigenetic marks, understanding of the functional outcomes of these epigenomic responses is still limited. Upcoming studies over the next few years should therefore focus on clarifying the causal role of the metabolically regulated epigenomic landscape in shaping phenotypic outcomes in physiology and disease. Recent advancements in state-of-the-art techniques offer promising toolkits for us to reach a comprehensive and quantitative understanding of the metabolism–epigenetics axis (BOX 3).

Also unclear is whether and how metabolism can dynamically influence the high-level architecture of chromosomes, such as through influencing chromatin accessibility, chromosomal looping and physical properties such as liquid–liquid phase separation. Several theoretical studies have demonstrated that these structural properties of chromatin can be predicted by specific signatures of epigenetic modifications[225–228], implying that changes in metabolism could probably alter the overall organization of a genome. Furthermore, how metabolic heterogeneity in single cells can influence tissue or organ function through epigenetic regulation is still unknown[229]. This is especially interesting in the context of development, where cells from different developmental

Box 3 | **Technologies for dissecting the metabolic and epigenomic landscape**

Two major challenges in the characterization of the metabolically regulated epigenomic landscape are the lack of high-throughput techniques to collect multidimensional epigenomic and metabolomic data in a quantitative fashion with sufficient resolution, as well as the difficulty of demonstrating causality in the association between the two elements. Although chromatin immunoprecipitation followed by sequencing (ChIP-seq) is still the most widely applied technique for genome-scale profiling of histone modifications, alternatives have been developed in order to increase the coverage and resolution of epigenomic profiles in both bulk tissues and single cells. Global chromatin profiling based on targeted mass spectrometry techniques[259] enables bulk-level, simultaneous quantification of 42 combinations of covalent modifications on histone H3 and has been applied to around 1,000 cancer cell lines in the Cancer Cell Line Encyclopedia (CCLE)[260]. Combined with DNA methylation, transcriptomic and metabolomic profiles[261] in the same collection of cell lines, this multi-omic data set is a valuable resource for studying the quantitative relationship between metabolic activity and the epigenomic landscape in cancer cells. A new chromatin-profiling technology, termed cleavage under targets and release using nuclease (CUT&RUN) — in which DNA fragments bound to the modified histones are directly cleaved and released, instead of undergoing crosslinking, sonication and immunoprecipitation as they do in standard ChIP-seq — has shown increased signal-to-noise ratio, efficiency and resolution and has enabled the profiling of chromatin modifications in very small numbers of cells[262,263]. Based on CUT&RUN, techniques for chromatin profiling at the single-cell level recently have also been developed[264,265]. Measurements of metabolomic profiles can achieve cellular or subcellular resolution through the application of mass spectrometry techniques[266,267], potentially allowing the integration of metabolomic and epigenomic profiles at the single-cell level.

Regarding the causality underlying any relationship between metabolism and epigenetics, it is of particular importance to understand whether changes in the abundance of a specific metabolite cause changes in the relevant epigenetic modifications and whether these changes in modifications directly cause the observed functional and phenotypic outcomes. Isotope tracing, historically used for the estimation of metabolic fluxes[268], can be applied to quantifying the flow of chemical groups from a metabolite to chromatin, thus offering a quantitative measurement of the direct contribution of metabolic pathway activity to chromatin modifications[72,75,221,269]. CRISPR–Cas9-based epigenome editing[270,271] and synthetic approaches[272], on the other hand, have enabled the targeted, locus-specific deposition or removal of specific epigenetic modifications and the programmable manipulation of components participating in chromatin regulation. These toolkits are providing a valuable opportunity for us to attain a complete and mechanistic understanding of the metabolically regulated epigenomic landscape in a variety of physiological contexts.

states coexist. Single-cell multi-omics techniques that enable simultaneous profiling of gene expression, DNA methylation and chromatin accessibility in single cells could help us understand this complexity[230–233].

Finally, the roles of metabolism and epigenetics in mediating health outcomes due to nutrition and microbiotal commensalism have been underexplored and are promising fields of research. Given the genomic and metabolic heterogeneity among individuals, the wide global spectrum of diets and microbiotal compositions, and the general complexity of chromatin, many functional links still are yet to be discovered and offer promising avenues for future research. The integration of large-scale human datasets with machine-learning methods and rigorous biochemistry could be helpful in reconciling these disparate factors in order to predict health outcomes[234,235] and shed light on future directions for incisive mechanistic studies.

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J.W.L. advises Restoration Foodworks, Nanocare Technologies and Raphael Pharmaceuticals. Z.D. and V.R. declare no competing interests.

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