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Review Article

Unconventional metabolites in chromatin regulation

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Chromatin, the complex of DNA and histone proteins, serves as a main integrator of cellular signals. Increasing evidence links cellular functional to chromatin state. Indeed, different metabolites are emerging as modulators of chromatin function and structure. Alterations in chromatin state are decisive for regulating all aspects of genome function and ultimately have the potential to produce phenotypic changes. Several metabolites such as acetyl-CoA, S-adenosylmethionine (SAM) or adenosine triphosphate (ATP) have now been well characterized as main substrates or cofactors of chromatin-modifying enzymes. However, there are other metabolites that can directly interact with chromatin influencing its state or that modulate the properties of chromatin regulatory factors. Also, there is a growing list of atypical enzymatic and nonenzymatic chromatin modifications that originate from different cellular pathways that have not been in the limelight of chromatin research. Here, we summarize different properties and functions of uncommon regulatory molecules originating from intermediate metabolism of lipids, carbohydrates and amino acids. Based on the various modes of action on chromatin and the plethora of putative, so far not described chromatin-regulating metabolites, we propose that there are more links between cellular functional state and chromatin regulation to be discovered. We hypothesize that these connections could provide interesting starting points for interfering with cellular epigenetic states at a molecular level.

Introduction

Chromatin is a macromolecular complex composed of distinct molecules. The fundamental, repeating unit of chromatin, the nucleosome, is composed of 146 base pairs (bp) of double-stranded DNA wrapped around an octamer made up of two copies each of the core histones H2A, H2B, H3 and H4 [1]. Linear stretches of DNA packaged into nucleosomes are arranged into higher order structures by additional proteins including the linker histone H1, RNA and the involvement of other molecules to form chromatin.

The regulation of chromatin organization is crucial for all aspects of DNA biology including genome replication, gene expression, repair of DNA damage and meiotic recombination. Chromatin organization is directed by a plethora of chemical modifications on any of the different histone proteins or via methylation and its oxidation products of DNA. The modification reactions occur either nonenzymatically, or via the action of specialized chromatin-modifying enzymes (in context of histones, these are often referred to as writers for modifying enzymes and erasers for demodifying enzymes) [2]. Chromatin modifications may modulate histone–DNA complex stability and/or intranucleosome interactions. Also, specialized chromatin reader proteins can recognize the modifications and provoke downstream regulatory effects. Furthermore, chromatin remodeling enzymes organize nucleosome positioning, swap histone components for specific variants, or exchange nucleosomes at different positions. DNA accessibility and regulatory chromatin interactions are controlled at multiple scales including global effects such as the massive changes of chromosome compaction observed during the cell cycle, as well as locus-specific effects that direct the activity of individual genes [3].

The physiological state of a cell feeds into the regulation of chromatin not only via the supply of the building blocks of chromatin (i.e. nucleotides for DNA and amino acids for histone proteins) and energy

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status (i.e. driving chromatin remodeling processes which are dependent on adenosine triphosphate (ATP) hydrolysis) but also via a rapidly growing range of metabolites. The molecules that serve as substrates for enzymatic and nonenzymatic histone modifications and cofactors of chromatin-modifying enzymes have been of particular interest. Well-described metabolites in this context include nicotinamide adenine dinucleotide (NAD^+), ATP, S-adenosylmethionine (SAM), α-ketoglutarate, acetyl-CoA and different acyl-CoA moieties. Their chromatin biology has been extensively reviewed in the recent literature [4–13]. In this article, we want to describe other less-frequently discussed metabolites that play various roles in chromatin regulation and assess whether there are additional modes of function besides the paradigm chromatin modification context.

Molecular mechanisms of metabolites in regulating chromatin

Considering putative modes of metabolite function on chromatin, different mechanisms of action can be envisioned (Figure 1). Metabolites can modulate chromatin directly via interaction with DNA or histones, thereby affecting the stability of nucleosomes or internucleosomal interactions that are crucial for establishing higher order (i.e. decondensed or compacted) chromatin states. Metabolites interacting with chromatin can also interfere with chromatin modification or remodeling processes directly or via the induced chromatin states. Further, metabolites can serve as substrates for chromatin modifications. Besides being attached to chromatin via the action of specific writer enzymes, it is now well established that different metabolites can directly target histones for nonenzymatic covalent modification [2,14]. Histones accumulate stable nonenzymatic modifications because of their long half-lives and nucleophilic sites particularly enriched in their exposed N-terminal regions. In this context, it has been speculated that histones adopt the roles of 'sponges' in cells as part of an epigenetic feedback loop in metabolic adaptation [11]. In an indirect fashion, metabolites regulate the activity and function of chromatin-modifying writer and eraser enzymes or chromatin remodelers. Lastly, metabolites can control the binding activities of readers recognizing and functionally translating chromatin modifications. In the following, we will discuss examples of different less common or more unconventional metabolites originating from the carbohydrate, lipid and amino acid metabolic pathways that have less-recognized functions in chromatin regulation but that cover a spectrum of these different chromatin-regulatory mechanisms (Figure 2).

Chromatin-regulating metabolites originating from carbohydrates

Lactate

Lactate is a product of anaerobic pyruvate reduction and thereby originates from glycolysis. It serves as an energy source, precursor of gluconeogenesis, and a signaling molecule [15]. Lactate has several roles in epigenetic regulation. It promotes histone acetylation and gene expression in cell culture as an endogenous inhibitor of histone deacetylase (HDAC) activity [16], as well as via providing acetyl-CoA upon oxidation.

Recently, lactate was found covalently attached to different histone lysine residues. The modifications seem to be carried out by the p300 co-activator and enzyme that has been implied in different histone lysine acylation reactions [13]. Histone lactylation levels were shown to increase in a dose-dependent manner upon providing exogenous lactate, as well as after stimulation of endogenous production. Histone lactylation was found on 28 conserved sites in human and mouse cell lines, on all of the core histones H2A, H2B, H3, and H4 [17]. The modification is generally promoting transcription, possibly through mechanisms similar to other histone acylation post-translational modifications (PTMs) by disturbing internucleosomal contacts and decondensing chromatin [13]. Particularly, histone lactylation was connected to facilitating the expression of the YTHDF2 RNA-binding protein in ocular melanoma cells [18]. Another study demonstrated that in macrophages, increased lactate levels lead to histone lactylation on promoters of profibrotic genes in a model of lung fibrosis [19]. A connection of lactate and gene regulation was made with a transcription factor, Glis1 that was shown to specifically activate glycolytic genes, subsequently increasing acetyl-CoA and lactate levels in mouse embryonic fibroblasts (MEFs). This in turn led to increase in pluripotency loci expression via histone acetylation and lactylation mechanisms [20].

Products of the tricarboxylic acid cycle

The best studied intermediate of the Krebs cycle in chromatin regulation is α-ketoglutarate that serves as a co-substrate of α-ketoglutarate-dependent dioxygenases, the Jumonji C domain (JMJD) containing histone lysine demethylases (KDM) and the ten eleven translocation (TET) methylcytosine DNA demethylases (reviewed in

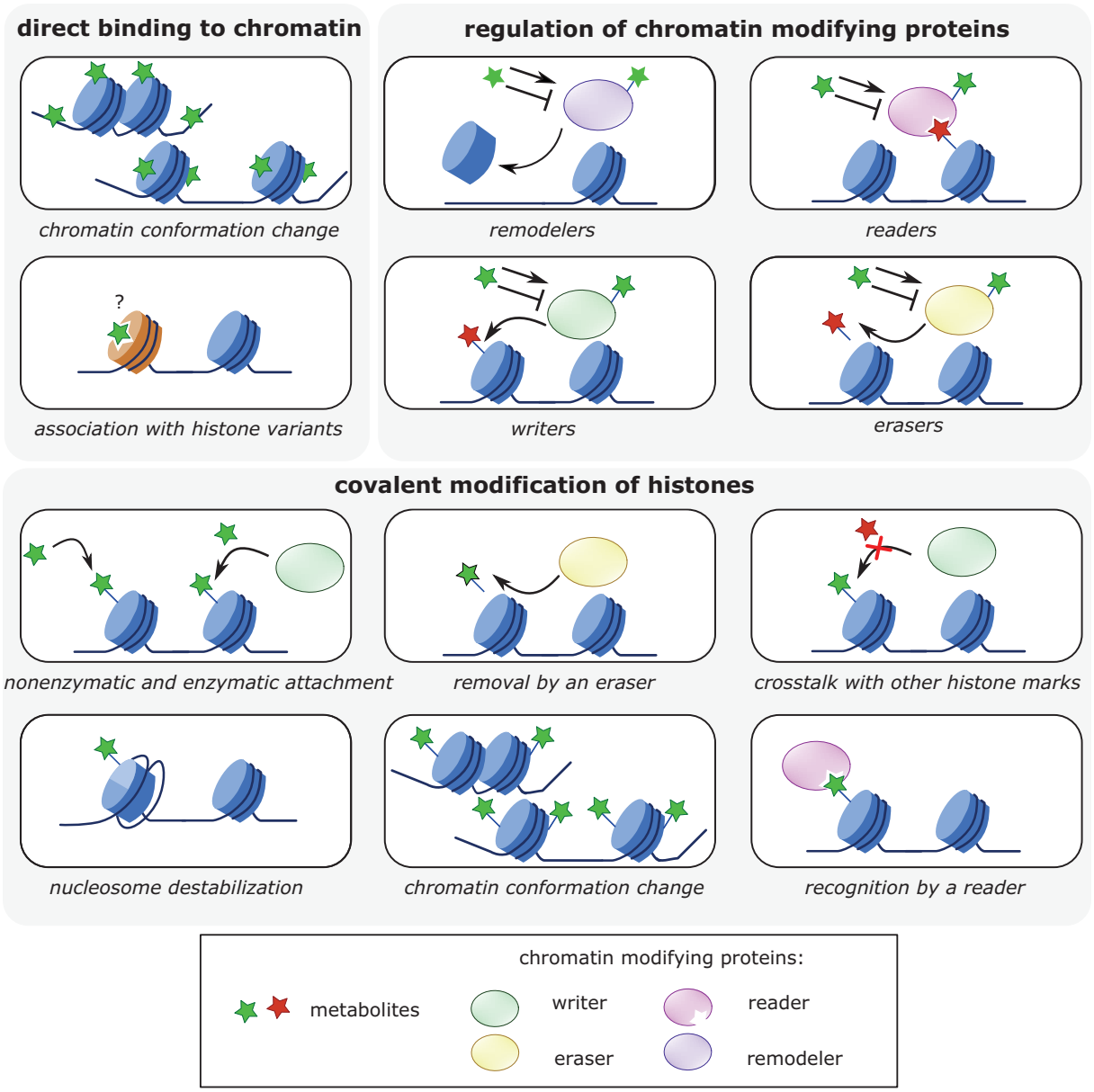

Figure 1. Molecular mechanisms of chromatin regulation by cellular metabolites

Metabolites interact with chromatin and chromatin-modifying proteins via binding and covalent modification (gray boxes). Different modes of function are illustrated for each category of metabolite–chromatin interaction. The question mark signifies the unknown functional relevance of the interaction.

[21,22]). Modulation of the α-ketoglutarate/succinate ratio is sufficient to regulate histone and DNA methylation that direct pluripotency-associated gene expression [21]. Other products of the tricarboxylic acid (TCA) cycle have less well-explored biology inside the nucleus [22,23] and this especially in form of reactive acyl-CoA compounds [24].

Histone lysine succinylation is a nonenzymatic modification originating from succinyl-CoA [25]. It can be actively removed by SIRT5 deacylase [26]. Histone succinylation sites have been mapped in various organisms, such as yeast, fruitfly, mouse and human cell lines, where they account for 13, 7, 10 and 7 sites, respectively [27,28]. Succinyl-CoA also stimulates HDAC activity *in vitro*. And it has been speculated that such effect might also be exerted by succinylated histones [27].

Fumarate and succinate inhibit the α-ketoglutarate-dependent dioxygenases, thereby affecting DNA replication and stability [29]. Fumarate may also serve as a substrate for succinylation of histone cysteines via nonenzymatic

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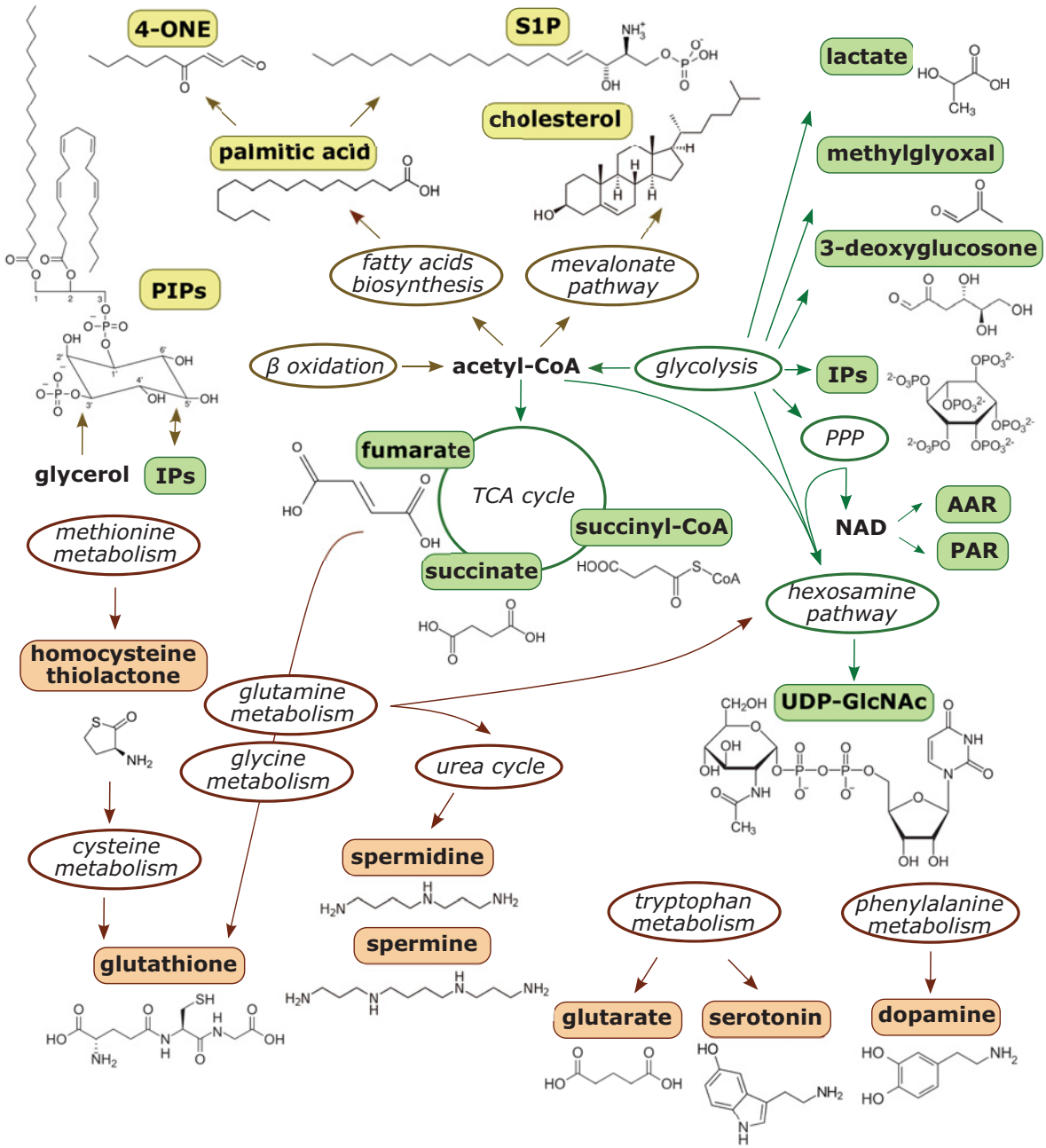

