Trends in Biochemical Sciences

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Forum

Does chromatin function as a metabolite reservoir?

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Alternative histone acylations integrate gene expression with cellular metabolic states. Recent measurements of cellular acyl-coenzyme A (acyl-CoA) pools highlight the potential that histone post-translational modifications (PTMs) contribute directly to the regulation of metabolite pools. A metabolite-centric view throws new light onto roles and evolution of histone PTMs.

The many roles of histone PTMs

Nuclear genomes are organised by nucleosomes composed of the histone core around which the DNA winds in almost two turns (Figure 1). Chromatin organisation and function, such as gene regulation, is controlled by a multitude of histone PTMs that mostly occur on histone tails protruding from the nucleosomes (N-terminal for all histones and C-terminal for H1, H2A, and H2B) [1]. Histone PTMs control chromatin structure by changing the charge of histones affecting interaction with DNA (e.g., acetylation) and by creating binding sites for chromatin remodelling factors [1]. Research of the past decade has underscored the close link between histone PTMs and cellular metabolic states [1–3]. As histones are some of the most abundant cellular proteins and are highly modified, they have the potential to serve as a reservoir for metabolites such as short chain carboxylic acids like acetate through histone modifications [2] (Figure 1).

Here, we discuss observations consistent with the idea that chromatin serves as metabolite reservoir, namely: (i) new insights into alternative histone acylations and cellular acyl-CoA levels; (ii) the important role of histone deacetylation in cellular states related to nutrient deprivation; and (iii) chromatin acetylation in prokaryotes.

Acyl-CoA pools and histone acylations are interlinked

Acyl-CoAs, composed of an acyl group (such a acetyl) linked by a thioester bond to cofactor coenzyme A, are critical for acyl transfer in lipid and amino acid synthesis and degradation, glycolysis, and the tricarboxylic acid cycle [2–5]. As acyl donors, acyl-CoA molecules have the potential to exert signalling functions through PTMs of proteins, especially histones, leading to acetylation, propionylation, and crotonylation, among many others [1,3] (Figure 1). The metabolism of acyl-CoAs is compartmentalised and enzymes that produce various acyl-CoA metabolites are also present in the nucleus, highlighting the role of acyl-CoA in connecting cell metabolism to chromatin regulation (reviewed in [3], see [6] as an example). Histone acylations are closely linked to the metabolic state of cells as the Michaelis constant K_M of acyl transferases for acyl-CoAs are in the range of the acyl-CoA cellular concentrations. Therefore, there is a correlation between concentrations of different acyl-CoAs and the global abundance of their respective histone acylation with ensuing changes in gene expression [1,3]. For example, the analysis of the yeast metabolic cycle (YMC) illustrates how alternative histone acylations, acetylation, or crotonylation at lysine 9 of histone H3, link cellular metabolism to gene regulation [7]. In the YMC, cyclical alterations between high oxygen and low oxygen consumption (LOC) are mirrored by cyclical global changes in histone crotonylation versus acetylation, with histone crotonylation promoted by fatty acid metabolism (which generates crotonyl-CoA) at the LOC stage [7]. Another example illustrating the axis between specific histone acylation and metabolism was uncovered using metabolite quantitation by liquid chromatography–mass spectrometry [4]. Here, the authors demonstrated that nuclear propionyl-CoA derives from isoleucine catabolism and promotes histone propionylation, a mark linked to active gene expression at specific histone lysine residues.

Histone acetylation and other histone acylations are dynamic with half-lives of the order of minutes and deac(et)ylation generates short chain carboxylic acids, such as acetate. The acetate can then be converted back to acetyl-CoA (Figure 2), and this holds true also for many other acyl groups [2,3]. Thus, chromatin can be rapidly loaded and unloaded with acyl groups.

