Trends in Genetics

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Opinion

Histone oxidation as a new mechanism of metabolic control over gene expression

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The emergence of aerobic respiration created unprecedented bioenergetic advantages, while imposing the need to protect critical genetic information from reactive byproducts of oxidative metabolism (i.e., reactive oxygen species, ROS). The evolution of histone proteins fulfilled the need to shield DNA from these potentially damaging toxins, while providing the means to compact and structure massive eukaryotic genomes. To date, several metabolism-linked histone post-translational modifications (PTMs) have been shown to regulate chromatin structure and gene expression. However, whether and how PTMs enacted by metabolically produced ROS regulate adaptive chromatin remodeling remain relatively unexplored. Here, we review novel mechanistic insights into the interactions of ROS with histones and their consequences for the control of gene expression regulation, cellular plasticity, and behavior.

Highlights

Histone oxidation provides a direct link between metabolically generated reactive oxygen species (ROS) and chromatin architectural changes enabling the activation of stress response gene expression.

Histone oxidation is enacted directly by reactive metabolites and does not depend on enzyme catalysis or cofactor/substrate availability.

Residues most susceptible to oxidative modification (cysteine, methionine, and tyrosine) are distinct from those modified by more traditional epigenetic writers (lysine and arginine), providing a distinct and independent pathway for metabolism-driven epigenetic regulation.

Genome organization by histone proteins and its impact on gene expression regulation

For decades, the process of gene transcription has been understood as a probabilistic event regulated primarily by the binding of activated transcription factors to target genes [1,2]. However, more recent findings support the idea that large eukaryotic genomes evolved additional biophysical mechanisms to regulate the accessibility of gene regulatory elements to transcription effectors [3]. This both increased transcriptional specificity and allowed for finer control over the kinetics of transcription [1,2,4]. Accessibility of gene regulatory sequences is largely determined by the 3D arrangement of chromatin, the molecular scaffolds of which work at very large scales by opening or compacting segments of chromosomes, or at much smaller scales by bending and coiling DNA to control accessibility to a few base pairs [5–8]. Histones are the major structural elements of this scaffold, and the extraordinarily high level of evolutionary conservation reflects their critical roles in ensuring genomic organization, integrity, and function [9–11]. Several studies have revealed a dizzying array of distinct PTMs on many of the highly conserved residues of histones, with particular focus on nucleosomal histone PTMs (H2A, H2B, H3, and H4). These led to the concept that a 'histone code' [12] is involved in gene expression kinetics [13–15], pausing, elongation [16–18], and fidelity [19]. Most of these modifications require the site-specific recruitment of 'writer' and 'eraser' enzymes for their placement and removal, respectively [20]. In addition to these catalytic requirements, well-studied modifications, such as lysine methylation and acetylation, also depend on the availability of metabolites that serve as donors of acetyl (i.e., acetyl-CoA) [21] or methyl [i.e., *S*-adenosylmethionine (SAM)] groups, respectively, to the ε-amino moiety of lysine. Cells maintain tight metabolic control over the available pools of both acetyl-CoA and SAM [22], thereby coupling lysine modification and chromatin structural changes, to the cellular metabolic activity. This results in metabolic control over the transcriptome, cell behavior, and identity, as best exemplified by the causal relationship between metabolic

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dysfunction and aberrant histone PTMs that emerge in disease states, such as cancer, where the cellular constraints that are essential for organized multicellular life are lost as the cellular metabolism drifts [23,24].