Figure 2. Origins of unconventional metabolites with potential for chromatin regulation

Chromatin-regulating metabolites (highlighted with colored boxes) originate from many cellular processes—including carbohydrate (green), lipid (yellow), and amino acids (orange) metabolic pathways (encircled). The structural formula of the different metabolites discussed in this article are presented, with exception of AAR and PAR. Intermediate steps of biosynthetic or degradation pathways are omitted for clarity. Abbreviations: 4-ONE, 4-oxo-2-nonenal; AAR, acetyl-adenosine-diphosphate-ribose; IP, inositol polyphosphate; NAD, nicotinamide adenine dinucleotide; PAR, poly-adenosine-diphosphate-ribose; PIP, phosphatidylinositol phosphate (phosphoinositide); PPP, pentose phosphate pathway; S1P, sphingosine-1-phosphate; TCA, tricarboxylic acid; UDP-GlcNAc, uridine diphosphate N-acetylglucosamine.

addition of fumarate to the thiol group of cysteines [22,30]. However, this modification has so far not been mapped to chromatin and its effects are not explored.

Methylglyoxal and 3-deoxyglucosone

Glycation of proteins is a common nonenzymatic covalent modification in diabetes and other hyperglycemic states. Glycation results from the condensation of the aldehyde form of monosaccharides or glycolytic by-products (such as methylglyoxal and 3-deoxyglucosone (3-DG)) with reactive amino acid residues (mainly lysines and arginines) via a nonenzymatic reaction [31]. This reaction was found to happen with methylglyoxal and all core histones, with prevalence of H3 [31]. Glycation of histones causes destabilization of nucleosomes *in vitro* and *in cellulo*, possibly by attaching to critical residues that are serving as intranucleosomal anchors and as binding sites for chromatin readers [32]. It is not clear whether glycation has specific downstream effectors, though it is actively removed from histones by the DJ-1 deglycase enzyme, which reduces disturbing effects of this modification [31].

3-DG is an α-oxoaldehyde, a reactive compound involved in vascular damage in diabetes. As with methylglyoxal, 3-DG reacts with histones, and glycation leads to the generation of advanced glycation end-products (AGEs). *In vitro* studies of 3-DG treatment of H1, H2A and H3 have shown that their secondary structures were altered upon glycation [33]. Histone glycation affects stability and function, as well as is implied in the autoimmune response [34].

Acetyl-ADP-ribose

ADP-ribosylation reactions can be divided into four groups: mono-ADP-ribosylation, poly-ADP-ribosylation, ADP-ribose cyclization, and formation of *O*-acetyl-ADP-ribose (AAR) [35]. Here, we discuss only AAR and poly-ADP-ribose (PAR, see next section) for their relevance in chromatin biology. These metabolites are derived from NAD^+ and act as secondary messengers in chromatin organization processes.

AAR is a by-product of histone deacetylation and NAD^+ hydrolysis, catalyzed by Sirtuin proteins in a wide range of model organisms. It can act as a signaling molecule and substrate for chromatin-modifying enzymes [36], and its level can also be regulated by designated Nudix (nucleoside diphosphate linked to another moiety X) hydrolases [37].

AAR regulates Silent Information Regulator (SIR) complex function in yeast [38]. SIR proteins mediate heterochromatin silencing. Sir2 initiates the formation of silent chromatin by deacetylation of histones, producing AAR. AAR in turn binds to Sir3 complexes and stabilizes the interaction with nucleosomes and oligomerization with other Sir3 proteins, thus provoking formation and spreading of heterochromatin [39]. It was also determined that AAR stays in a stable association with established heterochromatin [40].

In higher eukaryotes, SIRT1, a deacetylase associated with heterochromatin [41] also produces AAR as a by-product of deacetylation. *In vitro*, AAR is specifically recognized by the histone variant macroH2A1.1 via its macrodomain [42,43]. Histone variants substitute for the canonical core histones in specific regions of the genome and under defined conditions. While these generally support nucleosome assembly, the various changes in amino acid composition compared with the canonical histones confer changes in function. It is yet unclear what exactly the function of AAR binding to macroH2A1.1 is [44,45]. But the fact that macroH2A1.1 is enriched in repressive chromatin [46], and that only this splicing variant of macroH2A1 but not macroH2A1.2 strongly binds to AAR [42] suggests a specific role of AAR in heterochromatin formation. Since AAR production by sirtuins is evolutionarily conserved in organisms that do not contain macroH2A, and as not all macroH2As of different organisms seem to bind AAR [47], the existence of other reader proteins of AAR was suggested [48]. AAR has already become an attractive target for designing regulatory protein inhibitors [49,50].

PAR

PAR is a negatively charged polymer with variable structure of two or more ADP-ribose units that are derived from NAD^+ [51]. PAR is attached to proteins at different amino acids, including aspartate, glutamate, and lysine residues via enzymes of the PAR polymerases (PARPs) protein family [52,53]. The PARPs add single or multiple ADP-ribose units either connecting the ribose group of one ADP-ribose unit to the adenosine of the adjacent ADP-ribose unit (resulting in linear PAR polymers) or linking the nonadenosine ribose groups from neighboring ADP-ribose units (generating branched PAR) [54]. The levels of PAR are controlled by specific hydrolases, such as PARG.

PAR has many divergent roles in cellular signaling, chromatin maintenance, and stress response (reviewed in [33,52,53]). The polymer regulates nuclear processes via disruption of protein and DNA interactions, scaffolding of protein complexes, and cross-talking with other protein PTMs. Besides roles of PAR in establishing stress granules [55], organization of the nucleolus [56] and mitotic spindle formation [57], particularly its involvement in the DNA damage response is well documented [58].

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PARP1, the most studied PARP protein, is recruited to DNA strand-break sites and initiates local PAR synthesis. PAR is either covalently attached to histones H1 and H2A [59] and to other proteins (including PARP itself) [60], or accumulates as a free molecule [35]. PARylation of histones is linked to chromatin decondensation, which in turn allows for local DNA accessibility and promotes DNA repair [61]. PAR also recruits downstream effectors. For example, a chromatin remodeler ALC1 (Amplified in Liver Cancer 1, also known as CHD1L) is activated by binding to PAR via its macrodomain [62,63]. ALC1 promotes nucleosome sliding by interacting with the acidic patch on the nucleosome [64], thus amplifying chromatin decompaction. PAR may recruit other proteins to DNA break sites, such as CHFR, an E3 ubiquitin ligase [65] or condensin I [66], that in turn leads to global chromatin structural changes. It is proposed that PAR may regulate gene expression through the same mechanisms (chromatin structural change and recruitment of effector proteins) in normal conditions [67]. Because of the many roles of PAR and its specialized effector proteins, PAR has been targeted for pharmaceutical development [68,69].

Uridine diphosphate N-acetylglucosamine

Uridine diphosphate N-acetylglucosamine (UDP-GlcNAc) is among the most abundant high-energy metabolites and it is the final product of the hexosamine biosynthetic pathway—a branch of glycolysis responsible for the production of a key substrate for protein glycosylation. O-GlcNAcylation is a PTM of proteins catalyzed by the O-Linked N-acetylglucosamine (O-GlcNAc) transferase (OGT) and reversed by O-GlcNAcase (OGA) [70].

O-GlcNAcylation of all core histones has been described [71], with O-GlcNAc found on histone threonines and serines [72]. Specific sites that have been mapped include H2AT101, H2BS36, H3S10, H3S28, H3T32, and H4S47. Interestingly, the same sites were earlier described as phosphorylation targets, and this is why O-GlcNAcylation is thought to act as a nutrient-dependent sensor competing with phosphorylation signals and their effector pathways [73,74].

The OGT enzyme forms many functionally distinct complexes with other nuclear proteins, which determine the target location and the outcome of O-GlcNAcylation. For example, OGT is directed to chromatin by the TET DNA demethylase proteins, and many other OGT complexes have been described [75]. Recent findings suggest that O-GlcNAcylation directly regulates a range of chromatin-modifying proteins. Glycation of HDAC4 deacetylase was shown to be involved in improving diabetic complications of heart by preventing phosphorylation of the same site, which in turn is associated with a detrimental outcome [76]. O-GlcNAcylation of several residues on histone methyltransferase EZH2 was shown to differently regulate its stability and chromatin interactions. It was proposed that selective inhibition of this modification may be used to specifically modify EZH2 activity [77].

With only single copies of OGT and OGA enzymes in humans, and many roles of O-GlcNAcylation in the cell nucleus, UDP-GlcNAc metabolism is both an attractive target for modulation of its downstream effect and a vulnerable point involved in several pathologies [75].

Inositol polyphosphates

The *de novo* myo-inositol biosynthesis pathway converts glucose-6-phosphate into inositol 1,4,5-trisphosphate (IP3). IP3 can be subsequently phosphorylated by inositol kinases yielding several phosphorylated species (e.g. inositol 1,4,5,6 tetrakisphosphate (IP4), inositol 1,3,4,5,6 pentakisphosphate (IP5), inositol 1,2,3,4,5,6 hexakisphosphate (IP6), and 5-diphosphoinositol pentakisphosphate (IP7)) [78,79]. The second cellular source of inositol polyphosphates (IPs) is hydrolysis of membrane phospholipids—a process tightly involved in cellular signal transduction, where IPs act as messenger molecules mediating various processes.

IPs are highly negatively charged and they exert chromatin effects by interacting with specific protein targets. For example, IP6 inhibits nucleosome mobilization by the chromatin remodeling NURF, ISW2, and INO80 complexes. In contrast, IP4 and IP5 stimulate the chromatin remodeling (nucleosome-sliding) activity of SWI/SNF [80]. Besides control of enzymatic activity, the IPs direct the interaction of chromatin remodelers with the transcription factors Pho2 and Pho4, which is involved in regulation of some phosphate-responsive genes and inducing their transcription [81].

The enzymatic activity of class I HDAC1, 2 and 3, which form the catalytic subunits of several large transcriptional repression complexes, has been shown to be regulated by IPs. Initially, IP4 was found to be an intrinsic scaffolding part located at a binding pocket formed at the interface between the HDACs and their cognate corepressors NuRD, CoREST, SMRT, Sin3L/Rpd3L and others [82–87]. It was then demonstrated that IP4 allosterically activates the enzymatic activity of the HDACs which are not functional in its absence and outside the corepressor complexes [88–90]. Interestingly, IP5 and IP6 can substitute for IP4 at least *in vitro* [90]. It is at present not fully clear whether the IPs functionally regulate HDAC activity upon signaling events or serve as constitutive cofactors of the enzyme complexes.

IP7 functions to regulate its target proteins through allosteric interactions or protein pyrophosphorylation. Inositol hexakisphosphate kinase 1 (IP6K1), the enzyme responsible for the synthesis of IP7, associates with chromatin and interacts with the histone lysine demethylase, Jumonji domain containing 2C (JMJD2C). IP6K1 induces JMJD2C dissociation from chromatin and increases H3K9me3 levels, which depend on IP6K1 catalytic activity. Reducing IP6K1 expression levels or IP7 concentration causes a reduction in the levels of the H3K9me3 modification concomitant with an increase in the H3K9ac mark. The molecular mechanisms of this effect are not yet known but this phenomenon shows that there is localized production of IP to control histone methylation [91].

Chromatin-regulating metabolites originating from lipids

Cholesterol

Cholesterol possesses a tetracyclic steroid ring. It is synthesized via the mevalonate pathway, in which acetyl-CoA is converted by subsequent reactions into several fundamental end-products, including cholesterol and isoprenoids [92].

Cholesterol influences chromatin structure and stability by directly binding to nucleosomes inducing compaction of long chromatin fibers [93–95]. Docking and molecular dynamics simulations suggested that cholesterol interacts with nucleosomes through six binding sites nearby important interacting regions for nucleosome-binding proteins. Cholesterol is proposed to influence critical packing interactions at the nucleosome core particle and facilitate dewetting (i.e. exposure) of hydrophobic surfaces on the histones, leading to enhanced histone–histone contacts that drive chromatin condensation [96,97].

Further on the notion that cholesterol drives the compaction of nucleosomes, cholesterol was shown to be required for the transcriptional repressor brain acid soluble protein 1 (BASP1)-dependent histone modification and transcriptional repression. As such, BASP1-mediated recruitment of cholesterol might elicit direct effects on the nucleosome that contribute to establishing transcriptionally repressive condensed chromatin at specific genes; yet, further studies are needed to elucidate the exact mechanisms of action [98].