Progress in accurately measuring subcellular acyl-CoA pools allows one to gauge how these compare to the number of modifiable lysine residues on histones [4,5]. This indicates that the number of acetate molecules that could be released from chromatin potentially exceeds the number of acetyl-CoA molecules in the cell by orders of magnitude at a given time (Figure 1). Thus, histone acetylation has the potential to act as an acetate reservoir, where the acetate can be released by deacetylases, for example, on starvation, to regenerate acetyl-CoA for energy production and anabolism [2] (Figure 2). Furthermore, recent papers provide evidence that acetate from histones released by histone deacetylases can be recycled for histone modifications of other loci and other histone lysine residues on metabolic shifts, which in turn, is connected to changes in gene expression [6,8]. The recycling of acyl moieties potentially holds true for alternative histone acylations, such as propionylation or crotonylation.

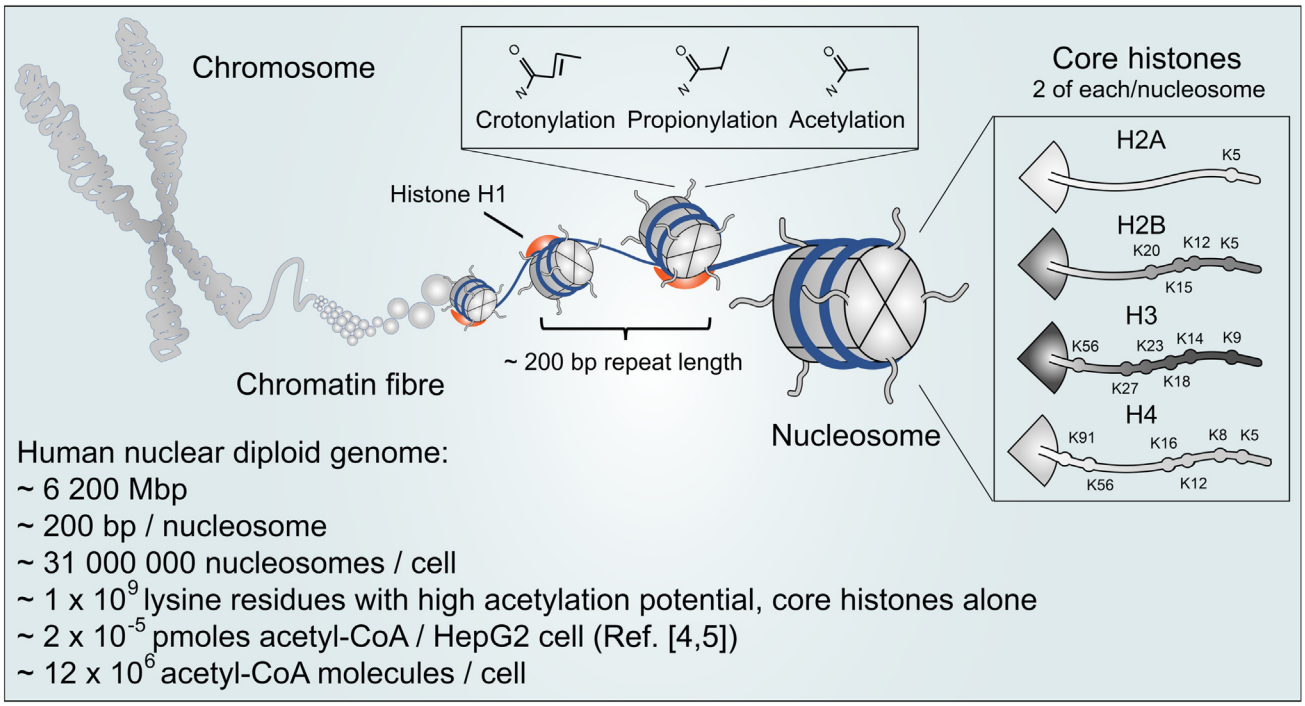

Figure 1. Chromatin has the potential to act as a reservoir for acyl groups. We compared the numbers of lysine residues of histones that can be modified by acylation, for example, acetylation, with the number of measured total acetyl-CoA molecules in a cell. Lysine residues (K) that are well documented to be acetylated are indicated in the insert. The percentage of histone residues that are acetylated varies depending on residue, cell type, growth condition etc., but can be in the double-digit numbers [15]. Histone H1 has multiple lysine residues at both the C and N termini that are acetylated, but precise positions are less documented compared with those in the core histones. Histone acylations described here as examples are illustrated on top. References used [4,5].