While the details of chromatin regulation are complex, the underpinning biophysical changes are driven largely by electrostatic changes to the histones themselves. For example, methylation and acetylation alter the net charge and polarity of positively charged lysine residues on the histones. This alters their electrochemically dominated interactions with the negatively charged DNA backbone, strengthening (methylation) or weakening (acetylation) histone–DNA contacts, thereby locally hindering or enhancing chromatin accessibility, respectively. Although critical, methylation and acetylation are only two of the many chemical modifications that can promote histone-mediated structural changes to chromatin [25]. While widely thought of mostly in the context of physiologic damage, redox-active biomolecules can stimulate a variety of PTMs to cysteine [26,27], methionine [28,29], and, to a lesser extent, tyrosine, tryptophan, and histidine residues. In fact, ROS, such as hydrogen peroxide (H_2O_2), are produced abundantly under selective metabolic states, including hypoxia [30] and, thus, also have the potential to couple protein modifications to cellular metabolism. Critically, these changes are produced by the direct interaction between ROS and histones and do not require the 'writer' enzymes mentioned in the preceding text. For example, H_2O_2 is soluble in aqueous media, readily crosses membranes, and instantly modifies proteins [31], including histones [32], leading to sulfenylation or glutathionylation, two forms of thiol oxidation that dramatically change the polarity of protein-bound cysteine residues. The change in charge and atomic composition of cysteine adducts causes the structure of the protein itself to change and alters its interactions with binding partners (e.g., [33,34]). It is well established that ROS drive transcriptomic and phenotypic changes associated with several disease states characterized by aberrant histone landscapes [35]. Taken together, these observations support the concept that oxidation belongs to the family of chromatin modifications that couple physiologically important metabolic cellular conditions with the epigenetic control of gene expression regulation, thereby functioning as a major driver of cellular behavior, lineage commitment, and response to stress (Figure 1). The evidence in support of this idea is reviewed in the following section.

ROS, histones, and DNA damage

Histones and their variants are essential structural components of chromatin that regulate DNA accessibility by undergoing a vast array of simultaneous PTMs. This expansive array of post-translational chemical modifications to the primary histone sequence provides a dynamic combinatorial platform for fine-tuning gene expression in response to intracellular and microenvironmental cues. While acetylation and methylation of lysine (and, to a lesser, extent arginine) residues are by far the best characterized metabolism-driven PTMs, others have been described, including oxidation by ROS [36,37], as well as modifications by electrophiles, such as carbonyls [38–40]. Relevant biological oxidative modifications more often involve cysteine, methionine and tyrosine (Figure 2). Most of the available studies appear to indicate that oxidative modifications occur in the case of both linker (i.e., H1) and nucleosomal (i.e., H2A, H2B, H3, and H4) histones. In addition, research indicates these oxidative modifications produce significant structural alterations, partial unfolding, and thermal destabilization, suggesting that ROS and reactive electrophiles (Box 1) directly impact chromatin structure and gene expression patterns via modifying redox-sensitive histones [32,36–40]. This is the case for H3 histone glutathionylation, detected in studies using proliferating tumor cells [32]. Biologically, H3 glutathionylation was shown to produce protein structural changes associated with nucleosome destabilization, chromatin opening, and activation of gene expression. Another study found that H3 glutathionylation, in the context of nitrosation, participates in the sensitization of breast cancer