Phosphoinositides

Phospholipids are a class of lipids that consists of fatty acids modified with phosphate groups, and in the case of the glycerophospholipids species, they contain an additional glycerol that bridges multiple fatty acid chains. A prominent example of glycerophospholipids are phosphoinositides (also referred to as phosphatidylinositol phosphates, PIPs). Multiple PIPs that differ in the phosphorylation positions and levels of the inositol polyalcohol are derived from phosphoinositol. The monophosphates are PI3P, PI4P (also referred to often as PIP) and PI5P; the bisphosphates are PI3,4P_2, PI3,5P_2 and PI4,5P_2 (also often referred to as PIP2), and PI3,4,5P_3 (also often referred to as PIP3) is the trisphosphate. Overall, PIPs occur in low to very low abundance when compared with other lipids. The different PIPs are well known for their biology at the cell membrane and in intracellular vesicle trafficking. In cell signaling PI4,5P_2 is hydrolyzed to form the second messengers, diacylglycerol (DAG) and IP3. But a separate biology of PIP has been emerging in the nucleus with their concentrations varying in dependence of cellular state (e.g. cell cycle, stress, transcriptional state etc.) [99,100].

Early studies of lipid analysis of isolated animal chromatin revealed different amounts of (phospho-)lipids associated with hetero- and euchromatin. In addition, higher turnover rates of (phospho-)lipids were found associated with euchromatin [101]. Later it was shown that hydrolysis of nuclear phospholipids via phospholipase C (PLC) changes chromatin structure [102]. Also, it was suggested that phospholipids are associated with the chromosomes during mitosis, whereas during interphase, they dissociate from chromatin, with the exception of heterochromatin [103]. Interestingly, addition of phospholipids to purified nuclei can affect transcription and replication of DNA *in vitro* [104]—an effect that is paralleled by changes in chromatin condensation [105]. Over the last years, several chromatin proteins have been found to bind to and be regulated by PIPs.

The ATPase subunit, named BRG-1, of the ATP-dependent chromatin remodeling complex, BAF (the mammalian ortholog of the yeast SWI/SNF complex) binds PI4,5P_2. The interaction modulates interaction of the BAF complex with actin and tethering to the nuclear matrix [106]. In T cells, the exogenous addition of PI4,5P_2 causes BAF to translocate from the soluble to the nuclear-insoluble protein fraction which allows it to participate in nuclear architecture formation [107]. BAF complex that contains PI4,5P_2 bound BRG-1 is not recruited to active promoters [108].

PI4,5P_2 has further been found to directly bind to histones and in particular linker histone. This interaction is blocked after phosphorylation of H1 by protein kinase C [109]. In a *Drosophila* transcription system, PI4,5P_2 binding to H1 counteracted repression of RNA polymerase II basal transcription [109]. More recently, PI4,5P_2 has been shown

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Table 1 Chromatin biology of unconventional metabolites

Type	Class	Metabolite	Target	Mechanism of function	Proposed biological effect	Level of evidence
carbohydrates		lactate	core histones	enzymatically catalyzed addition	chromatin decompaction; transcriptional activation; recruitment of downstream effectors	several *in vitro*, *in cellulo*, and *in vivo* studies in tissues and cells undergoing fluctuations of lactate (hypoxia, tumor, immune cells, stem cells)
			histone deacetylases	inhibition	chromatin decompaction; transcriptional activation	few studies using cell lines
	intermediates of the TCA cycle	succinyl-CoA	core histones	nonenzymatic covalent attachment	destabilization of the nucleosome; affects viability in yeast	mapped in different experimental systems; few *in vivo* studies (mutagenesis of succinylated lysine residues in yeast)
			histone deacetylases	activation	regulation of chromatin acetylation levels	few *in vitro* studies
		succinate and fumarate	DNA and histone demethylases	inhibition	chromatin replication and stability	multiple evidence from yeast genetics; different *in vitro* studies
		methylglyoxal; 3-deoxyglucosone	core histones	nonenzymatic covalent attachment	destabilization of the nucleosome leading to an open chromatin state	few studies looking at cell lines cultured on enriched media; different *in vitro* studies
	ADP-ribosylation	acetyl-ADP-ribose (AAR)	Sir3	binding to chromatin-modifying proteins	formation and spreading of heterochromatin	multiple *in vivo* studies in yeast; *in vitro* binding experiments
			macroH2A1.1	binding to histone variant	not yet known	several studies using human cell lines; structural evidence
		poly-ADP-ribose (PAR)	core histones	enzymatically catalyzed addition	chromatin decompaction; recruitment of downstream effectors	multiple studies in different *in vivo*, *in cellulo*, and *in vitro* systems including pathological conditions
		UDP-GlcNAc	core histones	enzymatically catalyzed addition	cross-talk with other histone marks	multiple studies in different *in vivo*, *in cellulo*, and *in vitro* systems
			readers erasers	enzymatically catalyzed addition	stability; chromatin interaction	multiple studies in different *in vivo*, *in cellulo*, and *in vitro* systems
	inositol polyphosphates (IPs)	IP4	class I HDAC	allosteric activation	chromatin and genome control	multiple studies in different *in vivo*, *in cellulo*, and *in vitro* systems; structural evidence
		IP4, IP5, IP6: chromatin remodelers	chromatin remodelers	regulation of activity; interaction with transcription factors	transcriptional regulation	several studies in yeast
		IP7	JMJD2C (histone demethylase)	dissociation from chromatin	ratio of repressive H3K9me3 and activating H3K9ac histone marks	several studies using different cell lines
lipids		cholesterol	chromatin	direct binding	chromatin compaction; transcriptional repression	several *in vitro* studies; *in silico* prediction
			BASP-1	interaction	chromatin compaction; transcriptional repression	few studies in cell lines

Continued over

Table 1 Chromatin biology of unconventional metabolites (Continued)

Type	Class	Metabolite	Target	Mechanism of function	Proposed biological effect	Level of evidence
	phosphoinositides (PIPs)	PI5P5	UHRF1 (reader)	allosteric activation	interaction with H3K9me3	few *in vitro* studies; few studies in cell lines
			ATX1 (histone methylase)	nuclear localization	transcriptional regulation	few *in vitro* studies; few studies in plants
			TAF3 (basal transcription factor)	control of activity	interaction with H3K4me3; transcriptional regulation	few *in vitro* studies; few studies in plants
			ING2 (reader)	nuclear localization; chromatin association	acetylation of p53; apoptotic response to DNA damage; transcriptional regulation	few *in vitro* studies; few studies in plants
		$PI4,5P_2$	BRG1 (chromatin remodeler)	binding to chromatin	transcriptional regulation	few *in vitro* studies; few studies in cell lines
			H1 (linker histone)	direct binding	transcriptional regulation	few *in vitro* studies; few studies in cell lines
			PHF8 (histone demethylase)	regulation of activity	rRNA gene transcription	few *in vitro* studies; few studies in cell lines
		$PI3,4,5P_3$	nucleophosmin (histone chaperone)	not yet known	apoptosis	few studies in cell lines
		diverse PIPs	SAP 30, SAP30L (HDAC corepressor components	not yet known	not yet known	few *in vitro* studies; few studies in cell lines
			different transcription factors	chromatin recruitment	transcriptional regulation	few *in vitro* studies; few studies in cell lines
		sphingosine-1-phosphate	HDAC1; HDAC2	inhibition	transcriptional activation	several *in vitro* studies and in different cell lines
		palmitic acid	histones H3 and H4	S-palmitoylation: nonenzymatic covalent attachment	not yet known	few indirect observations in cell lines
				O-palmitoylation: enzymatically catalyzed addition	decreased RNA synthesis, suggesting transcriptional repression	few indirect observations in cell lines
		4-oxo-2-nonenal	core histones	nonenzymatic covalent attachment	inhibition of nucleosome assembly	few studies *in vitro* and in cell lines; relevant in oxidative stress
amino acids		glutarate	core histones	enzymatically catalyzed addition	chromatin decompaction; transcriptional regulation	several studies *in vitro* and in cell lines; relevant in metabolic disorder
		homocysteine thiolactone	core histones	nonenzymatic covalent attachment	not yet known; cross-talk with other histone marks?	few studies in cell lines; relevant in metabolic disorder
		glutathione	histone H3	nonenzymatic covalent attachment	chromatin decompaction; destabilization of the nucleosome leading to an open chromatin state	few studies in cell lines
	monoamines	serotonin, dopamine	histone H3	enzymatically catalyzed addition	transcriptionally permissive chromatin state	few *in vivo* studies (neuronal cells) and in cell lines
	polyamines	spermine, spermidine	chromatin	direct binding	various effects not fully understood	multiple studies in different *in vivo*, *in cellulo* and *in vitro* systems

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to regulate the levels of H3K9me2 at the rDNA promoter by binding to and inhibiting the activity of the histone lysine demethylase PHD finger protein 8 (PHF8), likely resulting in a reduction in rRNA gene transcription [110].

The ING2 (inhibitor of growth protein-2), a component of the transcriptional corepressor Sin3a–HDAC1 complex binds PI5P through a plant homeodomain (PHD) finger domain [111,112]. Overexpression of the type II PI5P 4-kinase β, which decreases the levels of nuclear PI5P, alters ING2 translocation to the nucleus and chromatin association [111]. PI5P binding of ING2 has been implicated in the regulation of acetylation of the p53 tumor suppressor and the apoptotic response to DNA damaging agents [113]. PI5P was further demonstrated to be required for the association of ING2 with target gene promoters leading to their transcriptional repression [114]. Other PHD domain containing factors (e.g. ING1b, ING3, ACF, Rag2, PHF1) were also shown to bind PI5P albeit with unknown functional consequence [112]. In contrast, binding of PI5P to the PHD of ATX1, a plant H3K4 trimethyltransferase, causes the enzyme to detach from promoters and translocate from the nucleus to the cytosol [115]. Further, the PHD finger of TAF3 was shown to be affected by interaction with PI5P in its association with the H3K4me3 chromatin mark by a so far unknown allosteric mechanism. This control of a basal transcription factor seems to be involved in regulating gene transcription in myoblast differentiation [116].

Another chromatin protein that has been shown to be functionally regulated by PI5P is UHRF1 (ubiquitin-like with PHD and RING finger domains 1) that plays an important role in reading and maintaining epigenetic states [117]. UHRF1 contains multiple domains for recognizing chromatin modifications and in particular a tandem tudor domain (TTD) that binds H3K9me3 and a PHD domain that binds the unmodified N-terminus of H3. PI5P works as an allosteric regulator of UHRF1 chromatin interaction by inducing conformational rearrangement of the protein thereby establishing a synergistic binding function of the TTD and PHD domains [118,119]. The fact that multiple chromatin proteins with PHD domains that are known to bind methyl-lysines have been found to interact with and be regulated by PI5P raises the possibility of a more general cross-talk between such reader domains and the phosphoinositides. Such notion is supported by a binding screen conducted with 32 different PHD finger sequences that identified 17 of these as interactors of PI5P and other PIPs [116].

Further illustrating the diverse chromatin biology of nuclear PIPs is the association of nucleophosmin, a factor that besides other functions, serves as a histone chaperone, with PI3,4,5P_3 that was linked to apoptosis [120]. Accumulation of PI3,4,5P_3 was also found at sites of DNA damage and required for local recruitment of the ATR kinase [121]. The HDAC corepressor components SAP30 and SAP30L are negatively regulated in their association with DNA by different PIPs [122]. Diverse transcription factors that work in dependence of histone-modifying enzymes were shown to be functionally regulated in their chromatin recruitment by PI5P, PI3,5P_2, PI4,5P_2, and/or PI3,4,5P_3 [123]. Different biochemical screens have (besides other proteins) identified additional chromatin factors interacting with PI4,5P_2 and PI5P albeit with so far unclear functional implications [116,124].

Sphingolipids

Sphingolipids are a class of lipids containing a single fatty acid chain and amino alcohol group. An example of a nuclear sphingolipid that is involved in chromatin modification is sphingosine. Sphingosine-1-phosphate (S1P) has been found to regulate histone acetylation. Sphingosine kinase 2 (SphK2) which generates S1P, was found to be associated with histone H3 [125]. SphK2 enhanced local histone H3 acetylation via the direct binding of S1P to HDAC1 and HDAC2. S1P specifically binds to the active sites of HDAC1 and HDAC2 and inhibits their enzymatic activities, thereby preventing the removal of acetyl groups from lysine residues within histone tails and leading to increased histone acetylation. Thus, HDACs are direct intracellular targets of S1P and link nuclear S1P to epigenetic regulation of gene expression [126]. In fact, S1P treatment has been reported to ameliorate the cardiac hypertrophic response, which may be partly mediated by the suppression of HDAC2 activity. Therefore, S1P may be considered a potential therapy for the treatment of heart diseases caused by cardiac hypertrophy [127].

Palmitic acid

Palmitic acid is a major saturated fatty acid of 16 carbons (C16:0). S-palmitoylation and O-palmitoylation describe the addition of palmitic acid to protein cysteine and serine residues, respectively [128]. Thiol side chains of exposed cysteines can attack electrophilic species, including molecules with carboxylic acid substituents, such as palmitic acid [129]. The resulting thioester bond is energetically labile, allowing for reversibility. All H3 variant proteins but CENP-A share a conserved cysteine residue (at position 110 for human H3) as a primary site for S-palmitoylation [130].

O-palmitoylation occurs at histone serine residues whereby the serine hydroxyl group forms an oxygen ester bond with palmitate, that is a more stable bond compared with the cysteine thioester [131]. O-palmitoylation has been detected on H4S47 but not the only other serine residue at position 1, suggesting a specific mode of modification [132]. Indeed, acyl-CoA:lysophosphatidylcholine acyltransferase (Lpcat1) has been shown to colocalize with chromatin under specific conditions. Lpcat1 binds to histone H4 and catalyzes histone H4 palmitoylation at S47 [132]. Mutation of H4S47 reduces H4 O-palmitoylation levels and is concomitant with substantially decreased RNA synthesis. While this suggests a role of H4 O-palmitoylation in transcriptional repression, a more direct connection to regulation of gene expression is yet to be found [132].

