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Mini-Review

When histones are under glucose starvation

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Under nutritional stress, cells undergo metabolic rewiring that results in changes of various cellular processes that include gene transcription. This transcriptional regulation requires dynamic chromatin remodeling that involves histone post-translational modifications. There are several histone marks that may act as switches upon starvation for stress-response pathways.

Keywords. AMPK; histone modification; histone PTMs; metabolic rewiring; nutritional stress; stress-response

1. Introduction

Nutritional stress is a common event for most organisms. Upon stress, cells undergo metabolic rewiring to adapt to the new environmental conditions and to promote cell survival. This metabolic reprogramming incurs a massive change of various cellular processes that include gene transcription. This transcriptional regulation requires extensive chromatin remodeling as DNA is packed with histones into repressive nucleosome structures. These dynamic chromatin structure changes involve various post-translational modifications (PTMs) of histones that alter their interactions with other proteins as well as the innate interaction between DNA and histones. Indeed, many reports now describe histone post-translational modifications that change under conditions of nutritional stress and correlate with specific transcription changes that maintain cellular energy homeostasis. In this review, we focus on histone marks that may serve as switches to turn on stress-response pathways upon glucose starvation.

2. AMPK as the core regulator of global histone modification

Adenosine 5′ monophosphate-activated protein kinase (AMPK) functions as the key modulator for responses that occur upon nutritional stress (reviewed in Herzig and Shaw 2018). AMPK phosphorylates many transcription factors including PGC-1α, FOXO family proteins, and CREB, which are all involved in induction of the stress response (Cantó and Auwerx 2010). As reviewed recently by Gongol *et al.* (2018), AMPK can affect various global histone PTMs. It regulates global histone acetylation by increasing the available acetyl coenzyme A (acetyl-CoA) pool. Upon glucose deprivation, AMPK phosphorylates serine 659 of acetyl-CoA synthetase short-chain family member 2 (ACSS2), which converts acetate to acetyl-CoA. ACSS2 S659 phosphorylation then leads to nuclear localization of ACSS2, producing nuclear acetyl-CoA for histone acetyltransferases (HATs) (Li *et al.* 2017). AMPK increases acetyl-CoA indirectly by an inhibitory phosphorylation of acetyl-CoA carboxylase (ACC), an enzyme that normally catalyzes the conversion of acetyl-CoA to malonyl-CoA (Ha *et al.* 1994). AMPK also promotes histone acetylation by

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regulation of histone deacetylase (HDAC) function. Phosphorylation of Class IIa HDACs (HDAC4, 5, and 7) by AMPK results in their translocating out of the nucleus (Mihaylova *et al*. 2011), and phosphorylation of ACC by AMPK indirectly increases β-hydroxybutyrate via ketogenesis and inhibits class I and II HDACs (Zhou *et al.* 2001; Shimazu *et al*. 2013). AMPK modulates histone methylation by activating lysine demethylases KDM5 and LSD1 for H3 lysine 4 tri-methylation (Eissenberg and Shilatifard 2010) and inhibiting PRC2 via EZH2 phosphorylation for a H3 lysine 27 tri-methylation decrease (Tang *et al.* 2018). AMPK can also regulate histone methylation by adjusting levels of metabolites. For example, repressive phosphorylation of fumarase by AMPK leads to an increase of fumarate, which inhibits histone demethylase activity of KDM2A (Wang *et al.* 2017; Li *et al.* 2018; Schvartzman *et al.* 2017).

3. Histone phosphorylation by AMPK

As noted above, AMPK can impact global histone modifications by regulating the level of available cofactors or by regulating histone modifiers. In addition, several specific histone PTMs are directly regulated by AMPK activity. In budding yeast *S. cerevisiae,* Lo *et al.* showed that the yeast AMPK homolog Snf1 kinase phosphorylates histone H3 at serine 10 (H3pS10) in the promoter of the *INO1* gene (Lo *et al.* 2001). Both recombinant GST-Snf1 and Snf1 purified from yeast cells have H3pS10 kinase activity on free histones and on chicken mono-nucleosomes *in vitro*. Snf1 regulates transcription of the *INO1* gene for cell growth upon nutritional stress. Under stress conditions, transcription of *INO1* and H3pS10 both decreased in a *snf1* deletion strain. In addition, *INO1* transcription was reduced upon mutation of H3 serine 10 to alanine. Using Chromatin Immunoprecipitation (ChIP), the authors demonstrated that H3pS10 and H3 K14 acetylation (H3K14Ac) are impaired in the *INO1* promoter region in a *snf1* deletion mutant, suggesting that H3K14Ac is a downstream modification of H3pS10 that correlates with *INO1* activation upon nutritional stress.