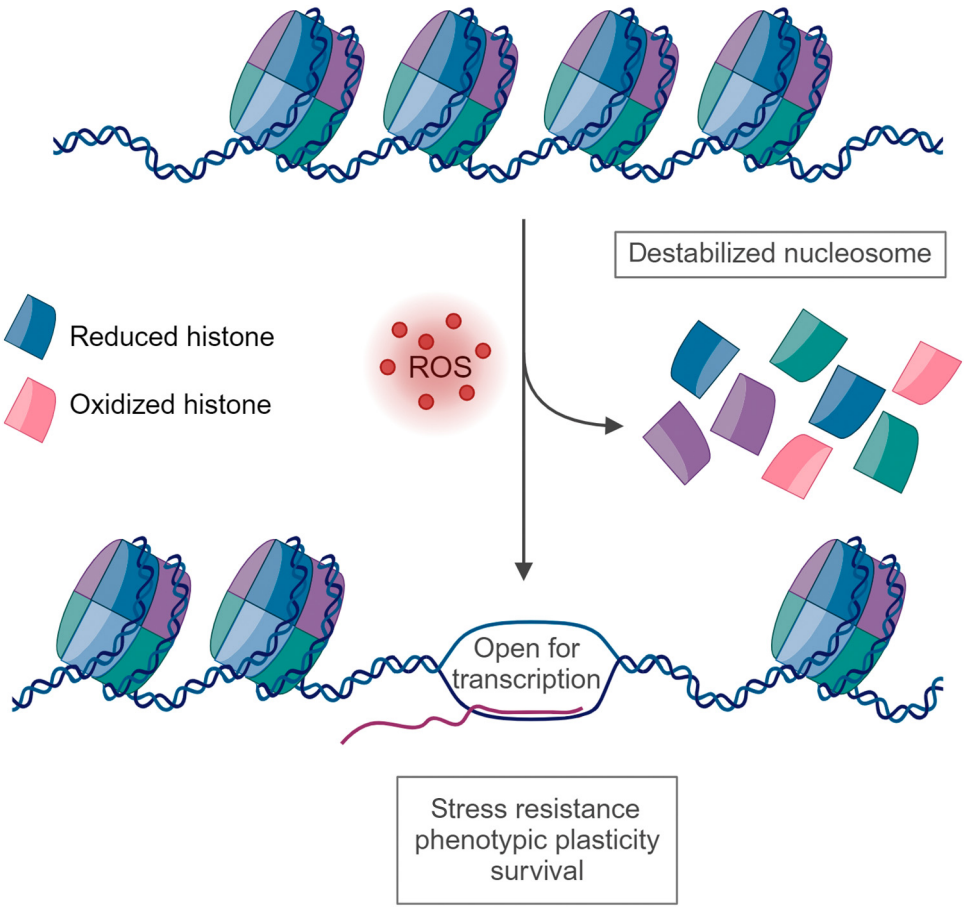

Figure 1. Proposed mechanism of redox-dependent activation of adaptive gene expression regulation induced by electrophilic stress. Oxidation of histone H3.1 promotes its eviction from chromatin, consequently increasing associated gene accessibility and expression. The transcriptional profile of cells exposed to physiological levels of reactive oxygen species (ROS) show upregulation of pathways involved in stress resistance, plasticity, and survival. Figure created with BioRender (biorender.com).

cells to doxorubicin, a chemotherapeutic drug [41]. However, it is unclear whether the sensitization effect was associated with changes in gene expression patterns caused by glutathionylation-induced chromatin remodeling, increased exposure of DNA to damaging agents, or both. Regardless, it appears that most available studies are consistent with the general idea that histones evolved to absorb a significant portion of oxidizing metabolites that could damage DNA, while suggesting that their PTMs by these reactive intermediates have important roles in the determination of nucleosome structure, chromatin stability, and gene transcription regulation.

Interestingly, other examples of functional nongenomic histone oxidation mechanisms have been demonstrated in cell biology [42]. In a recent study, tyrosine chlorination by hypochlorous acid was proposed as a novel mechanism regulating NETosis, a process by which activated neutrophils release chromatin-based nets to trap invading pathogens [43]. Studies of isolated histones exposed to HOCl revealed interesting patterns of PTMs of nontraditional amino acids including, for example, tyrosines. Mass spectrometry evidence showed that, in the case of all histones examined in the study (H1, H2A, H2B, H3, and H4), tyrosine chlorination was a