4-Oxo-2-nonenal

Lipids can be peroxidized to yield highly reactive, electrophilic α,β-unsaturated aldehydes, such as 4-oxo-2-nonenal (4-ONE) that are found to chemically modify a number of proteins and DNA [133]. Lipid peroxidation can be described generally as a process under which oxidants, such as free radicals, attack lipids containing carbon–carbon double bonds. 4-ONE have been shown to form adducts on all core histones *in vitro*, attaching to lysine residues via ketoamide adduction or attaching to histidines residues via Michael addition. Under oxidative stress, the adduct on histones disrupts the interaction with DNA, thereby preventing the assembly of nucleosomes [134].

Because the 4-ONyl modification is similar to fatty acyl groups, sirtuins and particular SIRT2 were suggested to hydrolyze histone 4-ONyl lysine adducts. This action mitigates the negative impact of this modification, namely the inhibition of nucleosome assembly, caused by oxidative stress [135].

Chromatin-regulating metabolites originating from amino acids

Glutarate

Glutarate can be derived from the metabolism of the essential amino acids lysine and tryptophan. It can form reactive glutaryl-CoA, and become a donor for glutarylation of proteins [136]. GCN5 (also referred to as KAT2A), which was originally described as a histone acetyltransferase, has been shown to mediate histone glutarylation [137,138]. At present, it is unclear whether GCN5 mediates all histone glutarylation, whether other enzymes for this modification exist or whether some sites are targets of nonenzymatic modification. So far, 27 glutarylation sites on histone lysines in HeLa cells have been mapped [137]. Glutarylated histones are enriched at transcriptional start sites and associated with permissive transcription. By introducing a negative charge, glutarylation is proposed to cause opening of chromatin similar to other acylation modifications and to destabilize the H2A/H2B and H3/H4 interactions within the nucleosome *in vitro* [137]. Since histone glutarylation is generally far less abundant than histone acetylation but appears to mediate similar effects, its independent chromatin signaling needs to be further investigated. Evidence for a physiological role separate from histone acetylation might come from the cellular study of a mimicking modification—H4K91 mutated to glutamic acid, bearing a negative charge like glutaryl itself. It was demonstrated that this substitution has an effect on cell proliferation and DNA damage response in yeast, as well as causing deregulation of a large set of genes [137]. SIRT5 and/or SIRT7 have been suggested to function as deglutarylation enzymes [136,137].

Homocysteine thiolactone

Homocysteine is an intermediate metabolite in the cysteine and methionine metabolism. S-adenosylhomocysteine (SAH) is the reaction product of SAM after donating an activated methyl-group for methylation reactions. Homocysteine is not proteinogenic, however it can be recognized by methionyl-tRNA and transformed into a cyclic thioester homocysteine thiolactone [139]. In one study, the expression level of genes involved in chromatin organization was altered upon treatment with homocysteine thiolactone [140], making a correlative link between this molecule and chromatin. One of the mechanisms for this link may be a direct histone modification, as homocysteine thiolactone reacts with histone lysines nonenzymatically forming a covalent bond [141]. This modification is particularly interesting in metabolic disorders and hyperhomocysteinemia, as homocysteinylation is regulated by intracellular levels of its precursor. A total of 39 homocysteinylation sites on all of the four core histones were identified in human embryonic brain cells and a possible cross-talk with other lysine modifications, such as acetylation and methylation, has been suggested [141]. H3K79Hcy is involved in fetal neuronal development via down-regulation of *Smarca4*, *Cecr2*, and *Dnmt3b*, genes that are playing critical roles in neural tube closure [142].

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Glutathione

Glutathione (GSH) is a tripeptide that consists of cysteine, glutamate, and glycine. This molecule is mainly known as a redox agent and buffer that prevents damage to cellular components caused by reactive oxygen species. However, there are also links between GSH metabolism and chromatin function on different levels [143,144]. Biosynthesis of GSH competes for substrate with methionine metabolism and SAM/SAH balance, putting it in a relation to DNA and histone methylation processes [143]. But GSH also has more direct roles in chromatin regulation, particularly it is a key molecule that aids rapid chromatin decondensation in sperm nuclei [145].

Most nuclear functions of GSH are associated with its free form [146], however GSH can be also covalently bound to the cysteine residues of H3 via disulfide linkage [143,147]. This attachment seems to happen nonenzymatically. *In vitro* studies showed that addition of GSH destabilizes the nucleosome and leads to an open chromatin state, but the exact functional implications of this modification are not known. The spread of this modification increases during proliferation and decreases with age [143].

Monoamines (serotonin, dopamine)

Dopamine is a product of the phenylalanine and tyrosine metabolism, whereas serotonin is derived from tryptophan. In addition to their well-known physiological roles as neurotransmitters and neuromodulators, monoamines have also been described in direct chromatin regulation. The extravesicular monoamines can be covalently attached to histones by the transglutaminase (Tgm2) enzyme. Serotonin was found on the H3Q5 residue [148], and this modification was also observed in conjunction with the activating mark H3K4me3. H3Q5 serotonylation has been generally correlated with a permissive transcription state and might function via facilitating binding of the TFIID basal transcription factor to H3K4me3. Histone serotonylation was found to be enriched at genes related to axon guidance and neuronal development [148].

Dopamine is another monoamine that can be used to modify histones, it is attached to H3Q5 by the same mechanism as serotonin [149]. H3Q5 dopaminylation has been studied in a particular context of drug-abuse behavior and cocaine addiction. In the brain region involved in reward behavior changes where dopamine is synthesized, H3Q5 dopaminylation was reduced in samples derived from overdosed cocaine users. In a rat model, the modification is gradually re-established after a prolonged time since the last cocaine administration. Artificially reducing H3Q5 dopaminylation in rats resulted in absence of drug-seeking behavior during withdrawal. The findings imply that this histone monoamine modification has a prolonged effect on cell physiology enacted via disrupting gene expression patterns [149].

Polyamines (spermine, spermidine)

Polyamines are formed by enzymatic decarboxylation of the amino acids ornithine or arginine. The most common polyamines are spermidine, spermine, and their biosynthetic precursor putrescine. Though the primary role of polyamines seems to be in RNA translation in the cytoplasm [150], they are also imported into the nucleus and involved in several processes, including chromatin conformation maintenance, DNA replication, and gene expression [151]. There are several controversial observations (which might be explained by the differences in experimental systems) about a direct action of polyamines on chromatin components (for a detailed review, see [152]). Some of the peculiar examples are induction of DNA conformational change from B-DNA to Z-DNA [153], *in vitro* chromatin condensation at the nucleosome level, and modulating of expression and activity of chromatin-modifying enzymes (HAT, HDAC, LSD1) upon polyamines administration or depletion. Interestingly, polyamines are themselves subject to modification by acetylation. This regulates their chromatin association [154] and also cross-talk to histone acetylation [155]. To this point, the findings are largely correlational and do not yet provide a detailed mechanistic insight into the nuclear functions of polyamines.

Despite the absence of a clear understanding of polyamines function on chromatin, polyamine-based anticancer drugs are being developed. Polyamine analogs, such as polyaminohydroxamic acids (PAHAs) and polyaminobenzamides (PABAs), demonstrated potent inhibition of HDACs, re-expression of p21 and significant inhibition of tumor growth [156].

Origin of metabolites regulating chromatin biology

With the small size, the metabolites we have discussed can likely freely diffuse in and out of the nucleus though its pores. While this has been postulated to establish a connection between the cytoplasmic and nuclear state of a cell [157,158], it is emerging that many enzymes controlling the concentration of metabolites regulating chromatin

biology localize to the nucleus under specific cellular conditions or have specific isoforms that are constitutively found in the vicinity of chromatin [11,159–161].

This phenomenon is now well documented for enzymes metabolizing the common and well-studied substrates and cofactors of chromatin modification. For example, the acetyl-CoA synthesizing enzymes acyl-CoA synthetase short-chain family member 2 (ACSS2), ATP-citrate lyase (ACLY), and the pyruvate dehydrogenase complex (PDC) are all found nuclear besides their cytoplasmic or mitochondrial primary localization [159,160]. Similarly, methionine adenosyltransferase 2A (MAT2A) that converts methionine into SAM is found not only in the cytoplasm but also in the nucleus [162]. Of relevance for the consideration of unconventional metabolites in chromatin regulation, different enzymes of carbohydrate metabolism including the glycolytic enzymes pyruvate kinase M2 (PKM2), 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 4 (PFKFB4), fructose-1,6-bisphosphatase 1 (FBP1), glyceraldehyde-3-phosphate dehydrogenase (GAPDH), and triose phosphate isomerase 1 (TPI1) were described with nuclear localization under specific conditions [11,163]. Further, several enzymes of the TCA cycle such as α-ketoglutarate dehydrogenase (α-KGDH) and fumarase (lactate dehydrogenase, LDH, [164]) have a nuclear appearance. Indeed, all mitochondrial enzymes executing the different steps of converting pyruvate into α-ketoglutarate were found to transiently operate in the nucleus of the developing zygote [165]. The pathways of synthesis and salvage of NAD^+ are also compartmentalizing to the cell nucleus [166,167]. This seems particularly interesting in light that NAD^+ itself is consumed in poly-ADP-ribosylation or production of acetyl-ADP-ribose instead of changing its oxidation state as in cytoplasmic energy conversion. Also, several enzymes of inositolphosphate metabolisms such as phospholipase C and different inositol phosphate kinases are suggested to have a nuclear life based on screens conducted in yeast [168], and several of these seem to shuttle in and out of the nucleus [169].

For the chromatin-regulating metabolites linked to lipids, it is interesting to notice that two main enzymes involved in lipid biosynthesis, acetyl-CoA carboxylase 1 (ACC1) that catalyzes the rate-limiting step of lipid biosynthesis, the conversion of acetyl-CoA into malonyl-CoA and fatty acid synthase (FASN) have been described to show oscillations between cytoplasmic and nuclear localization [170]. Very well documented are specific isoforms of different kinases and phosphatases that interconvert the different phosphoinositides and which are found exclusively in the cytoplasm or in the nucleus [171,172]. Other enzymes of PIP metabolism change their subcellular localization upon defined stimuli, which has been linked to dynamic changes of the nuclear PIP pool [123,173,174].

Besides a general nuclear presence, it is more and more emerging that different metabolic enzymes might be recruited to specific chromatin regions, for example via interaction with transcription factors [175–180]. This has been proposed to modulate the local metabolite concentration of genomic microdomains, thereby establishing local hubs of metabolite production and chromatin regulation [181]. The recent discovery of phase separated systems in the cell nucleus that seem to establish localized hubs of concentrated enzymes and regulation further supports such idea [160].

Perspective

Clear linkage among cellular state, metabolism, chromatin status, and epigenetics has been established over the last years [182–185]. While several central metabolites have been extensively studied in this context and in different model systems [4–13], we deduce from our discussion of less common metabolites and their effects on chromatin signaling that the full extent of this connection cannot yet be comprehended.

First, there is a plethora of options where metabolites that might affect chromatin could originate (see Figure 2). Besides primary and secondary metabolism, this includes molecules that are 'by-products' of classical biosynthesis and degradation pathways. At present, there are, however, only limited experimental schemes that can identify and characterize metabolites with chromatin function. The most developed approach is the mass spectrometry characterization of covalent histone modifications [186–188]. Not surprisingly, the majority of uncommon metabolites that we discussed here form nonenzymatic or enzymatic histone PTMs. Identifying metabolites with direct chromatin effects or modulating the biology of chromatin regulators (Figure 1), however, is far less straightforward. In many cases, the chromatin biology of metabolites in these categories was discovered by accident or serendipity. For example, the essential role of IP4 in activation of class I HDACs only became apparent after purification and crystallization of corepressor complexes isolated from mammalian cell lines [82]. Identifying the chromatin functions of PIPs was based on educated guesses [111] and/or cumbersome purification schemes derived from activity assays [118]. We believe that many more metabolites with roles in chromatin biology will be discovered once systematic approaches for their identification and in different functional context become available.

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Second, the interfaces metabolites can have with chromatin systems are plenty and there are multiple levels where these might exert chromatin regulatory function (see Figure 1). Our discussion of less common metabolites in chromatin biology revealed that examples for most of the (theoretical) options for molecular working modes do exist. In this context, it needs to be acknowledged that not all metabolites we looked at have been studied to the same degree (see Table 1). The fact that for different metabolites such as PAR, IP, and PIP multiple modes and functions in chromatin regulation have been identified, makes us, nonetheless, hypothesize that many more links between already known as well as still to be described metabolites with roles in chromatin biology await discovery. This will, however, require new and additional experimental procedures. At present, the functional characterization of metabolites in question is mostly driven by *in vitro* characterization of chromatin effects and modulation of binding or enzymatic activities. The *in cellulo* and *in vivo* analysis of the biology of chromatin-regulating metabolites requires approaches that enable the perturbation, control, and quantification of cellular (better nuclear) levels of the molecules in question. Currently, this is limited to exogenous administration of metabolites or their precursors and/or manipulation of the enzyme system controlling their (sub-)cellular levels. Both approaches are, however, fully indirect which makes drawing solid conclusions challenging.

Third, we project that different metabolites and their multiple modes of chromatin function will open future avenues for intervention with important pathways of genome regulation. On one hand, the levels of chromatin-regulating metabolites might be changed in different disease states. Determining and controlling their levels could provide interesting avenues for diagnosis and therapy. On the other hand, the regulatory mode metabolites exert on chromatin modifiers and in particular via allosteric regulation might enable novel approaches for specifically interfering with histone-modifying enzymes, chromatin remodelers, and histone modification-binding proteins.

There are clearly many things to be discovered about the interplay of metabolites and chromatin, and we are looking forward to new findings in this exciting research area in the near future.

Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

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Abbreviations

AAR, *O*-acetyl-ADP-ribose; ALC1, amplified in liver cancer 1; ATP, adenosine triphosphate; BASP1, brain acid soluble protein 1; CENP_A, centromere protein A; EZH2, enhancer of zeste homolog 2; GSH, glutathione; HDAC, histone deacetylase; H3K9me3, histone H3 lysine 9 trimethylation; ING2, inhibitor of growth protein-2; IP, inositol polyphosphate; IP3, inositol 1,4,5-trisphosphate; IP4, inositol 1,4,5,6 tetrakisphosphate; IP5, inositol 1,3,4,5,6 pentakisphosphate; IP6, inositol 1,2,3,4,5,6 hexakisphosphate; IP6K1, inositol hexakisphosphate kinase 1; IP7, 5-diphosphoinositol pentakisphosphate; JMJD2C, Jumonji domain containing 2C; Lpcat1, lysophosphatidylcholine acyltransferase; NAD^+, nicotinamide adenine dinucleotide; OGA, O-GlcNAcase; OGT, O-GlcNAc transferase; O-GlcNAc, O-linked N-acetylglucosamine; PAR, poly-ADP-ribose; PARP, PAR polymerase; PHD, plant homeodomain; PHF8, PHD finger protein 8; PIP, phosphatidylinositol phosphate; PTM, post-translational modification; SAH, S-adenosylhomocysteine; SAM, S-adenosylmethionine; SIR, silent information regulator; SphK2, sphingosine kinase 2; SWI/SNF , switch/sucrose non-fermentable; S1P , sphingosine-1-phosphate; TCA, tricarboxylic acid; TET, ten eleven translocation; TTD, tandem tudor domain; UDP-GlcNAc, uridine diphosphate N-acetylglucosamine; UHRF1, ubiquitin-like with PHD and RING finger domains 1; 3-DG, 3-deoxyglucosone; 4-ONE, 4-oxo-2-nonenal.

References

1 Luger, K., Mäder, A.W., Richmond, R.K., Sargent, D.F. and Richmond, T.J. (1997) Crystal structure of the nucleosome core particle at 2.8 A resolution. *Nature* **389**, 251–260, https://doi.org/10.1038/38444

2 Chan, J.C. and Maze, I. (2020) Nothing Is yet set in (hi)stone: novel post-translational modifications regulating chromatin function. *Trends Biochem. Sci.* **45**, 829–844, https://doi.org/10.1016/j.tibs.2020.05.009

3 Fischle, W., Wang, Y. and Allis, C.D. (2003) Histone and chromatin cross-talk. *Curr. Opin. Cell Biol.* **15**, 172–183, https://doi.org/10.1016/S0955-0674(03)00013-9

4 Dai, Z., Ramesh, V. and Locasale, J.W. (2020) The evolving metabolic landscape of chromatin biology and epigenetics. *Nat. Rev. Genet.* **21**, 737–753, https://doi.org/10.1038/s41576-020-0270-8
5 Rabhi, N., Hannou, S.A., Froguel, P. and Annicotte, J.S. (2017) Cofactors as metabolic sensors driving cell adaptation in physiology and disease. *Front. Endocrinol.* **8**, 304, https://doi.org/10.3389/fendo.2017.00304
6 Berger, S.L. and Sassone-Corsi, P. (2016) Metabolic signaling to chromatin. *Cold Spring Harb. Perspect. Biol.* **8**, 1–23, https://doi.org/10.1101/cshperspect.a019463
7 Gao, T., Diaz-Hirashi, Z. and Verdeguer, F. (2018) Metabolic signaling into chromatin modifications in the regulation of gene expression. *Int. J. Mol. Sci.* **19**, 4108, https://doi.org/10.3390/ijms19124108
8 Janke, R., Dodson, A.E. and Rine, J. (2015) Metabolism and epigenetics. *Annu. Rev. Cell Dev. Biol.* **31**, 473–496, https://doi.org/10.1146/annurev-cellbio-100814-125544
9 Wong, C.C., Qian, Y. and Yu, J. (2017) Interplay between epigenetics and metabolism in oncogenesis: mechanisms and therapeutic approaches. *Oncogene* **36**, 3359–3374, https://doi.org/10.1038/onc.2016.485
10 Diehl, K.L. and Muir, T.W. (2020) Chromatin as a key consumer in the metabolite economy. *Nat. Chem. Biol.* **16**, 620–629, https://doi.org/10.1038/s41589-020-0517-x
11 Li, X., Egervari, G., Wang, Y., Berger, S.L. and Lu, Z. (2018) Regulation of chromatin and gene expression by metabolic enzymes and metabolites. *Nat. Rev. Mol. Cell Biol.* **19**, 563–578, https://doi.org/10.1038/s41580-018-0029-7
12 Boon, R., Silveira, G.G. and Mostoslavsky, R. (2020) Nuclear metabolism and the regulation of the epigenome. *Nat. Metab.* **2**, 1190–1203, https://doi.org/10.1038/s42255-020-00285-4
13 Sabari, B.R., Zhang, D., Allis, C.D. and Zhao, Y. (2017) Metabolic regulation of gene expression through histone acylations. *Nat. Rev. Mol. Cell Biol.* **18**, 90–101, https://doi.org/10.1038/nrm.2016.140
14 Zheng, Q., Maksimovic, I., Upad, A. and David, Y. (2020) Non-enzymatic covalent modifications: a new link between metabolism and epigenetics. *Protein Cell* **11**, 401–416, https://doi.org/10.1007/s13238-020-00722-w
15 Magistretti, P.J. and Allaman, I. (2018) Lactate in the brain: from metabolic end-product to signalling molecule. *Nat. Rev. Neurosci.* **19**, 235–249, https://doi.org/10.1038/nrn.2018.19
16 Latham, T., Mackay, L., Sproul, D., Karim, M., Culley, J., Harrison, D.J. et al. (2012) Lactate, a product of glycolytic metabolism, inhibits histone deacetylase activity and promotes changes in gene expression. *Nucleic Acids Res.* **40**, 4794–4803, https://doi.org/10.1093/nar/gks066
17 Zhang, Z., Tan, M., Xie, Z., Dai, L., Chen, Y. and Zhao, Y. (2011) Identification of lysine succinylation as a new post-translational modification. *Nat. Chem. Biol.* **7**, 58–63, https://doi.org/10.1038/nchembio.495
18 Yu, J., Chai, P., Xie, M., Ge, S., Ruan, J., Fan, X. et al. (2021) Histone lactylation drives oncogenesis by facilitating m6A reader protein YTHDF2 expression in ocular melanoma. *Genome Biol.* **22**, 85, https://doi.org/10.1186/s13059-021-02308-z
19 Cui, H., Xie, N., Banerjee, S., Ge, J., Jiang, D., Dey, T. et al. (2021) Lung myofibroblasts promote macrophage profibrotic activity through lactate-induced histone lactylation. *Am. J. Respir. Cell Mol.* **64**, 115–125, https://doi.org/10.1165/rcmb.2020-0360OC
20 Li, L., Chen, K., Wang, T., Wu, Y., Xing, G., Chen, M. et al. (2020) Glis1 facilitates induction of pluripotency via an epigenome–metabolome–epigenome signalling cascade. *Nat. Metab.* **2**, 882–892, https://doi.org/10.1038/s42255-020-0267-9
21 Carey, B.W., Finley, L.W.S., Cross, J.R., Allis, C.D. and Thompson, C.B. (2015) Intracellular α-ketoglutarate maintains the pluripotency of embryonic stem cells. *Nature* **518**, 413–416, https://doi.org/10.1038/nature13981
22 Bénit, P., Letouzé, E., Rak, M., Aubry, L., Burnichon, N., Favier, J. et al. (2014) Unsuspected task for an old team: succinate, fumarate and other Krebs cycle acids in metabolic remodeling. *Biochim. Biophys. Acta Bioenerg.* **1837**, 1330–1337, https://doi.org/10.1016/j.bbabio.2014.03.013
23 Lin, H., Su, X. and He, B. (2012) Protein lysine acylation and cysteine succination by intermediates of energy metabolism. *ACS Chem. Biol.* **7**, 947–960, https://doi.org/10.1021/cb3001793
24 Wagner, G.R., Bhatt, D.P., O'Connell, T.M., Thompson, J.W., Dubois, L.G., Backos, D.S. et al. (2017) A class of reactive acyl-CoA species reveals the non-enzymatic origins of protein acylation. *Cell Metab.* **25**, 823–837, https://doi.org/10.1016/j.cmet.2017.03.006
25 Zhang, D., Tang, Z., Huang, H., Zhou, G., Cui, C., Weng, Y. et al. (2019) Metabolic regulation of gene expression by histone lactylation. *Nature* **574**, 575–580, https://doi.org/10.1038/s41586-019-1678-1
26 Park, J., Chen, Y., Tishkoff, D.X., Peng, C., Tan, M., Dai, L. et al. (2013) SIRT5-mediated lysine desuccinylation impacts diverse metabolic pathways. *Mol. Cell* **50**, 919–930, https://doi.org/10.1016/j.molcel.2013.06.001
27 Vogelauer, M., Krall, A.S., McBrian, M.A., Li, J.-Y. and Kurdistani, S.K. (2012) Stimulation of histone deacetylase activity by metabolites of intermediary metabolism. *J. Biol. Chem.* **287**, 32006–32016, https://doi.org/10.1074/jbc.M112.362467
28 Xie, Z., Dai, J., Dai, L., Tan, M., Cheng, Z., Wu, Y. et al. (2012) Lysine succinylation and lysine malonylation in histones. *Mol. Cell. Proteomics* **11**, 100–107, https://doi.org/10.1074/mcp.M111.015875
29 Saatchi, F. and Kirchmaier, A.L. (2019) Tolerance of DNA replication stress is promoted by fumarate through modulation of histone demethylation and enhancement of replicative intermediate processing in Saccharomyces cerevisiae. *Genetics* **212**, 631–654, https://doi.org/10.1534/genetics.119.302238
30 Blatnik, M., Thorpe, S.R. and Baynes, J.W. (2008) Succination of proteins by fumarate. *Ann. N.Y. Acad. Sci.* **1126**, 272–275, https://doi.org/10.1196/annals.1433.047
31 Zheng, Q., Omans, N.D., Leicher, R., Osunsade, A., Agustinus, A.S., Finkin-Groner, E. et al. (2019) Reversible histone glycation is associated with disease-related changes in chromatin architecture. *Nat. Commun.* **10**, 1289, https://doi.org/10.1038/s41467-019-09192-z
32 Galligan, J.J., Wepy, J.A., Streeter, M.D., Kingsley, P.J., Mitchener, M.M., Wauchope, O.R. et al. (2018) Methylglyoxal-derived posttranslational arginine modifications are abundant histone marks. *Proc. Natl. Acad. Sci. U.S.A.* **115**, 9228–9233, https://doi.org/10.1073/pnas.1802901115

33 Ashraf, J.M., Ahmad, S., Rabbani, G., Hasan, Q., Jan, A.T., Lee, E.J. et al. (2015) 3-Deoxyglucosone: a potential glycating agent accountable for structural alteration in H3 histone protein through generation of different AGEs. *PLoS ONE* **10**, e0116804, https://doi.org/10.1371/journal.pone.0116804

34 Ashraf, J.M., Abdullah, S.M.S., Ahmad, S., Fatma, S., Baig, M.H., Iqbal, J. et al. (2017) Prevalence of autoantibodies against 3-DG-glycated H2A protein in type 2 diabetes. *Biochemistry (Mosc.)* **82**, 579–586, https://doi.org/10.1134/S0006297917050066

35 Hassa, P.O., Haenni, S.S., Elser, M. and Hottiger, M.O. (2006) Nuclear ADP-ribosylation reactions in mammalian cells: where are we today and where are we going? *Microbiol. Mol. Biol. Rev.* **70**, 789–829, https://doi.org/10.1128/MMBR.00040-05

36 Tong, L. and Denu, J.M. (2010) Function and metabolism of sirtuin metabolite O-acetyl-ADP-ribose. *Biochim. Biophys. Acta Proteins Proteom.* **1804**, 1617–1625, https://doi.org/10.1016/j.bbapap.2010.02.007

37 Tong, L., Lee, S. and Denu, J.M. (2009) Hydrolase regulates NAD+ metabolites and modulates cellular redox. *J. Biol. Chem.* **284**, 11256–11266, https://doi.org/10.1074/jbc.M809790200

38 Wang, S.-H., Lee, S.-P., Tung, S.-Y., Tsai, S.-P., Tsai, H.-C., Shen, H.-H. et al. (2019) Stabilization of Sir3 interactions by an epigenetic metabolic small molecule, O-acetyl-ADP-ribose, on yeast SIR-nucleosome silent heterochromatin. *Arch. Biochem. Biophys.* **671**, 167–174, https://doi.org/10.1016/j.abb.2019.07.005

39 Tung, S.-Y., Wang, S.-H., Lee, S.-P., Tsai, S.-P., Shen, H.-H., Chen, F.-J. et al. (2017) Modulations of SIR-nucleosome interactions of reconstructed yeast silent pre-heterochromatin by O-acetyl-ADP-ribose and magnesium. *Mol. Biol. Cell* **28**, 381–386, https://doi.org/10.1091/mbc.e16-06-0359

40 Tung, S.-Y., Hong, J.-Y., Walz, T., Moazed, D. and Liou, G.-G. (2012) Chromatin affinity-precipitation using a small metabolic molecule: its application to analysis of O-acetyl-ADP-ribose. *Cell. Mol. Life Sci.* **69**, 641–650, https://doi.org/10.1007/s00018-011-0771-x

41 Vaquero, A., Scher, M., Lee, D., Erdjument-Bromage, H., Tempst, P. and Reinberg, D. (2004) Human SIRT1 interacts with histone H1 and promotes formation of facultative heterochromatin. *Mol. Cell* **16**, 93–105, https://doi.org/10.1016/j.molcel.2004.08.031

42 Kustatscher, G., Hothorn, M., Pugieux, C., Scheffzek, K. and Ladurner, A.G. (2005) Splicing regulates NAD metabolite binding to histone macroH2A. *Nat. Struct. Mol. Biol.* **12**, 624–625, https://doi.org/10.1038/nsmb956

43 Timinszky, G., Till, S., Hassa, P.O., Hothorn, M., Kustatscher, G., Nijmeijer, B. et al. (2009) A macrodomain-containing histone rearranges chromatin upon sensing PARP1 activation. *Nat. Struct. Mol. Biol.* **16**, 923–929, https://doi.org/10.1038/nsmb.1664

44 Novikov, L., Park, J.W., Chen, H., Klerman, H., Jalloh, A.S. and Gamble, M.J. (2011) QKI-mediated alternative splicing of the histone variant macroH2A1 regulates cancer cell proliferation. *Mol. Cell. Biol.* **31**, 4244–4255, https://doi.org/10.1128/MCB.05244-11

45 Till, S. and Ladurner, A.G. (2009) Sensing NAD metabolites through macro domains. *Front. Biosci.* **14**, 3246–3258, https://doi.org/10.2741/3448