Therefore, one would expect that global histone acetylation drops on starvation and that histone deacetylases are important for viability during starvation. Studies on quiescence in yeast indicate that these predictions hold true.

Role of histone deacetylation during entry into quiescence

Quiescence is a reversible metabolic state in which cells temporarily abandon the cell cycle, exhibit a decrease in cell size, and shut down transcription and translation of proteins, all leading to greater stress resistance. Several models show that changes in histone PTMs occur with quiescence and are linked to a more compacted chromatin state [9]. The McKnight *et al.* analysis of chromatin changes in budding yeast *Saccharomyces cerevisiae* during the transition to quiescence highlights the importance of histone deacetylation in this process [10]. There are two distinct phases in budding yeast transition from growth phase to quiescence after consumption of the medium's glucose. The first phase called diauxic shift consists of the stress response and shutdown of the transcriptional machinery in response to carbon source limitation, and the second phase, quiescence itself, consists of loss of global histone acetylation and increase in occupation of promoter regions by nucleosomes. The quiescence process depends on the highly conserved Rpd3 histone deacetylase: in the diauxic shift, Rpd3 targets genes related to ribosome biosynthesis and function; during quiescence, it represses about half of the known genes of *S. cerevisiae* [10]. As a consequence of Rpd3 function, an overall dramatic reduction in histone acetylation occurs after entry into the quiescence state and mRNA levels decrease 30-fold relative to logarithmic growth [10]. Remarkably, deletion of *RPD3* leads to a significant loss of viability of the cells entering quiescence [10]. While these findings indicate a role of global histone deacetylation to promote correct gene regulation for entry into quiescence, they are also consistent with the role of bulk histone deacetylation to promote viability of the cells by providing acetate to sustain metabolism during the metabolic shift. Importantly, these two functions are not mutually exclusive.

Histone-like protein acetylation and cellular metabolism in prokaryotes

One might hypothesise that during evolution a metabolism-linked role of chromatin modification may have preceded or developed in parallel to the established signalling role. If chromatin has a role as

