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Chromatin and signaling

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Signaling involves the coordinated action of multiple molecules including stimuli, receptors and enzymes part of which interact with the transcriptional machinery and target chromatin. Signaling systems regulate the cell events responsible for survival, development and homeostasis. Many of the signaling pathways induce target gene activation through interaction with the transcription machinery, including RNA polymerase II, and with histone modifying complexes. These studies are having a broad impact on chromatin biology. Recent studies suggest that chromatin itself receives the signals. Increasing examples are illustrating novel regulatory mechanisms that promote our understanding of development and disease.

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Introduction

Signals are employed in cells and are established by the coordination of the required molecules for fundamental cellular processes. For example, stress-activated protein kinases (SAPK), which are also known as mitogen-activated protein kinases (MAPKs), are essential for the proper adaptation to extracellular stimuli. Studies of MAPKs have shown that phosphorylation of transcription factors by MAPKs is a trigger for the recruitment of the transcriptional machinery to target genes [1–3]. Signals modify chromatin at target genes by controlling the recruitment and function of transcription cofactors. An interesting example was found in the case of the Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway. The STAT transcription factors are phosphorylated/activated by cytokine activated JAKs and associate with the promoters of cytokine-inducible genes, resulting in transcriptional activation [4]. A recent study found that Type I interferons (IFNs) activate STAT3 in cell-specific manner. This is accomplished in part by the SIN3 transcription regulator homolog A (Sin3a) histone deacetylase (HDAC) complex. Sin3a represses STAT3 activity by promoting its deacetylation in some of the cell types. Thus Sin3a is a cell-specific repressor of STAT3. Sin3a is generally known as a repressor. However, in other cells the Sin3a complex is required for basal and IFN-α-dependent transcription of several ISGs (IFN-stimulated genes) and, as a consequence, for efficient IFN-α-induced protection against viral infection. Thus, by carrying out different functions in different cells Sin3a controls their response to cytokine signaling [5].

In this review, we discuss how signaling dynamically interacts with chromatin and how the context of signals mediates and responds to chromatin modifications.

MAPK triggers changes to chromatin structure

SAPK, which are also known as MAPKs, are essential for the proper adaptation to extracellular stimuli. MAPK pathways comprise consecutively activated protein kinases, and distinct kinases are devoted to responding to individual stimuli.

Single-cell analysis has shown that the response to MAPK signaling can be bimodal where a threshold for activation of target genes in each cell is dictated by chromatin remodeling. At high doses of osmotic stress (from 0.4 M to 0.8 M NaCl) the transcriptional response of target genes driven by the yeast MAPK Hog1 (high-osmolality-glycerol 1) such as *STL1*, increased linearly. However, under weak osmotic stress (from 0.15 M to 0.2 M NaCl) the transcriptional response of the *STL1* gene was bimodal [6••]. Quantitative ChIP data showed that the degree of histone H3 eviction at the promoter reflected bimodal Hog-1 driven gene expression. Hog1 recruits the remodels the structure of chromatin (RSC) remodeling complex. In the absence of Hog-1 histone eviction at the promoter is lost [7]. Thus, the need for chromatin remodeling at the promoter created a threshold that had to be overcome in each cell to activate the target gene. Chromatin remodeling is apparently facilitated by histone acetylation as loss of the Spt-Ada-Gcn5-acetyltransferase (SAGA) complex reduced bimodality of expression [6,8]. Histone eviction at Hog-1 driven genes is likely to require other components (e.g. histone chaperones to accept displaced histones) and may also require the transcriptional machinery, including recruitment of RNA polymerase II (Pol II), which can be induced by MAPK signaling [3].

MAPK signaling and the transcription machinery in muscle development

MAPKs also play important roles for muscle differentiation. Blocking p38alpha/beta kinase activity by treatment with

SB203580 inhibits the myogenic program through suppressing transcription of muscle regulatory genes [9]. In mouse myogenesis, p38 alpha phosphorylates the switch/sucrose nonfermentable (SWI/SNF) subunit, BRG1 (Brahma-related gene-1)/brm (Brahma)-associated factor 60c (BAF60c) Thr229 [10], which interacts with muscle determination transcription factor, MyoD, perhaps before transcription activation [11]. Phosphorylation of BAF60c is required for its incorporation into the BRG1-containing SWI/SNF complex and for its recruitment onto the myogenin promoter in C2C12 cells expressing BAF60c WT or The229Ale mutant by ChIP assay [11]. Thus, transcription regulation via MAPK signaling is crucial for not only stress response but also muscle development.