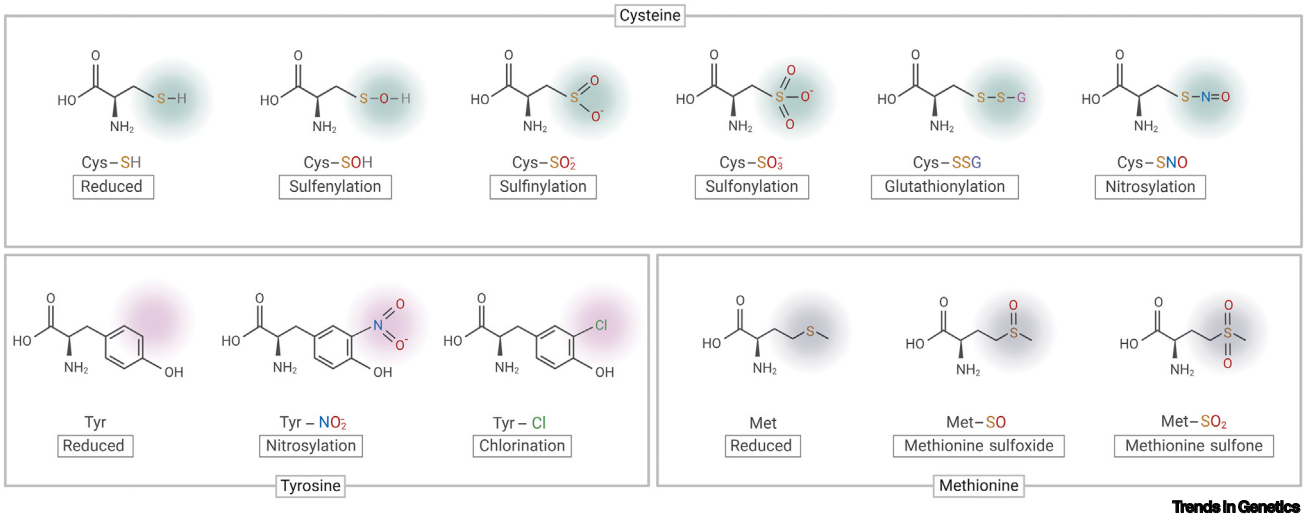

Figure 2. Examples of oxidative modifications of cysteine, tyrosine, and methionine residues. The most common oxidative modifications of cysteine residues include sulfenylation (-SOH), sulfinylation ($-SO_2^-$), sulfonylation ($-SO_3^-$), glutathionylation (-SSG), and nitrosation (-SNO). Nitration (NO_2^-) is also observed in tyrosine residues as well as chlorination (-Cl). Methionine sulfoxide (-SO) and methionine sulfone ($-SO_2$) are common products of methionine oxidation. Figure created with BioRender (biorender.com).

prevalent product, with methionine oxidation and lysine chloramine formation being among the other products detected. Although the study focused on a rather extreme example by which HOCl can change the biochemical and biophysical properties of chromatin related to its ability to trap pathogens, it is possible that, under more subtle conditions, lower levels of HOCl could impact gene expression via producing histone chlorination. An interesting thought is that HOCl and similar biological oxidants, such as HOBr, repress gene expression via crosslinking histones or histones and nucleosome-associated DNA. However, to our knowledge, this idea remains to be tested experimentally.

Box 1. Basics of reactive species chemistry, reactivity, and role in biology

Reactive oxygen (ROS) and nitrogen species (RNS) are general terms used to describe large groups of molecules that have some characteristics in common, such as high reactivity, short half-lives, and high avidity for electron-rich substrates. This makes ROS and RNS oxidants by definition, either extracting electrons or producing adducts with electron-rich moieties, such as thiols and amines. Biophysical and chemical characteristics of ROS and RNS vary widely, making them more or less selective to specific substrates. For this discussion, we emphasize ROS, RNS, and reactive species most prevalently produced in cells and *in vivo*, such as H_2O_2 (ROS), nitric oxide (NO), a primary source of RNS, and 4-hydroxy-nonenal, a product of lipid peroxidation representing reactive carbonyls. H_2O_2 is the product of superoxide radical dismutation and is abundantly produced by mitochondria under stress conditions. It reacts directly with thiol residues, including with those in proteins and histones. A recent example of the epigenetic effects of H_2O_2 was the demonstration that cysteine 96 on histone H3.1 can be oxidized, leading to regiospecific chromatin opening [37]. It is likely that other thiol residues on different histones can also be directly oxidized by H_2O_2. These, and their consequential effects on chromatin structure and gene expression regulation, remain to be investigated.

NO is produced physiologically by NO synthases. It reacts rapidly with metals and inhibits histone demethylases directly via forming iron-nitrosyl (Fe-NO) adducts with these enzymes [58]. NO also reacts with oxygen to produce nitrogen dioxide ($\bullet NO_2$) [59], a powerful nitrating species. $\bullet NO_2$ can nitrate tyrosine residues, leading to tyrosine nitration [60,61]. Nitration interferes with tyrosine phosphorylation [66,67] and, in the case of histones, may alter how the chromatin reacts to stimuli. The implication of this type of modification for gene expression regulation remains understudied.

Finally, carbonyls are reactive aldehydes produced through lipid and carbohydrate oxidation. Reactive carbonyls form adducts with amines and thiols. In the case of 4-hydroxy nonenal, adduct formation with histones has been detected both *in vitro* and in disease models and has been shown to destabilize nucleosomes [39,62].

Histone oxidation expands the accessible genomic landscape, providing a path for stress survival

