Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Cell Biology

Dietary control of chromatin

Zhiguang Huang[1], Ling Cai[2] and Benjamin P Tu[1]

Organisms must be able to rapidly alter gene expression in response to changes in their nutrient environment. This review summarizes evidence that epigenetic modifications of chromatin depend on particular metabolites of intermediary metabolism, enabling the facile regulation of gene expression in tune with metabolic state. Nutritional or dietary control of chromatin is an often-overlooked, yet fundamental regulatory mechanism directly linked to human physiology. Nutrient-sensitive epigenetic marks are dynamic, suggesting rapid turnover, and may have functions beyond the regulation of gene transcription, including pH regulation and as carbon sources in cancer cells.

Addresses
[1] Department of Biochemistry, UT Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390, USA
[2] Children's Medical Center Research Institute, UT Southwestern Medical Center, 6000 Harry Hines Boulevard, Dallas, TX 75390, USA

Corresponding author: Tu, Benjamin P (Benjamin.Tu@UTSouthwestern.edu)

Current Opinion in Cell Biology 2015, **34**:69–74

This review comes from a themed issue on **Cell nucleus**

Edited by **Karsten Weis** and **Katherine L Wilson**

http://dx.doi.org/10.1016/j.ceb.2015.05.004

Rapid changes in gene expression in response to nutrient shifts

Nutritional influences on chromatin and gene regulation are readily observed in single-celled eukaryotes such as the budding yeast, which frequently encounter a wide variety of growth environments. Changes in nutrient availability promptly impact the expression of genes that regulate cell growth or survival. For example, glucose repletion to a starved yeast culture was found to rapidly induce massive changes in gene expression on a global scale [1,2]. Studies of yeast chemostat cultures growing under various nutrient limitations also revealed rapid changes in gene transcript levels, with certain groups of genes correlating either positively or negatively with growth rate [3,4]. These adjustments in mRNA abundance occurred very quickly in response to changes in growth rate. Moreover, continuous yeast cultures can also exhibit robust oscillations in oxygen consumption that are accompanied by periodic changes in transcript levels of the majority of genes. These oscillations had periods as short as 40 min [5], or on the time scale of hours [6]. In each scenario, the dynamic regulation of gene expression involves metabolic and nutritional influences on chromatin and chromatin-associated processes [7,8].

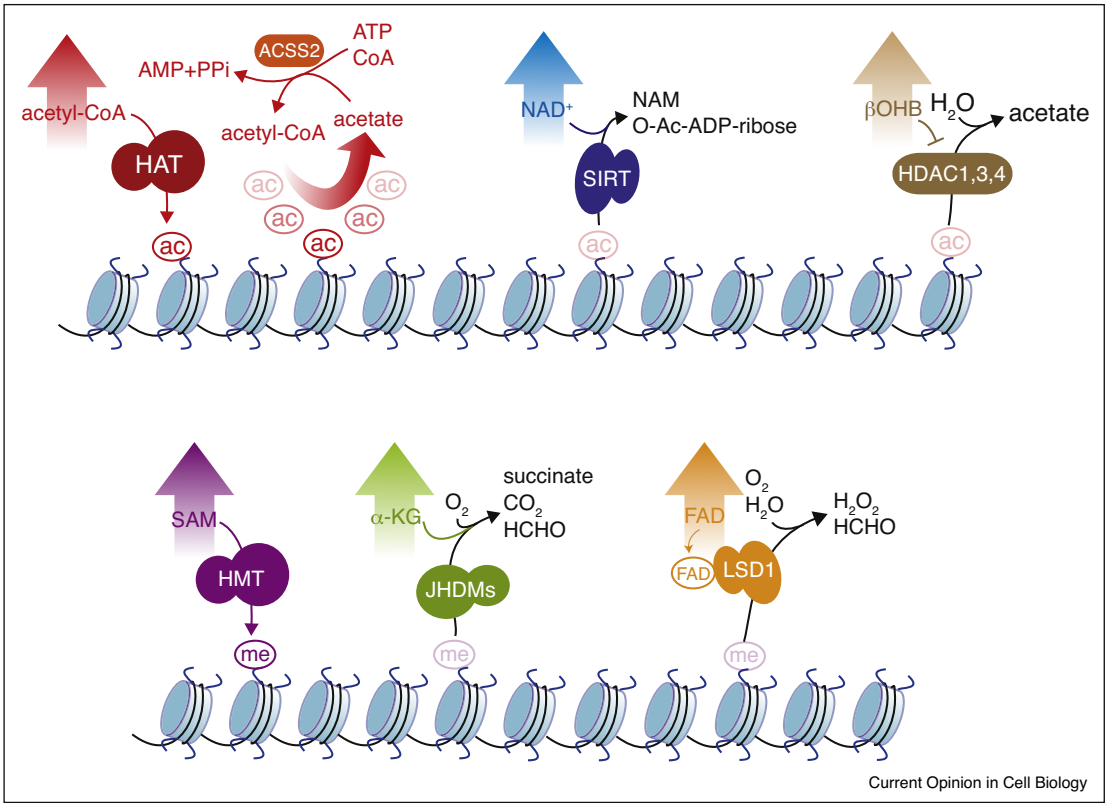
How can changes in the nutrient environment influence gene transcription so rapidly? Here we discuss emerging evidence that particular histone modifications depend on metabolites, either as cofactors or substrates, providing mechanisms by which fluctuating levels of specific metabolites directly and rapidly influence gene activity. As such, these metabolites may be viewed as 'gatekeepers of chromatin', enabling modulation of the chromatin landscape in response to key nutritional cues [9].

