Review

MOLECULAR METABOLISM

Metabolic intermediates — Cellular messengers talking to chromatin modifiers

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ABSTRACT

Background: To maintain homeostasis, cells need to coordinate the expression of their genes. Epigenetic mechanisms controlling transcription activation and repression include DNA methylation and post-translational modifications of histones, which can affect the architecture of chromatin and/or create 'docking platforms' for multiple binding proteins. These modifications can be dynamically set and removed by various enzymes that depend on the availability of key metabolites derived from different intracellular pathways. Therefore, small metabolites generated in anabolic and catabolic processes can integrate multiple external and internal stimuli and transfer information on the energetic state of a cell to the transcriptional machinery by regulating the activity of chromatin-modifying enzymes.

Scope of review: This review provides an overview of the current literature and concepts on the connections and crosstalk between key cellular metabolites, enzymes responsible for their synthesis, recycling, and conversion and chromatin marks controlling gene expression.

Major conclusions: Whereas current evidence indicates that many chromatin-modifying enzymes respond to alterations in the levels of their cofactors, cosubstrates, and inhibitors, the detailed molecular mechanisms and functional consequences of such processes are largely unresolved. A deeper investigation of mechanisms responsible for altering the total cellular concentration of particular metabolites, as well as their nuclear abundance and accessibility for chromatin-modifying enzymes, will be necessary to better understand the crosstalk between metabolism, chromatin marks, and gene expression.

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Keywords Metabolism; Histone modifications; Gene expression; Metabolic enzymes

1. INTRODUCTION

The term 'epigenetics' was originally coined by Waddington in 1942 [1]; however, the usage and definition of 'epigenetics' has changed throughout the years. The Greek prefix 'epi-' (meaning 'over' or 'above') emphasizes phenomena that reach beyond well established genetic (DNA sequence based) mechanisms. In the same notion, in 2008, an 'epigenetic trait' was defined as a 'stably heritable phenotype resulting from changes in a chromosome without alterations in the DNA sequence' [2]. Therefore, one of the key implications of 'epigenetics' is that a cell can preserve a memory of past states and signals, triggering its future behavior, in the absence of both the initial signal and alterations in the DNA sequence.

In multicellular organisms epigenetic factors can enable cells to activate or repress particular sets of genes. There are several mechanisms that are implicated in mediating inheritance and maintenance of such gene expression states. The most common mechanisms, and the only ones discussed in this review, are covalent modifications of chromatin. This review focuses on a new aspect of 'epigenetics', the link between the metabolic state of a cell and chromatin architecture. In particular it discusses the metabolites, generated and converted in various physiological pathways, which are of great importance to many epigenetic 'writers' and 'erasers', namely: S-adenosylmethionine (SAM), α-ketoglutarate (α-KG), succinate, fumarate, acetyl-CoA, short chain acyl-CoAs and NAD^+. We summarize the existing body of knowledge on metabolism of the aforementioned compounds, their subcellular localization and impact on chromatin modification and, thus, gene expression. Although many aspects of the links between metabolism and epigenetics have been excellently reviewed elsewhere (see for example: [3—11]), here we touch on frequently neglected aspects of subcellular distribution of metabolites and enzymes as well as on kinetic parameters of chromatin-modifying enzymes and on physiological concentrations of key cofactors. Finally, we highlight the existing gaps in the field and suggest potential future directions.

2. EPIGENETIC MECHANISMS REGULATING CHROMATIN FUNCTIONS

Early studies in mouse revealed that a modification of DNA itself, DNA methylation, could act as an 'epigenetic' mark, for example in X chromosome inactivation [12]. The discovery of enzymatic semi-conservative propagation of such DNA methylation patterns at CpG sites after replication and mitotic division gave the first insights into how such 'epigenetic' information could be maintained through cell divisions. Attention is now being focused on the possible transgenerational transmission of these patterns, the contribution of DNA methylation to

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gene silencing, mechanisms initiating or preventing methylation on fully unmethylated sites, and the enzymes catalyzing this modification [13]. DNA methylation patterns are not static and can be highly dynamic; for example, during preimplantation development, major changes in DNA methylation patterns occur in the mammalian genome. In the preimplantation state, methylation marks on both the maternal and paternal DNA are largely erased and subsequently reestablished *de novo*. This requires another set of enzymes, different from the ones responsible for maintenance of CpG methylation in somatic cells.

Eukaryotic DNA exists as a complex of DNA and proteins, which are collectively the chromatin. The most abundant proteins in chromatin are histones, discovered by Kossel in the nineteenth century [14]. Histones, the main structural components of eukaryotic chromatin, are highly basic proteins that, together with the DNA wrapped around them, form nucleosomes. Initial suggestions that histones are merely general repressors of gene expression were refined after a breakthrough discovery by Allfrey and Mirsky in 1964; they showed that histones can be modified by lysine acetylation and that this acetylation is positively correlated with gene activation [15]. Since that time, interest in histone modifications and their role in gene expression have been growing. The functional significance of various chemical groups attached to histones became clearer when the structure of the nucleosomal core particle was determined [16]. The nucleosomal core particle is composed of 147 bp of DNA wrapped around a histone octamer consisting of 2 copies of each of the core histones: H2A, H2B, H3, and H4, with their globular domains forming a 'spool' for the DNA and the terminal tails protruding from the core of nucleosome. Histone H1, also known as the linker histone, binds to the linker DNA region between nucleosomal core particles.