46 Ouararhni, K., Hadj-Slimane, R., Ait-Si-Ali, S., Robin, P., Mietton, F., Harel-Bellan, A. et al. (2006) The histone variant mH2A1.1 interferes with transcription by down-regulating PARP-1 enzymatic activity. *Genes Dev.* **20**, 3324–3336, https://doi.org/10.1101/gad.396106

47 Borra, M.T., O'Neill, F.J., Jackson, M.D., Marshall, B., Verdin, E., Foltz, K.R. et al. (2002) Conserved enzymatic production and biological effect of O-acetyl-ADP-ribose by silent information regulator 2-like NAD+-dependent deacetylases. *J. Biol. Chem.* **277**, 12632–12641, https://doi.org/10.1074/jbc.M111830200

48 Karlberg, T., Langelier, M.-F., Pascal, J.M. and Schüler, H. (2013) Structural biology of the writers, readers, and erasers in mono- and poly(ADP-ribose) mediated signaling. *Mol. Aspects Med.* **34**, 1088–1108, https://doi.org/10.1016/j.mam.2013.02.002

49 Comstock, L.R. and Denu, J.M. (2007) Synthesis and biochemical evaluation of O-acetyl-ADP-ribose and N-acetyl analogs. *Org. Biomol. Chem.* **5**, 3087, https://doi.org/10.1039/b710231c

50 Dvorakova, M., Nencka, R., Dejmek, M., Zbornikova, E., Brezinova, A., Pribylova, M. et al. (2013) Synthesis of alkylcarbonate analogs of O-acetyl-ADP-ribose. *Org. Biomol. Chem.* **11**, 5702, https://doi.org/10.1039/c3ob41016a

51 Rack, J.G.M., Liu, Q., Zorzini, V., Voorneveld, J., Ariza, A., Honarmand Ebrahimi, K. et al. (2021) Mechanistic insights into the three steps of poly(ADP-ribosylation) reversal. *Nat. Commun.* **12**, 4581, https://doi.org/10.1038/s41467-021-24723-3

52 Hottiger, M.O., Hassa, P.O., Luscher, B., Schuler, H. and Koch-Nolte, F. (2010) Toward a unified nomenclature for mammalian ADP-ribosyltransferases. *Trends Biochem. Sci.* **35**, 208–219, https://doi.org/10.1016/j.tibs.2009.12.003

53 Gibson, B.A. and Kraus, W.L. (2012) New insights into the molecular and cellular functions of poly(ADP-ribose) and PARPs. *Nat. Rev. Mol. Cell Biol.* **13**, 411–424, https://doi.org/10.1038/nrm3376

54 Miwa, M., Kanai, M., Kondo, T., Hoshino, H., Ishihara, K. and Sugimura, T. (1981) Inhibitors of poly(ADP-ribose) polymerase enhance unscheduled DNA synthesis in human peripheral lymphocytes. *Biochem. Biophys. Res. Commun.* **100**, 463–470, https://doi.org/10.1016/S0006-291X(81)80119-2

55 Duan, Y., Du, A., Gu, J., Duan, G., Wang, C., Gui, X. et al. (2019) PARylation regulates stress granule dynamics, phase separation, and neurotoxicity of disease-related RNA-binding proteins. *Cell Res.* **29**, 233–247, https://doi.org/10.1038/s41422-019-0141-z

56 Engbrecht, M. and Mangerich, A. (2020) The nucleolus and PARP1 in cancer biology. *Cancers* **12**, 1813, https://doi.org/10.3390/cancers12071813

57 Compton, D.A. (2005) Mitosis: PARty time in the spindle. *Curr. Biol.* **15**, R178–R179, https://doi.org/10.1016/j.cub.2005.02.047

58 Ahel, D., Horejsi, Z., Wiechens, N., Polo, S.E., Garcia-Wilson, E., Ahel, I. et al. (2009) Poly(ADP-ribose)-dependent regulation of DNA repair by the chromatin remodeling enzyme ALC1. *Science* **325**, 1240–1243, https://doi.org/10.1126/science.1177321

59 Schreiber, V., Dantzer, F., Ame, J.-C. and de Murcia, G. (2006) Poly(ADP-ribose): novel functions for an old molecule. *Nat. Rev. Mol. Cell Biol.* **7**, 517–528, https://doi.org/10.1038/nrm1963

60 Gottschalk, A.J., Timinszky, G., Kong, S.E., Jin, J., Cai, Y., Swanson, S.K. et al. (2009) Poly(ADP-ribosyl)ation directs recruitment and activation of an ATP-dependent chromatin remodeler. *Proc. Natl. Acad. Sci. U.S.A.* **106**, 13770–13774, https://doi.org/10.1073/pnas.0906920106

61 Malanga, M. and Althaus, F.R. (2005) The role of poly(ADP-ribose) in the DNA damage signaling network. *Biochem. Cell Biol.* **83**, 354–364, https://doi.org/10.1139/o05-038

62 Lehmann, L.C., Hewitt, G., Aibara, S., Leitner, A., Marklund, E., Maslen, S.L. et al. (2017) Mechanistic insights into autoinhibition of the oncogenic chromatin remodeler ALC1. *Mol. Cell* **68**, 847–859, https://doi.org/10.1016/j.molcel.2017.10.017

63 Singh, H.R., Nardozza, A.P., Möller, I.R., Knobloch, G., Kistemaker, H.A.V., Hassler, M. et al. (2017) A poly-ADP-ribose trigger releases the auto-inhibition of a chromatin remodeling oncogene. *Mol. Cell* **68**, 860–871, https://doi.org/10.1016/j.molcel.2017.11.019
64 Lehmann, L.C., Bacic, L., Hewitt, G., Brackmann, K., Sabantsev, A., Gaullier, G. et al. (2020) Mechanistic insights into regulation of the ALC1 remodeler by the nucleosome acidic patch. *Cell Rep.* **33**, 108529, https://doi.org/10.1016/j.celrep.2020.108529
65 Wang, Y., Wang, Y., Wang, N., You, L., Long, F., Shao, C. et al. (2019) Poly(ADP-ribose) polymerase 1/2 inhibitors decrease the ubiquitination of ALC1 mediated by CHFR in breast cancer. *Oncol. Rep.* **42**, 1467–1474, https://doi.org/10.3892/or.2019.7242
66 Heale, J.T., Ball, A.R., Schmiesing, J.A., Kim, J.-S., Kong, X., Zhou, S. et al. (2006) Condensin I interacts with the PARP-1-XRCC1 complex and functions in DNA single-strand break repair. *Mol. Cell* **21**, 837–848, https://doi.org/10.1016/j.molcel.2006.01.036
67 Tulin, A. and Spradling, A. (2003) Chromatin loosening by poly(ADP)-ribose polymerase (PARP) at Drosophila puff loci. *Science* **299**, 560–562, https://doi.org/10.1126/science.1078764
68 Fu, W., Yao, H., Bütepage, M., Zhao, Q., Lüscher, B. and Li, J. (2021) The search for inhibitors of macrodomains for targeting the readers and erasers of mono-ADP-ribosylation. *Drug Discov. Today* **26**, 2547–2558, https://doi.org/10.1016/j.drudis.2021.05.007
69 Thomas, C., Ji, Y., Lodhi, N., Kotova, E., Pinnola, A.D., Golovine, K. et al. (2016) Non-NAD-like poly(ADP-ribose) polymerase-1 inhibitors effectively eliminate cancer in vivo. *EBioMedicine* **13**, 90–98, https://doi.org/10.1016/j.ebiom.2016.10.001
70 Yang, X. and Qian, K. (2017) Protein O-GlcNAcylation: emerging mechanisms and functions. *Nat. Rev. Mol. Cell Biol.* **18**, 452–465, https://doi.org/10.1038/nrm.2017.22
71 Sakabe, K., Wang, Z. and Hart, G.W. (2010) β-N-acetylglucosamine (O-GlcNAc) is part of the histone code. *Proc. Natl. Acad. Sci. U.S.A.* **107**, 19915–19920, https://doi.org/10.1073/pnas.1009023107
72 Zhang, S., Roche, K., Nasheuer, H.-P. and Lowndes, N.F. (2011) Modification of histones by sugar β-N-acetylglucosamine (GlcNAc) occurs on multiple residues, including histone H3 serine 10, and is cell cycle-regulated. *J. Biol. Chem.* **286**, 37483–37495, https://doi.org/10.1074/jbc.M111.284885
73 Hanover, J.A., Krause, M.W. and Love, D.C. (2012) Linking metabolism to epigenetics through O-GlcNAcylation. *Nat. Rev. Mol. Cell Biol.* **13**, 312–321, https://doi.org/10.1038/nrm3334
74 Hart, G.W., Slawson, C., Ramirez-Correa, G. and Lagerlof, O. (2011) Cross talk between O-GlcNAcylation and phosphorylation: roles in signaling, transcription, and chronic disease. *Annu. Rev. Biochem.* **80**, 825–858, https://doi.org/10.1146/annurev-biochem-060608-102511
75 Wu, D., Cai, Y. and Jin, J. (2017) Potential coordination role between O-GlcNAcylation and epigenetics. *Protein Cell* **8**, 713–723, https://doi.org/10.1007/s13238-017-0416-4
76 Kronlage, M., Dewenter, M., Grosso, J., Fleming, T., Oehl, U., Lehmann, L.H. et al. (2019) O-GlcNAcylation of histone deacetylase 4 protects the diabetic heart from failure. *Circulation* **140**, 580–594, https://doi.org/10.1161/CIRCULATIONAHA.117.031942
77 Lo, P.-W., Shie, J.-J., Chen, C.-H., Wu, C.-Y., Hsu, T.-L. and Wong, C.-H. (2018) O-GlcNAcylation regulates the stability and enzymatic activity of the histone methyltransferase EZH2. *Proc. Natl. Acad. Sci. U.S.A.* **115**, 7302–7307, https://doi.org/10.1073/pnas.1801850115
78 Lee, J.-Y., Kim, Y., Park, J. and Kim, S. (2012) Inositol polyphosphate multikinase signaling in the regulation of metabolism. *Ann. N.Y. Acad. Sci.* **1271**, 68, https://doi.org/10.1111/j.1749-6632.2012.06725.x
79 Lee, B., Park, S.J., Hong, S., Kim, K. and Kim, S. (2021) Inositol polyphosphate multikinase signaling: multifaceted functions in health and disease. *Mol. Cell* **44**, 187–194, https://doi.org/10.14348/molcells.2021.0045
80 Shen, X., Xiao, H., Ranallo, R., Wu, W. and Wu, C. (2003) Modulation of ATP-dependent chromatin-remodeling complexes by inositol polyphosphates. *Science* **299**, 112–114, https://doi.org/10.1126/science.1078068
81 Steger, D.J., Haswell, E.S., Miller, A.L., Wente, S.R. and OòShea, E.K. (2003) Regulation of chromatin remodeling by inositol polyphosphates. *Science* **299**, 114–116, https://doi.org/10.1126/science.1078062
82 Watson, P.J., Fairall, L., Santos, G.M. and Schwabe, J.W. (2012) Structure of HDAC3 bound to co-repressor and inositol tetraphosphate. *Nature* **481**, 335–340, https://doi.org/10.1038/nature10728
83 Millard, C.J., Watson, P.J., Celardo, I., Gordiyenko, Y., Cowley, S.M., Robinson, C.V. et al. (2013) Class I HDACs share a common mechanism of regulation by inositol phosphates. *Mol. Cell* **51**, 57–67, https://doi.org/10.1016/j.molcel.2013.05.020
84 Millard, C.J., Watson, P.J., Fairall, L. and Schwabe, J.W. (2013) An evolving understanding of nuclear receptor coregulator proteins. *J. Mol. Endocrinol.* **51**, T23–T36, https://doi.org/10.1530/JME-13-0227
85 Millard, C.J., Fairall, L. and Schwabe, J.W.R. (2014) Towards an understanding of the structure and function of MTA1. *Cancer Metastasis Rev.* **33**, 857–867, https://doi.org/10.1007/s10555-014-9513-5
86 Itoh, T., Fairall, L., Muskett, F.W., Milano, C.P., Watson, P.J., Arnaudo, N. et al. (2015) Structural and functional characterization of a cell cycle associated HDAC1/2 complex reveals the structural basis for complex assembly and nucleosome targeting. *Nucleic Acids Res.* **43**, 2033–2044, https://doi.org/10.1093/nar/gkv068
87 Millard, C.J., Varma, N., Saleh, A., Morris, K., Watson, P.J., Bottrill, A.R. et al. (2016) The structure of the core NuRD repression complex provides insights into its interaction with chromatin. *eLife* **5**, e13941, https://doi.org/10.7554/eLife.13941
88 Li, J., Guo, C., Rood, C. and Zhang, J. (2021) A C-terminus-dependent conformational change is required for HDAC3 activation by nuclear receptor corepressors. *J. Biol. Chem.* **297**, 101192, https://doi.org/10.1016/j.jbc.2021.101192
89 Marcum, R.D. and Radhakrishnan, I. (2019) Inositol phosphates and core subunits of the Sin3L/Rpd3L histone deacetylase (HDAC) complex up-regulate deacetylase activity. *J. Biol. Chem.* **294**, 13928–13938, https://doi.org/10.1074/jbc.RA119.009780
90 Watson, P.J., Millard, C.J., Riley, A.M., Robertson, N.S., Wright, L.C., Godage, H.Y. et al. (2016) Insights into the activation mechanism of class I HDAC complexes by inositol phosphates. *Nat. Commun.* **7**, 11262, https://doi.org/10.1038/ncomms11262
91 Burton, A., Azevedo, C., Andreassi, C., Riccio, A. and Saiardi, A. (2013) Inositol pyrophosphates regulate JMJD2C-dependent histone demethylation. *Proc. Natl. Acad. Sci. U.S.A.* **110**, 18970–18975, https://doi.org/10.1073/pnas.1309699110
92 Goldstein, J.L. and Brown, M.S. (1990) Regulation of the mevalonate pathway. *Nature* **343**, 425–430, https://doi.org/10.1038/343425a0