Dynamic histone acetylation and deacetylation

Histones are acetylated by a group of enzymes called histone acetyltransferases (HATs), which use acetyl-CoA as the acetyl donor. These enzymes are also known as lysine acetyltransferases (KATs) since they can also modify other (non-histone) proteins. Acetylation of the ε-amino group of histone tail lysyl residues neutralizes their positive charge and promotes a more 'relaxed' chromatin structure, in which DNA is more accessible for binding of various factors. The general view is that histone acetylation is controlled by transcription factor-mediated recruitment of HATs to gene promoters and regulatory regions [10,11]. However, numerous studies provide compelling evidence that histone acetylation is also regulated by fluctuations in the concentration of acetyl-CoA [7,12–14]. For example, various acetyltransferase enzymes have K_m values in the low μM range [15,16], within the range of estimated intracellular concentrations of acetyl-CoA [13]. Studies of the yeast metabolic cycle (YMC) revealed changes in histone acetylation predominantly at genes involved in cell growth, precisely in phase with increased cellular levels of acetyl-CoA [13]. These observations showed how the regulation of cell growth genes is coupled to the level of acetyl-CoA, a key indicator of metabolic state (see Figure 1).

Histones and other proteins are deacetylated by enzymes known as histone deacetylases (HDACs) or lysine deacetylases (KDACs). Histone deacetylation typically results in a more condensed chromatin structure that correlates with repressed transcription. HDACs fall into two general groups, based on their catalytic mechanism [17,18]. Most HDACs (classes I, II, and IV) use activated water as the nucleophile, whereas class III HDACs (also

Figure 1



Dynamic regulation of histone acetylation and methylation. *Top*: dynamic regulation of histone acetylation and deacetylation. Histone acetylation can be stimulated by intracellular levels of acetyl-CoA through HATs. Histone deacetylation can produce acetate. Acetate can be converted into acetyl-CoA by the acetyl-CoA synthetase enzyme ACSS2. Acetylated histones can be deacetylated by sirtuins that use NAD^+ as cofactor, or by other HDACs that use activated water as nucleophile. The activity of HDACs (1,3,4) is inhibited by the ketone body βOHB. *Bottom*: dynamic regulation of histone methylation and demethylation. Histone methylation can be stimulated by intracellular levels of SAM through HMTs. Methylated histones can be demethylated by JHDMs dependent on α-KG, or by LSD1/amine oxidases dependent on FAD. *Abbreviations*: HAT, histone acetyltransferase; ACSS2, acyl-CoA synthetase short-chain family member 2; SIRT, Sirtuin; NAD^+, nicotinamide adenine dinucleotide; NAM, nicotinamide; HDAC, histone deacetylase; βOHB, β-hydroxybutyrate; ac, acetylation; SAM, S-adenosylmethionine; αKG, α-ketoglutarate; JHDM, Jumonji C-terminal-domain-containing histone demethylase; LSD1, lysine (K)-specific demethylase 1; FAD, flavin adenine dinucleotide.

known as 'sirtuins') use a cofactor, nicotinamide adenine dinucleotide (NAD^+), to catalyze deacetylation [19] (Figure 1). NAD^+ is a key electron carrier in the oxidation of hydrocarbon fuels. The discovery of sirtuins as NAD^+-dependent deacylases suggested a link between cellular levels of NAD^+ and the regulation of chromatin and gene expression [20,21]. Indeed, dietary restriction is proposed to promote health and longevity in model organisms by activating sirtuins [20,21]. Interestingly the other group of HDACs (water-as-nucleophile) may also be coupled to metabolism, since the ketone body β-hydroxybutryate (βOHB) is reported to function as an endogenous inhibitor of these enzymes [22••] (Figure 1). The concentration of βOHB in blood can reach low millimolar concentrations during fasting [23,24]. Furthermore, βOHB inhibits HDAC1 and HDAC3 (both class I) and HDAC4 (class II) *in vitro* with an IC_{50} of 2–5 mM, suggesting HDAC activity may be physiologically inhibited by βOHB during fasting conditions. This mechanism may extend to our gut microbiome since butyrate, a product of bacterial fermentation, is proposed to inhibit HDAC activity in colonocytes [25].

Histones are so abundant that their acetylation and deacetylation may impact beyond chromatin. Each histone octamer, occupying ~146 bp of DNA, represents nearly 20 acetylatable lysines. Moreover, these acetyl moieties have very short half-lives, on the order of ~2–3 min [26,27]. These considerations led to the realization that substantial amounts of acetate might be 'stored' on histones and liberated by deacetylation [28,29••]. Released acetate could be re-captured by acetyl-CoA synthetase enzymes, which convert acetate to acetyl-CoA in an ATP-dependent reaction. Supporting this idea, there is strong evidence that acetate functions as an important carbon source for cancer cells, and is used to synthesize acetyl-CoA in challenging growth environments [29••,30,31,32]. In two models of hepatocellular carcinoma, adult mice