Findings of oxidative DNA damage under a variety of physiologically relevant conditions [44–46] have undoubtedly contributed to establishing the idea that ROS reach the nucleus and directly interact with chromatin elements. It also emphasizes that, in addition to their potential as DNA-damaging species, ROS may have other functions in the nucleus, including signaling, regulation of the transcriptional machinery, and potentially sculpting the epigenetic landscape via mechanisms that remain to be fully explored. In support of this, several recent findings provided evidence that ROS are critical messengers enabling sophisticated mechanisms of mitochondria–nucleus communication [47,48]. In addition, recent studies using redox ratiometric probes and synthetic chemogenic strategies in live cells demonstrated that the origin and levels of ROS reaching the nucleus directly regulate gene expression [49,50]. Using chemogenic approaches localized to specific subcellular compartments, Dansen and colleagues investigated whether H_2O_2 produced in mitochondria (even at supraphysiological levels) could cause DNA damage. By quantifying DNA strand breaks as well as activation of the DNA damage response elicited by D-alanine oxidase-derived H_2O_2 produced either in mitochondria or the nucleus, the investigators concluded that H_2O_2 generated outside of the nucleus (i.e., in mitochondria) is unlikely to cause genomic DNA damage even at relatively high concentrations. Their results also appear to suggest that, while ROS generated directly in the nucleus (e.g., by ionizing radiation) have the potential to damage DNA, cellular ROS produced under physiological conditions are more likely to impact chromatin in subtle ways, potentially via the oxidation of redox-sensitive structural elements controlling gene accessibility and expression. Using similar approaches, and consistent with the general idea that oxidants sculpt the epigenetic landscape via interaction with architectural chromatin components, it was found that the variant histone, H3.1, is uniquely susceptible to oxidation and that this has important implications for the regulation of the transcriptome, cell

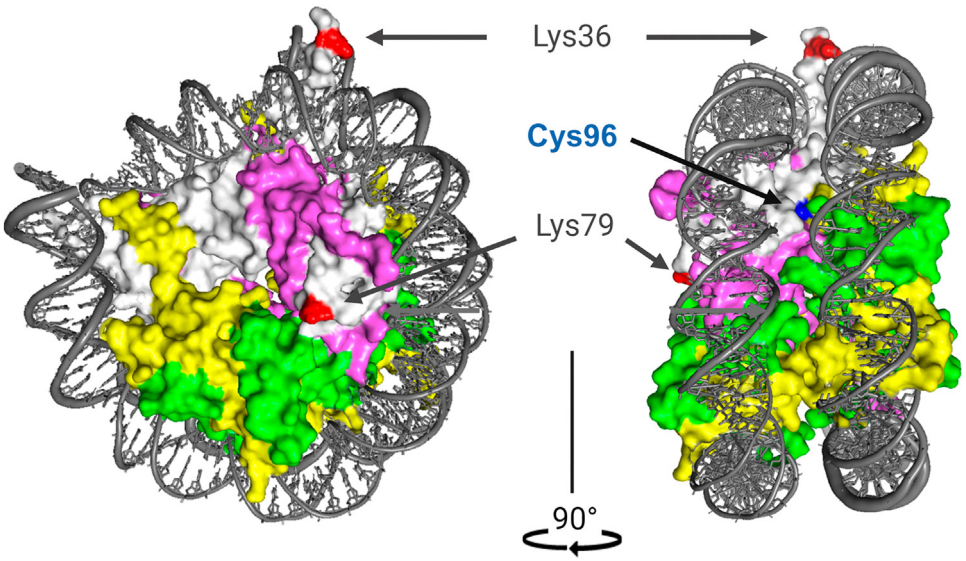

Figure 3. Structural model of the nucleosome showing that H3.1 Cys96 is buried within the core of the nucleosome. The nucleosome is based on Protein Data Bank (PDB) ID: 5ZBX, and contains H3.1 (white), H4 (purple), H2A (yellow), H2B (green), and the associated DNA strand (gray); it also has two sites of post-translational modification (H3K36 and H3K79) indicated in red (other sites known to be modified, such as H3K27, are located further out on the histone tail, which is not rendered in this structure). Unlike the other sites, H3C96, labeled in blue, is located further within the structure of the nucleosome, rendering it less accessible to solvent and bulky enzymes (e.g., epigenetic writers and erasers).

Box 2. Perspectives on the direct and indirect epigenetic effects of reactive species

ROS, RNS, and carbonyls can directly modify histones and DNA, thereby changing patterns of gene expression [37,46,63]. Reactive species also modify epigenetic enzymes, thereby indirectly affecting histone PTMs [58,63]. The amplitude and durability of these ROS-dependent effects were clearly demonstrated by the finding that SETD2 is regulated by ROS early in the *Caenorhabditis elegans* life cycle, resulting in adaptive epigenetic effects that prolong lifespan [63]. Other effects of ROS directly or indirectly affecting histone PTMs have also been demonstrated [64,65]. These pioneer examples indicate that reactive species are epigenetically active metabolites impacting gene expression regulation via their impact on histone and DNA biochemistry, structure, and function.