93 Erickson, S.K., Da Vison, A.M. and Gould, R.G. (1975) Correlation of rat liver chromatin-bound free and esterified cholesterol with the circadian rhythm of cholesterol biosynthesis in the rat. *Biochim. Biophys. Acta Mol. Cell. Biol. Lipids* **409**, 59–67, https://doi.org/10.1016/0005-2760(75)90080-6

94 Regenass-Klotz, M. and Heiniger, H.-J. (1984) Specific binding of cholesterol to chromatin prepared from mouse spleen cells. *Biochem. Cell Biol.* **62**, 94–99, https://doi.org/10.1139/o84-014

95 Zaina, S., Døssing, K.B.V., Lindholm, M.W. and Lund, G. (2005) Chromatin modification by lipids and lipoprotein components: an initiating event in atherogenesis? *Curr. Opin. Lipidol.* **16**, 549–553, https://doi.org/10.1097/01.mol.0000180165.70077.ee

96 Santos, G.M., Teles, K., Ribeiro, C. and Fernandes, V. (2018) Fat nucleosome: role of lipids on chromatin. *FASEB J.* **32**, 29–34, https://doi.org/10.1096/fasebj.2018.32.1˙supplement.523.7

97 Silva, I.T.G., Fernandes, V., Souza, C., Treptow, W. and Santos, G.M. (2017) Biophysical studies of cholesterol effects on chromatin. *J. Lipid Res.* **58**, 934–940, https://doi.org/10.1194/jlr.M074997

98 Loats, A.E., Carrera, S., Fleming, A.F., Roberts, A.R.E., Sherrard, A., Toska, E. et al. (2021) Cholesterol is required for transcriptional repression by BASP1. *Proc. Natl. Acad. Sci. U.S.A.* **118**, e2101671118, https://doi.org/10.1073/pnas.2101671118

99 Fiume, R., Keune, W.J., Faenza, I., Bultsma, Y., Ramazzotti, G., Jones, D.R. et al. (2012) Nuclear phosphoinositides: location, regulation and function. *Subcell. Biochem.* **59**, 335–361, https://doi.org/10.1007/978-94-007-3015-1˙11

100 Lemmon, M.A. (2008) Membrane recognition by phospholipid-binding domains. *Nat. Rev. Mol. Cell Biol.* **9**, 99–111, https://doi.org/10.1038/nrm2328

101 Rose, H.G. and Frenster, J.H. (1965) Composition and metabolism of lipids within repressed and active chromatin of interphase lymphocytes. *Biochim. Biophys. Acta* **106**, 577–591, https://doi.org/10.1016/0005-2760(65)90073-1

102 Maraldi, N.M., Capitani, S., Caramelli, E., Cocco, L., Barnabei, O. and Manzoli, F.A. (1984) Conformational changes of nuclear chromatin related to phospholipid induced modifications of the template availability. *Adv. Enzyme Regul.* **22**, 447–464, https://doi.org/10.1016/0065-2571(84)90025-6

103 La Cour, L.F., Chayen, J. and Gahan, P.S. (1958) Evidence for lipid material in chromosomes. *Exp. Cell Res.* **14**, 469–485, https://doi.org/10.1016/0014-4827(58)90155-1

104 Capitani, S., Cocco, L., Maraldi, N.M., Papa, S. and Manzoli, F.A. (1986) Effect of phospholipids on transcription and ribonucleoprotein processing in isolated nuclei. *Adv. Enzyme Regul.* **25**, 425–438, https://doi.org/10.1016/0065-2571(86)90027-0

105 Kuvichkin, V.V. (2002) DNA-lipid interactions in vitro and in vivo. *Bioelectrochemistry* **58**, 3–12, https://doi.org/10.1016/S1567-5394(02)00123-8

106 Rando, O.J., Zhao, K., Janmey, P. and Crabtree, G.R. (2002) Phosphatidylinositol-dependent actin filament binding by the SWI/SNF-like BAF chromatin remodeling complex. *Proc. Natl. Acad. Sci. U.S.A.* **99**, 2824–2829, https://doi.org/10.1073/pnas.032662899

107 Zhao, K., Wang, W., Rando, O.J., Xue, Y., Swiderek, K., Kuo, A. et al. (1998) Rapid and phosphoinositol-dependent binding of the SWI/SNF-like BAF complex to chromatin after T lymphocyte receptor signaling. *Cell* **95**, 625–636, https://doi.org/10.1016/S0092-8674(00)81633-5

108 Memedula, S. and Belmont, A.S. (2003) Sequential recruitment of HAT and SWI/SNF components to condensed chromatin by VP16. *Curr. Biol.* **13**, 241–246, https://doi.org/10.1016/S0960-9822(03)00048-4

109 Yu, H., Fukami, K., Watanabe, Y., Ozaki, C. and Takenawa, T. (1998) Phosphatidylinositol 4,5-bisphosphate reverses the inhibition of RNA transcription caused by histone H1. *Eur. J. Biochem.* **251**, 281–287, https://doi.org/10.1046/j.1432-1327.1998.2510281.x

110 Ulicna, L., Kalendova, A., Kalasova, I., Vacik, T. and Hozák, P. (2018) PIP2 epigenetically represses rRNA genes transcription interacting with PHF8. *Biochimi. Biophys. Acta. Mol. Cell Biol. Lipids* **1863**, 266–275, https://doi.org/10.1016/j.bbalip.2017.12.008

111 Gozani, O., Karuman, P., Jones, D.R., Ivanov, D., Cha, J., Lugovskoy, A.A. et al. (2003) The PHD finger of the chromatin-associated protein ING2 functions as a nuclear phosphoinositide receptor. *Cell* **114**, 99–111, https://doi.org/10.1016/S0092-8674(03)00480-X

112 Bua, D.J. and Binda, O. (2009) The return of the INGs, histone mark sensors and phospholipid signaling effectors. *Curr. Drug Targets* **10**, 418–431, https://doi.org/10.2174/138945009788185112

113 Zou, J., Marjanovic, J., Kisseleva, M.V., Wilson, M. and Majerus, P.W. (2007) Type I phosphatidylinositol-4,5-bisphosphate 4-phosphatase regulates stress-induced apoptosis. *Proc. Natl. Acad. Sci. U.S.A.* **104**, 16834–16839, https://doi.org/10.1073/pnas.0708189104

114 Bua, D.J., Martin, G.M., Binda, O. and Gozani, O. (2013) Nuclear phosphatidylinositol-5-phosphate regulates ING2 stability at discrete chromatin targets in response to DNA damage. *Sci. Rep.* **3**, 2137, https://doi.org/10.1038/srep02137

115 Ndamukong, I., Jones, D.R., Lapko, H., Divecha, N. and Avramova, Z. (2010) Phosphatidylinositol 5-phosphate links dehydration stress to the activity of ARABIDOPSIS TRITHORAX-LIKE factor ATX1. *PLoS ONE* **5**, e13396, https://doi.org/10.1371/journal.pone.0013396

116 Stijf-Bultsma, Y., Sommer, L., Tauber, M., Baalbaki, M., Giardoglou, P., Jones, D.R. et al. (2015) The basal transcription complex component TAF3 transduces changes in nuclear phosphoinositides into transcriptional output. *Mol. Cell* **58**, 453–467, https://doi.org/10.1016/j.molcel.2015.03.009

117 Bronner, C., Krifa, M. and Mousli, M. (2013) Increasing role of UHRF1 in the reading and inheritance of the epigenetic code as well as in tumorigenesis. *Biochem. Pharmacol.* **86**, 1643–1649, https://doi.org/10.1016/j.bcp.2013.10.002

118 Gelato, K.A., Tauber, M., Ong, M.S., Winter, S., Hiragami-Hamada, K., Sindlinger, J. et al. (2014) Accessibility of different histone H3-binding domains of UHRF1 is allosterically regulated by phosphatidylinositol 5-phosphate. *Mol. Cell* **54**, 905–919, https://doi.org/10.1016/j.molcel.2014.04.004

119 Tauber, M., Kreuz, S., Lemak, A., Mandal, P., Yerkesh, Z., Veluchamy, A. et al. (2020) Alternative splicing and allosteric regulation modulate the chromatin binding of UHRF1. *Nucleic Acids Res.* **48**, 7728–7747, https://doi.org/10.1093/nar/gkaa520

120 Ahn, J.Y., Liu, X., Cheng, D., Peng, J., Chan, P.K., Wade, P.A. et al. (2005) Nucleophosmin/B23, a nuclear PI(3,4,5)P(3) receptor, mediates the antiapoptotic actions of NGF by inhibiting CAD. *Mol. Cell* **18**, 435–445, https://doi.org/10.1016/j.molcel.2005.04.010

121 Wang, Y.H., Hariharan, A., Bastianello, G., Toyama, Y., Shivashankar, G.V., Foiani, M. et al. (2017) DNA damage causes rapid accumulation of phosphoinositides for ATR signaling. *Nat. Commun.* **8**, 2118, https://doi.org/10.1038/s41467-017-01805-9

122 Viiri, K.M., Korkeamaki, H., Kukkonen, M.K., Nieminen, L.K., Lindfors, K., Peterson, P. et al. (2006) SAP30L interacts with members of the Sin3A corepressor complex and targets Sin3A to the nucleolus. *Nucleic Acids Res.* **34**, 3288–3298, https://doi.org/10.1093/nar/gkl401

123 Castano, E., Yildirim, S., Faberova, V., Krausova, A., Ulicna, L., Paprckova, D. et al. (2019) Nuclear phosphoinositides-versatile regulators of genome functions. *Cells* **8**, 649, https://doi.org/10.3390/cells8070649

124 Lewis, A.E., Sommer, L., Arntzen, M.O., Strahm, Y., Morrice, N.A., Divecha, N. et al. (2011) Identification of nuclear phosphatidylinositol 4,5-bisphosphate-interacting proteins by neomycin extraction. *Mol. Cell. Proteomics* **10**, M110.003376, https://doi.org/10.1074/mcp.M110.003376
125 Spiegel, S. and Milstien, S. (2007) Functions of the multifaceted family of sphingosine kinases and some close relatives. *J. Biol. Chem.* **282**, 2125–2129, https://doi.org/10.1074/jbc.R600028200
126 Hait, N.C., Allegood, J., Maceyka, M., Strub, G.M., Harikumar, K.B., Singh, S.K. et al. (2009) Regulation of histone acetylation in the nucleus by sphingosine-1-phosphate. *Science* **325**, 1254–1257, https://doi.org/10.1126/science.1176709
127 Yan, H., Yi, S., Zhuang, H., Wu, L., Wang, D. and Jiang, J. (2017) Sphingosine-1-phosphate ameliorates the cardiac hypertrophic response through inhibiting the activity of histone deacetylase-2. *Int. J. Mol. Med.* **41**, 1704–1714, https://doi.org/10.3892/ijmm.2017.3325
128 Schönfeld, P. and Wojtczak, L. (2016) Short- and medium-chain fatty acids in energy metabolism: the cellular perspective. *J. Lipid Res.* **57**, 943–954, https://doi.org/10.1194/jlr.R067629
129 Chamberlain, L.H. and Shipston, M.J. (2015) The physiology of protein S-acylation. *Physiol. Rev.* **95**, 341–376, https://doi.org/10.1152/physrev.00032.2014
130 Wilson, J.P., Raghavan, A.S., Yang, Y.-Y., Charron, G. and Hang, H.C. (2011) Proteomic analysis of fatty-acylated proteins in mammalian cells with chemical reporters reveals S-acylation of histone H3 variants. *Mol. Cell. Proteomics* **10**, M110.001198, https://doi.org/10.1074/mcp.M110.001198
131 Bischoff, R. and Schlüter, H. (2012) Amino acids: chemistry, functionality and selected non-enzymatic post-translational modifications. *J. Proteom.* **75**, 2275–2296, https://doi.org/10.1016/j.jprot.2012.01.041
132 Zou, C., Ellis, B.M., Smith, R.M., Chen, B.B., Zhao, Y. and Mallampalli, R.K. (2011) Acyl-CoA:lysophosphatidylcholine acyltransferase I (Lpcat1) catalyzes histone protein O-palmitoylation to regulate mRNA synthesis. *J. Biol. Chem.* **286**, 28019–28025, https://doi.org/10.1074/jbc.M111.253385
133 Pisoschi, A.M. and Pop, A. (2015) The role of antioxidants in the chemistry of oxidative stress: a review. *Eur. J. Med. Chem.* **97**, 55–74, https://doi.org/10.1016/j.ejmech.2015.04.040
134 Galligan, J.J., Rose, K.L., Beavers, W.N., Hill, S., Tallman, K.A., Tansey, W.P. et al. (2014) Stable histone adduction by 4-Oxo-2-nonenal: a potential link between oxidative stress and epigenetics. *J. Am. Chem. Soc.* **136**, 11864–11866, https://doi.org/10.1021/ja503604t
135 Jin, J., He, B., Zhang, X., Lin, H. and Wang, Y. (2016) SIRT2 reverses 4-oxononanoyl lysine modification on histones. *J. Am. Chem. Soc.* **138**, 12304–12307, https://doi.org/10.1021/jacs.6b04977
136 Tan, M., Peng, C., Anderson, K.A., Chhoy, P., Xie, Z., Dai, L. et al. (2014) Lysine glutarylation is a protein posttranslational modification regulated by SIRT5. *Cell Metab.* **19**, 605–617, https://doi.org/10.1016/j.cmet.2014.03.014
137 Bao, X., Liu, Z., Zhang, W., Gladysz, K., Fung, Y.M.E., Tian, G. et al. (2019) Glutarylation of histone H4 lysine 91 regulates chromatin dynamics. *Mol. Cell* **76**, 660–675, https://doi.org/10.1016/j.molcel.2019.08.018
138 Wang, Y.G., Guo, Y.R., Xing, D., Tao, Y.J. and Lu, Z. (2018) Supramolecular assembly of KAT2A with succinyl-CoA for histone succinylation. *Cell Discov.* **4**, 47, https://doi.org/10.1038/s41421-018-0048-8
139 Marczak, L., Sikora, M., Stobiecki, M. and Jakubowski, H. (2011) Analysis of site-specific N-homocysteinylation of human serum albumin in vitro and in vivo using MALDI-ToF and LC-MS/MS mass spectrometry. *J. Proteomics* **74**, 967–974, https://doi.org/10.1016/j.jprot.2011.01.021
140 Gurda, D., Handschuh, L., Kotkowiak, W. and Jakubowski, H. (2015) Homocysteine thiolactone and N-homocysteinylated protein induce pro-atherogenic changes in gene expression in human vascular endothelial cells. *Amino Acids* **47**, 1319–1339, https://doi.org/10.1007/s00726-015-1956-7
141 Xu, L., Chen, J., Gao, J., Yu, H. and Yang, P. (2015) Crosstalk of homocysteinylation, methylation and acetylation on histone H3. *Analyst* **140**, 3057–3063, https://doi.org/10.1039/C4AN02355B
142 Zhang, Q., Bai, B., Mei, X., Wan, C., Cao, H., Dan, L. et al. (2018) Elevated H3K79 homocysteinylation causes abnormal gene expression during neural development and subsequent neural tube defects. *Nat. Commun.* **9**, 3436, https://doi.org/10.1038/s41467-018-05451-7
143 García-Giménez, J.L., Olaso, G., Hake, S.B., Bönisch, C., Wiedemann, S.M., Markovic, J. et al. (2013) Histone H3 glutathionylation in proliferating mammalian cells destabilizes nucleosomal structure. *Antioxid. Redox Signal.* **19**, 1305–1320, https://doi.org/10.1089/ars.2012.5021
144 Pallardó, F.V., Markovic, J., García, J.L. and Viña, J. (2009) Role of nuclear glutathione as a key regulator of cell proliferation. *Mol. Aspects Med.* **30**, 77–85, https://doi.org/10.1016/j.mam.2009.01.001
145 Reyes, R., Rosado, A., Hernández, O. and Delgado, N.M. (1989) Heparin and glutathione: physiological decondensing agents of human sperm nuclei. *Gamete Res.* **23**, 39–47, https://doi.org/10.1002/mrd.1120230105
146 Scirè, A., Cianfruglia, L., Minnelli, C., Bartolini, D., Torquato, P., Principato, G. et al. (2019) Glutathione compartmentalization and its role in glutathionylation and other regulatory processes of cellular pathways. *Biofactors* **45**, 152–168, https://doi.org/10.1002/biof.1476
147 García-Giménez, J.L., Romá-Mateo, C., Pérez-Machado, G., Peiró-Chova, L. and Pallardó, F.V. (2017) Role of glutathione in the regulation of epigenetic mechanisms in disease. *Free Radic. Biol. Med.* **112**, 36–48, https://doi.org/10.1016/j.freeradbiomed.2017.07.008
148 Farrelly, L.A., Thompson, R.E., Zhao, S., Lepack, A.E., Lyu, Y., Bhanu, N.V. et al. (2019) Histone serotonylation is a permissive modification that enhances TFIID binding to H3K4me3. *Nature* **567**, 535–539, https://doi.org/10.1038/s41586-019-1024-7
149 Lepack, A.E., Werner, C.T., Stewart, A.F., Fulton, S.L., Zhong, P., Farrelly, L.A. et al. (2020) Dopaminylation of histone H3 in ventral tegmental area regulates cocaine seeking. *Science* **368**, 197–201, https://doi.org/10.1126/science.aaw8806
150 Mandal, S., Mandal, A., Johansson, H.E., Orjalo, A.V. and Park, M.H. (2013) Depletion of cellular polyamines, spermidine and spermine, causes a total arrest in translation and growth in mammalian cells. *Proc. Natl. Acad. Sci. U.S.A.* **110**, 2169–2174, https://doi.org/10.1073/pnas.1219002110
151 Madeo, F., Eisenberg, T., Pietrocola, F. and Kroemer, G. (2018) Spermidine in health and disease. *Science* **359**, eaan2788, https://doi.org/10.1126/science.aan2788
152 Pasini, A., Caldarera, C.M. and Giordano, E. (2014) Chromatin remodeling by polyamines and polyamine analogs. *Amino Acids* **46**, 595–603, https://doi.org/10.1007/s00726-013-1550-9