In mammals, Bungard *et al.* reported that AMPK activity is required for histone H2B S36 phosphorylation (H2BpS36) (Bungard *et al.* 2010). The authors showed that AMPK is activated by various stresses including glucose starvation. Upon glucose starvation, AMPK localizes at promoters and activates p53-responsive genes, which are important for cell survival upon metabolic stress. AMPK purified from ampk α-/- MEF cells expressing ectopic myc-AMPK under low glucose was able to phosphorylate recombinant human H2B at serine 36 (H2BpS36), while a myc-tagged AMPK catalytic mutant was not able to phosphorylate H2B. H2BpS36 increased within 5 min of glycolytic inhibitor 2-Deoxyglucose (2-DG) treatment, but this increase was impaired in ampk α-/- mutant MEF cells and in MEF cells mutant for the AMPK upstream activator lkb1 -/-. H2B serine 36 appears to be critical for the interaction between AMPK and H2B as myc-AMPK associated with FLAG-H2B in 293T cells but not with H2BS36A upon treatment with the AMPK agonist 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR). ChIP analysis revealed that H2BpS36 and AMPK are associated with the promoter and transcribed region of AMPK-dependent genes, such as *cpt1c* and *p21*, upon 2-DG treatment. Upon glucose starvation, MEFs expressing ectopic H2BS36A displayed reduced viability and reduced induction of AMPK target genes, *p21*, *cpt1c*, *reprimo*, and *cyclinG* compared to those expressing ectopic wild-type H2B. Furthermore, the Pol II ChIP signal was reduced in the transcribed region of *cpt1c* upon glucose starvation in the H2BS36A expressing cells, suggesting a role for H2BpS36 in AMPK-dependent gene transcription.

4. Autophagy-specific histone arginine methylation by CARM1

In response to prolonged nutrient starvation, cells undergo autophagy, a highly conserved self-digestion process also mediated by AMPK activation (Hardie 2011). Shin *et al.* (2016) reported H3 Arginine 17 dimethylation (H3R17me2) as the histone mark of autophagy induced by nutrient starvation. H3R17me2 is mediated by CARM1, which can be inhibited by ellagic acid (Selvi *et al.* 2010). Shin et al. showed that Carm1 knockout or treatment with ellagic acid suppresses proper autophagy. The authors found that CARM1 protein stability is regulated by the SKP2-containing SCF E3 ligase complex in the nucleus. Upon glucose starvation, AMPK phosphorylates FOXO3a, and then FOXO3a and AMPK bind to the SKP2 promoter and suppress SKP2 at the level of transcription. SKP2 suppression leads to an increase of CARM1 in the nucleus, where it acts as a coactivator of transcription factor EB in regulation of autophagy-related and lysosomal gene transcription. CARM1 protein levels increase in the liver of fasted mice; however, ellagic acid treatment dampens autophagy, suggesting

the importance of H3R17me2 in CARM1-dependent autophagic transcription control.

5. CK2 and Sch9-dependent histone phosphorylation

Besides AMPK signaling, other signaling pathways are also involved in nutritional stress-specific histone modification. Recent work by Oh *et al*. (2018) showed that phosphorylation at H3 Threonine 11 (H3pT11) functions as a nutritional stress marker in *S. cerevisiae*. H3pT11 has been reported in regulation of the DNA damage response and transcription regulation in mammals, and meiosis in yeast (Metzger *et al.* 2008; Shimada *et al*. 2008; Kniewel *et al*. 2017). In this work, the authors found that H3pT11 is also upregulated upon glucose starvation independent of meiotic H3pT11. Upon glucose depletion, H3pT11 specifically increases at promoters of genes involved in the nutritional stress response. Moreover, these glucose-dependent changes are perturbed in an H3T11A mutant. Previously, Li *et al.* (2015) reported that the pyruvate kinase Cdc19 in Serine-responsive SAM-containing Metabolic Enzyme complex (SESAME) can phosphorylate H3 at T11 under glucose-rich conditions. Interestingly, SESAME-subunit-deleted mutants were dispensable for H3pT11 upon nutritional stress conditions. Instead, Oh *et al.* found that the CK2 catalytic subunit Cka1 and yeast Akt or S6 kinase homolog Sch9 were responsible for H3pT11 under these conditions. Intriguingly, CK2 is a constitutively active kinase complex. In addition, Sch9 is active under glucose-rich conditions. However, H3pT11 increases upon glucose depletion. How these two signaling pathways meet and regulate H3pT11 under stress is still unknown, and how this modification regulates downstream transcription remains elusive. One interesting possibility is that H3pT11 may interact with surrounding histone modifications such as H3pS10. These two modifications are adjacent and, as we discussed earlier, H3pS10 is governed by AMPK, which is activated upon nutritional stress. Supporting this idea, Clements *et al.* (2003) showed that both H3pS10 and H3pT11 are required for full activation of *INO1* transcription.

6. Summary

In summary, several specific histone marks have been identified, and well-studied signaling kinases such as AMPK and CK2 are involved in the regulation of these modifications. However, many questions remain. Among these questions are (1) how do these specific marks regulate the transcription of their target genes, and (2) how do different signaling pathways interrelate with each other in the regulation of these marks? In addition, how do these marks interact with each other? With increasing interest in metabolism research and that perturbation of these metabolic pathways is associated with various chronic diseases, more studies in the specific chromatin modifications that occur upon nutritional stress will be crucial in developing specific therapeutic targets.

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