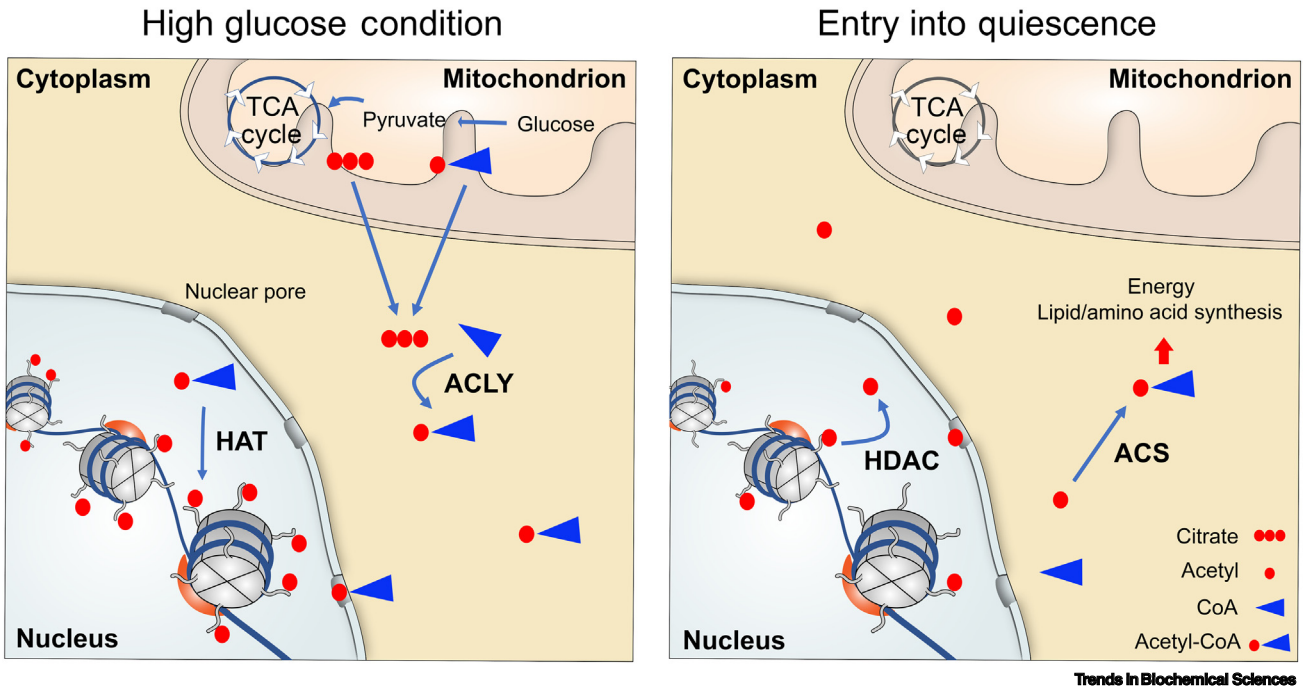

Figure 2. Entry into quiescence is accompanied by histone deacetylase (HDAC)-mediated release of acetate from chromatin in budding yeast. In nutrient-rich conditions (left panel), glucose feeds into the TCA (Krebs) cycle in the mitochondria where it is converted into citrate which is exported into the cytosol. There, the citrate provides the acetyl groups for the enzyme ATP citrate lyase (ACLY) to generate acetyl-CoA, which, in turn, is used to mediate histone acetylation by histone acetyltransferases (HATs). On entry into quiescence, HDACs, such as Rpd3, release acetate from histones, which can be used for energy production or anabolic reactions, such as amino acid or fatty acid synthesis, after being joined with CoA to generate acetyl-CoA by an acetyl-CoA synthetase (ACS) enzyme.

metabolite reservoir, then this function may also be found in prokaryotes where chromatin is organised by abundant proteins, too. Indeed, chromatin proteins that are functionally (eubacteria) and evolutionary (archaea) related to histones are found to be acetylated [11,12]. Noteworthy is the identification of lysine deacetylase Bkd1 that is able to shape the acetylome of the whooping cough agent *Bordetella pertussis,* including of chromatin associated histone-like proteins [13]. While deletion of Bkd1 affected virulence in a mouse model to some degree, the authors conclude that the lysine deacetylase and N-ε-lysine acetylation primarily modulate the general metabolism of *B. pertussis* [13]. Thus, at least in some prokaryotes, abundant histone-like proteins are modified by acetylation with a link to metabolism, suggesting that a potential reservoir function of chromatin may also exist in prokaryotes.

Concluding remarks

Testing a reservoir function of chromatin for metabolites will be challenging, just alone because of the difficulty to trace and follow metabolites; for example, through heavy isotope labelling. Furthermore, not only have steady-state levels of metabolites to be considered, but also fluxes. Disentangling indirect effects via gene regulation from direct effects on metabolites will be a formidable challenge. Furthermore, most work in this context has been performed in yeast, and future studies should test a reservoir function of histone modifications in higher eukaryotes. Yet, the recent discovery that histones themselves have oxidoreductive functions highlight the importance to consider the nucleus a metabolic organelle [14]. Considering a function of chromatin as a metabolite reservoir has the potential to throw new light onto old facts and will reveal additional roles of histone modification.

Acknowledgments

We dedicate this piece to the memory of Jeffrey N. McKnight (1984–2020). We thank Marco Aurélio Ramirez Vinolo for support and discussion, Karoline Luger, Alexey Soshnev, and Jose C. Reyes for advice on the figures, Vladimir Teif for advice on nucleosome spacing in human cells and Joaquín de Navascués, Vladimir Teif, Charalampos Rallis, and N. Radu Zabet for comments that improved the manuscript. P.D.V.-W.'s work is supported by the University of Essex, a grant from N3CRs (NC/W001047/1), and a FAPESP São Paulo Excellence Chairs special scheme (2019/16113-5); V.D.N. and D. R.d.P. by direct fellowships from FAPESP (2021/00393-9, 2021/00398-0); and N.V.P.A. by a postdoctoral fellowship from FAPESP (2021/05269-4).

Declaration of interests

No interests are declared.

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https://doi.org/10.1016/j.tibs.2022.03.016

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