153 Ohishi, H., Odoko, M., Grzeskowiak, K., Hiyama, Y., Tsukamoto, K., Maezaki, N. et al. (2008) Polyamines stabilize left-handed Z-DNA: using X-ray crystallographic analysis, we have found a new type of polyamine (PA) that stabilizes left-handed Z-DNA. *Biochem. Biophys. Res. Commun.* **366**, 275–280, https://doi.org/10.1016/j.bbrc.2007.10.161

154 Pollard, K.J., Samuels, M.L., Crowley, K.A., Hansen, J.C. and Peterson, C.L. (1999) Functional interaction between GCN5 and polyamines: a new role for core histone acetylation. *EMBO J.* **18**, 5622–5633, https://doi.org/10.1093/emboj/18.20.5622

155 Burgio, G., Corona, D.F., Nicotra, C.M., Carruba, G. and Taibi, G. (2016) P/CAF-mediated spermidine acetylation regulates histone acetyltransferase activity. *J. Enzyme Inhib. Med. Chem.* **31**, 75–82, https://doi.org/10.1080/14756366.2016.1205045

156 Huang, Y., Marton, L.J., Woster, P.M. and Casero, R.A. (2009) Polyamine analogues targeting epigenetic gene regulation. *Essays Biochem.* **46**, 95–110, https://doi.org/10.1042/bse0460007

157 Cambronne, X.A., Stewart, M.L., Kim, D., Jones-Brunette, A.M., Morgan, R.K., Farrens, D.L. et al. (2016) Biosensor reveals multiple sources for mitochondrial NAD(+). *Science* **352**, 1474–1477, https://doi.org/10.1126/science.aad5168

158 Wente, S.R. and Rout, M.P. (2010) The nuclear pore complex and nuclear transport. *Cold Spring Harb. Perspect. Biol.* **2**, a000562, https://doi.org/10.1101/cshperspect.a000562

159 Boukouris, A.E., Zervopoulos, S.D. and Michelakis, E.D. (2016) Metabolic enzymes moonlighting in the nucleus: metabolic regulation of gene transcription. *Trends Biochem. Sci.* **41**, 712–730, https://doi.org/10.1016/j.tibs.2016.05.013

160 Boon, R. (2021) Metabolic fuel for epigenetic: nuclear production meets local consumption. *Front. Genet.* **12**, 768996, https://doi.org/10.3389/fgene.2021.768996

161 Suganuma, T. and Workman, J.L. (2018) Chromatin and metabolism. *Annu. Rev. Biochem.* **87**, 27–49, https://doi.org/10.1146/annurev-biochem-062917-012634

162 Greco, C.M., Cervantes, M., Fustin, J.M., Ito, K., Ceglia, N., Samad, M. et al. (2020) S-adenosyl-l-homocysteine hydrolase links methionine metabolism to the circadian clock and chromatin remodeling. *Sci. Adv.* **6**, eabc5629, https://doi.org/10.1126/sciadv.abc5629

163 Zhang, J.J., Fan, T.T., Mao, Y.Z., Hou, J.L., Wang, M., Zhang, M. et al. (2021) Nuclear dihydroxyacetone phosphate signals nutrient sufficiency and cell cycle phase to global histone acetylation. *Nat. Metab.* **3**, 859–875, https://doi.org/10.1038/s42255-021-00405-8

164 Ferriero, R., Nusco, E., De Cegli, R., Carissimo, A., Manco, G. and Brunetti-Pierri, N. (2018) Pyruvate dehydrogenase complex and lactate dehydrogenase are targets for therapy of acute liver failure. *J. Hepatol.* **69**, 325–335, https://doi.org/10.1016/j.jhep.2018.03.016

165 Nagaraj, R., Sharpley, M.S., Chi, F., Braas, D., Zhou, Y., Kim, R. et al. (2017) Nuclear localization of mitochondrial TCA cycle enzymes as a critical step in mammalian zygotic genome activation. *Cell* **168**, 210–223, e11., https://doi.org/10.1016/j.cell.2016.12.026

166 Boon, R., Kumar, M., Tricot, T., Elia, I., Ordovas, L., Jacobs, F. et al. (2020) Amino acid levels determine metabolism and CYP450 function of hepatocytes and hepatoma cell lines. *Nat. Commun.* **11**, 1393, https://doi.org/10.1038/s41467-020-15058-6

167 Cambronne, X.A. and Kraus, W.L. (2020) Location, location, location: compartmentalization of NAD(+) synthesis and functions in mammalian cells. *Trends Biochem. Sci.* **45**, 858–873, https://doi.org/10.1016/j.tibs.2020.05.010

168 Chi, T.H. and Crabtree, G.R. (2000) Perspectives: signal transduction. Inositol phosphates in the nucleus. *Science* **287**, 1937–1939, https://doi.org/10.1126/science.287.5460.1937

169 Monserrate, J.P. and York, J.D. (2010) Inositol phosphate synthesis and the nuclear processes they affect. *Curr. Opin. Cell Biol.* **22**, 365–373, https://doi.org/10.1016/j.ceb.2010.03.006

170 Wang, J., Mauvoisin, D., Martin, E., Atger, F., Galindo, A.N., Dayon, L. et al. (2017) Nuclear proteomics uncovers diurnal regulatory landscapes in mouse liver. *Cell Metab.* **25**, 102–117, https://doi.org/10.1016/j.cmet.2016.10.003

171 Barlow, C.A., Laishram, R.S. and Anderson, R.A. (2010) Nuclear phosphoinositides: a signaling enigma wrapped in a compartmental conundrum. *Trends Cell Biol.* **20**, 25–35, https://doi.org/10.1016/j.tcb.2009.09.009

172 Poli, A., Zaurito, A.E., Abdul-Hamid, S., Fiume, R., Faenza, I. and Divecha, N. (2019) Phosphatidylinositol 5 Phosphate (PI5P): from behind the scenes to the front (nuclear) stage. *Int. J. Mol. Sci.* **20**, 2080, https://doi.org/10.3390/ijms20092080

173 Fiume, R., Faenza, I., Sheth, B., Poli, A., Vidalle, M.C., Mazzetti, C. et al. (2019) Nuclear phosphoinositides: their regulation and roles in nuclear functions. *Int. J. Mol. Sci.* **20**, 2991, https://doi.org/10.3390/ijms20122991

174 Chen, M., Wen, T., Horn, H.T., Chandrahas, V.K., Thapa, N., Choi, S. et al. (2020) The nuclear phosphoinositide response to stress. *Cell Cycle* **19**, 268–289, https://doi.org/10.1080/15384101.2019.1711316

175 Katoh, Y., Ikura, T., Hoshikawa, Y., Tashiro, S., Ito, T., Ohta, M. et al. (2011) Methionine adenosyltransferase II serves as a transcriptional corepressor of Maf oncoprotein. *Mol. Cell* **41**, 554–566, https://doi.org/10.1016/j.molcel.2011.02.018

176 Wang, T., Yu, Q., Li, J., Hu, B., Zhao, Q., Ma, C. et al. (2017) O-GlcNAcylation of fumarase maintains tumour growth under glucose deficiency. *Nat. Cell Biol.* **19**, 833–843, https://doi.org/10.1038/ncb3562

177 Li, X., Yu, W., Qian, X., Xia, Y., Zheng, Y., Lee, J.H. et al. (2017) Nucleus-translocated ACSS2 promotes gene transcription for lysosomal biogenesis and autophagy. *Mol. Cell* **66**, 684–697, https://doi.org/10.1016/j.molcel.2017.04.026

178 Richard, A.J., Hang, H. and Stephens, J.M. (2017) Pyruvate dehydrogenase complex (PDC) subunits moonlight as interaction partners of phosphorylated STAT5 in adipocytes and adipose tissue. *J. Biol. Chem.* **292**, 19733–19742, https://doi.org/10.1074/jbc.M117.811794

179 Matsuda, S., Adachi, J., Ihara, M., Tanuma, N., Shima, H., Kakizuka, A. et al. (2016) Nuclear pyruvate kinase M2 complex serves as a transcriptional coactivator of arylhydrocarbon receptor. *Nucleic Acids Res.* **44**, 636–647, https://doi.org/10.1093/nar/gkv967

180 Li, S., Swanson, S.K., Gogol, M., Florens, L., Washburn, M.P., Workman, J.L. et al. (2015) Serine and SAM responsive complex SESAME regulates histone modification crosstalk by sensing cellular metabolism. *Mol. Cell* **60**, 408–421, https://doi.org/10.1016/j.molcel.2015.09.024

181 Katada, S., Imhof, A. and Sassone-Corsi, P. (2012) Connecting threads: epigenetics and metabolism. *Cell* **148**, 24–28, https://doi.org/10.1016/j.cell.2012.01.001

182 Etchegaray, J.P. and Mostoslavsky, R. (2016) Interplay between metabolism and epigenetics: a nuclear adaptation to environmental changes. *Mol. Cell* **62**, 695–711, https://doi.org/10.1016/j.molcel.2016.05.029

183 Tzika, E., Dreker, T. and Imhof, A. (2018) Epigenetics and metabolism in health and disease. *Front. Genet.* **9**, 361, https://doi.org/10.3389/fgene.2018.00361

184 Reid, M.A., Dai, Z. and Locasale, J.W. (2017) The impact of cellular metabolism on chromatin dynamics and epigenetics. *Nat. Cell Biol.* **19**, 1298–1306, https://doi.org/10.1038/ncb3629

185 Montellier, E. and Gaucher, J. (2019) Targeting the interplay between metabolism and epigenetics in cancer. *Curr. Opin. Oncol.* **31**, 92–99, https://doi.org/10.1097/CCO.0000000000000501

186 Su, X., Ren, C. and Freitas, M.A. (2007) Mass spectrometry-based strategies for characterization of histones and their post-translational modifications. *Expert. Rev. Proteomics* **4**, 211–225, https://doi.org/10.1586/14789450.4.2.211

187 Zheng, Y., Huang, X. and Kelleher, N.L. (2016) Epiproteomics: quantitative analysis of histone marks and codes by mass spectrometry. *Curr. Opin. Chem. Biol.* **33**, 142–150, https://doi.org/10.1016/j.cbpa.2016.06.007

188 Thomas, S.P., Haws, S.A., Borth, L.E. and Denu, J.M. (2020) A practical guide for analysis of histone post-translational modifications by mass spectrometry: best practices and pitfalls. *Methods* **184**, 53–60, https://doi.org/10.1016/j.ymeth.2019.12.001