Chromatin architecture and dynamics contribute significantly to gene expression. A wide range of histone post-translational modifications (PTMs) plays an important role in establishing various chromatin states. This may be achieved by both changing the physical properties of nucleosomes and by recruiting different binding proteins that then exert effects on downstream events such as transcription. Some of the most studied histone PTMs are phosphorylation, methylation, acetylation, and ubiquitylation, thoroughly reviewed in [17–20]. Additionally, novel histone modifications are continuously being identified. It is now known that histone PTMs contribute to the mechanisms by which DNA-sequence specific transcription factors and additional transcriptional regulators modulate expression and silencing of genes. One of the first examples supporting this notion came from the work on a yeast protein Gcn5, a component of the SAGA complex, previously associated with active transcription. Gcn5 was shown to possess histone acetyltransferase activity and hence to act as a 'writer' of histone modifications [21]. Acetylation of lysines within N-terminal histone tails is highly enriched at the promoter regions of genes and is generally associated with chromatin decompaction, promoting high levels of gene expression. The function of histone methylation on lysines and arginines and its contribution to gene expression depends on the modified residue. For example, mono- and tri-methylations are found to be enriched on active promoters (e.g. H3K4me3), active enhancers (H3K4me1), inactive promoters (e.g. H3K27me3) and coding regions of active genes (e.g. H3K36me3). Most histone modifications are reversible and can be removed by so-called 'erasers'. The combined range of histone PTMs and DNA modifications can constitute particular epigenetic patterns that can be specifically recognized and bound by so-called 'reader' proteins. Some of these readers have their own histone-modifying activity, where their role can be to recognize and bind a particular PTM, introduce the same mark onto the adjacent nucleosome and thus propagate a particular modification in a defined region of the genome [22]. Other 'readers' can be e.g. subunits of ATP-dependent chromatin-remodeling complexes that modulate gene expression by ejecting or 'sliding' nucleosomes. Combinatorial patterns of histone PTMs are crucial determinants of the state and architecture of chromatin — that can be accessible to transcription, DNA repair and replication or compacted and usually devoid of transcribed genes.

Apart from recruiting 'reader' proteins, some histone PTMs have been shown to affect the structure or dynamics of chromatin on their own. These effects are mainly observed for modifications of residues within globular domains of histones. Acetylation of H3K64 by p300 destabilizes nucleosomes and can promote histone eviction and transcription [23]. Similarly, acetylation of H3K122, a residue that physically interacts with DNA and thus has been anticipated to affect nucleosome stability, stimulates transcription of *in vitro* assembled chromatin [24,25]. Acetylation of H4K16 is so far the only tail modification that directly affects chromatin structure [26] — when incorporated into *in vitro* reconstituted nucleosomal arrays, this modification was shown to prevent chromatin from forming higher order structures. Since covalent modifications of chromatin components underlie gene expression programs, the activity of the enzymes responsible for placing these modifications and their removal can be a crucial factor controlling transcription. In the last few years it has become evident that small metabolic intermediates can be common denominators between two elementary biological processes: energy metabolism and gene regulation. Cells in a particular metabolic condition established by available nutrients, external stimulation and their intrinsic metabolic status, produce specific sets of metabolites, many of which can serve as cofactors or inhibitors of chromatin-modifying enzymes and hence regulate their activity or specificity (Figure 1).

3. SAM AS A COMMON COFACTOR FOR METHYLATION OF CHROMATIN

3.1. DNA and RNA methylation as epigenetic marks

Methylation of DNA was first reported in 1963 [27]. Since the discovery that hypo-methylation of particular genes is associated with some human cancers, its role in normal human development, aging and tumorigenesis has been thoroughly explored [28,29]. Enzymatic transfer of a methyl group to the C-5 position of the cytosine is catalysed by DNA methyltransferases (DNMTs), of which are three main ones in mammals: DNMT3A, DNMT3B and DNMT1. While DNMT3A/B are mainly responsible for setting *de novo* methylation patterns (e.g. in early embryo development) and are able to methylate non-methylated cytosines, DNMT1 — the most abundant methyltransferase — acts predominantly on hemi-methylated CpG dinucleotides and thus provides stability of methylation patterns after DNA replication through cell division, making DNA methylation a truly 'epigenetic' mark [30,31].

From the more than 100 various covalent modifications of RNA that have been identified, methylation of adenine at the N-6 position (m^6A) is the most prevalent in eukaryotic mRNA [32]. Although studies have reported different effects of m^6A on RNA functions and correlations between alterations in m^6A patterns and various human diseases, including many cancers, its functional role is just emerging and needs further investigation [33].

3.2. Histone methylation can repress or activate transcription

The catalogue of histone methylation states is ample as methylation can occur on lysine (Lys), arginine (Arg) and histidine (His) residues. Moreover each Lys residue can carry one, two or three methyl groups (mono-, di- and tri-methylation, respectively) and each arginine can be mono- and symmetrically or asymmetrically di-methylated. The most

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