The associations of MAPK with nucleosomes

In pancreatic beta cells in response to glucose the extracellular signal-related kinases (ERK) 1/2 bind directly to the insulin gene promoter [12]. The MEK1/2 inhibitors U0126, PD98059, or the calcineurin inhibitor blocked binding of ERK1/2 to the *fos* and insulin gene promoters indicating that their kinase activities are required for binding. Thus ERK1/2 directly occupy target genes implying they regulate transcription directly.

MAPKs may have many downstream targets, and interestingly this includes histones bound to target genes. Phosphorylation of histone H3S10 occurs in several MAPK signaling pathways [13,14]. Non-histone proteins, including several MAPKs, are known to be reversibly phosphorylated and dephosphorylated [15]. However, the phosphorylation of histones on the target genes implies that MAPK may epigenetically control target nucleosomes. Less is known about corresponding phosphatases that may act on histones [16].

H3S10 phosphorylation and H3K14 acetylation are observed generally at promoters as markers for active gene transcription [17]. In addition to studies in yeast, SAGA-dependent H3K14 acetylation, in response to signaling, has been observed in mammals [13]. A variety of nucleosome modifying complexes has been shown to play important roles in regulating gene expression in response to MAPK signaling. Understanding how MAPKs select histone-modifying complexes for basal transcription and activate transcription in response to stimuli will provide further mechanistic insights into signal transduction.

Sense for sugar

Drosophila Polycomb group (PcG) gene, *Super sex comb* (*sxc*) encodes the *O*-linked N-acetyl glucosamine (GlcNAC) transferase, Ogt, which is responsible for maintaining Polycomb gene repression [18•]. Chip-chip data showed that among the 1% top-ranked Ogt sites nearly all (111 of 114) overlapped with Ph (polyhomeotic) and PhoRC (pleiohomeotic-repressive complex) binding regions. Sxc (Ogt) is a subunit of PRC1 (polycomb repressor complex 1), which also contains Ph, PC (Polycomb), Ring (Ring finger protein), and Scm, and is co-localized with PRC1 at Polycomb response elements (PREs). Ph is glycosylated by Sxc/Ogt. Sxc/Ogt is not essential for recruitment of PRC2, which catalyzes histone H3K27me3 on target genes, however, Sxc/Ogt is responsible for maintaining Polycomb transcriptional repression. Hence, in the absence of Sxc/Ogt binding of PcG complex to PREs is insufficient to maintain repression. However, it is unclear whether Ogt catalytic activity is required for transcriptional repression. Since GlcNAc is a monosaccharide derivative of glucose and is thought to be the terminal output from biosynthetic pathways involving glucose, glutamine, acetyl-Coenzyme A, and the uridine-diphosphate synthetic pathway [19], it is also possible that Ogt connects metabolized GlcNAC to PRC1 and may serve to sense the balance of nutrients such as glucose in cells during development [18] (Figure 1). It would be interesting to see whether impairing GlcNAc synthesis pathways altered polycomb transcriptional repression. The possibility of cross talk between histone GlcNAcylation and Polycomb-dependent histone modifications, H3K27me3 and/or H2AK119 monoubiquitination [20], is unknown.

Mammalian adenosine monophosphate-activated protein kinase (AMPK) is activated by phosphorylation at Thr172 in response to UV irradiation, H2O2 and glucose starvation. AMPK was found to activate p53-responsive gene transcription in part by directly phosphorylating histone H2B on S36 [21••]. In response to metabolic stress by depletion of glucoses, AMPK associates with both the promoter and transcribed region where H2BS36 phosphorylation occurs. Expression of a H2BS36A mutant form of H2B reduced expression of AMPK target genes such as p53-responsive genes, and reduced cell survival in response to stress [21••]. H2BS36 phosphorylation triggered by glucose depletion promotes RNA polymerase II (RNA pol II) recruitment on the transcribed region of these genes, in contrast, the RNA pol II occupancy on the gene was reduced in H2BS36A mice embryonic fibroblast cell lines (Figure 1) [21••]. Hence, nucleosomes respond to metabolic signals.

Can signal specific histone modification be a marker for tumor malignancy?

Pyruvate kinase M2 (PKM2) is phosphotyrosine binding protein and catalyzes the last step in glycolysis [22]. The conversion of phosphoenolpyruvate to pyruvate produces ATP. A recent study showed a non-metabolic function of PKM2. Histone H3T11 is phosphorylated upon epidermal growth factor (EGF) receptor (EGFR) activation, and phosphorylated H3T11 (H3T11p) is directly bound by PKM2 [23]. H3T11p is required for H3K9 acetylation, which resulted in the dissociation of HDAC3 from the promoters of EGFR target genes such as *CCND1* and *MYC*. PKM2 binding to H3T11p subsequently facilitates