behavior and function [37]. Importantly, the study highlighted that the presence of a conserved cysteine residue, positioned at the nucleosome core (position 96) renders H3.1 oxidant sensitive [37], indicated in blue on the PyMOL-rendered structure of an H3.1-containing nucleosome [Protein Data Bank (PDB) ID: 5ZBX] [51] (Figure 3 and Box 2). Interestingly, the impact of nuclear ROS over promoting transcription was not universal, since genes involved in the acquisition of cell plasticity appeared to be disproportionally affected by nuclear ROS [37]. This is consistent with these genes being 'indexed', or silenced specifically by H3.1, and may help to explain the functional changes observed in the cells after oxidant treatment, including the loss of lineage-specific identity markers [37,52]. Moreover, protecting H3.1 from oxidation by ROS had important implications for the susceptibility of tumor cells to chemotherapeutic drugs, suggesting a direct connection between histone oxidation and epigenetic mechanisms regulating cell plasticity and adaptability to selective pressures [37].

Concluding remarks

Evidence compiled here highlights the concept that eukaryotic chromatin evolved to absorb the potentially damaging impact of an expanding spectrum of metabolic processes. As the higher bioenergetic yield of oxidative metabolism became more central to metazoan life, the capacity to quench ROS before they could damage DNA would also have become a more central role for specialized chromatin components, such as histone proteins. While minimizing DNA oxidation may have been a primary benefit linked to the evolution of histones, the resulting oxidative modifications to histones themselves would have provided an unprecedented evolutionary opportunity to couple the epigenetic regulation of gene expression to the functional state of the oxidative metabolism. Several lines of evidence support this idea. There is a clear precedent for the coupling of chromatin structural dynamics to other metabolic pathways. For example, histone methylation requires a pool of SAM, which is itself dependent on glycolytic intermediates, folate metabolism, and protein synthesis, among other pathways. Histone acetylation requires acetyl-CoA, a common intermediate resulting from the breakdown of both glucose and lipids, as well as the functional status of the tricarboxylic acid (TCA) cycle, and a variety of other processes.

Beyond this, the use of novel chemogenic tools in living cells is revealing that oxidative species are not simply endured, but that their landscape is far more complex and compartmentalized than previously thought. These studies indicate the existence of complex cellular mechanisms that control and direct the flow of oxidants between organelles, which remain poorly understood (e.g., [47]). Importantly, recent findings indicate that gene transcription is regulated by oxidation of a distinctive cysteine residue present only in histone variant H3.1 [37]. Given the highly conserved nature of the histone sequences, Hake and Allis first predicted important roles for this cysteine substitution in H3.1 almost 20 years ago [53]. We propose that one of these functions is to act as a sensor of redox signals transmitted by H_2O_2, a unique product of oxidative metabolism that is well known to serve as a critical activator of cellular stress responses [54–56]. Structurally, unlike most 'epigenetic marks', which are found on the histone tails, position 96 is buried on a part of histone H3 located within the nucleosomal core, which is predicted to make the site relatively inaccessible to the bulky enzymes required for other PTMs (e.g., lysine methylation and

Outstanding questions

How does the biophysical and/or biochemical chromatin microenvironment (e.g., DNA or histone modifications) impact the reactivity (and, therefore, sensitivity) of histone thiols to oxidation?

How do distinct histone oxidative modifications engage with different epigenetic processes? Do they recruit specific epigenetic readers, writers, or erasers, and how does this impact transcription?

Are histone oxidative PTMs reversible? If so, what are the mechanisms?

acetylation, arginine methylation, etc.). Given that H_2O_2 can transit easily through both hydrophilic and hydrophobic environments, it can readily access this site and modify H3.1-Cys96, resulting in destabilization of the H3.1-bearing nucleosomes. Coupling H3.1 exchange to oxidative signaling could have wide-ranging consequences because H3.1 is deposited during the S phase of the cell cycle, and transcription of H3.1-decorated sites requires extensive nucleosome remodeling, including the exchange of H3.1 for H3.3 [57]. The finding that H_2O_2 promotes H3 variant exchange via H3.1-Cys96 oxidation provides a new direct pathway for oxidative metabolism to exert epigenetic regulatory control over transcription and, thus, represents a critical mechanism underlying the known role for ROS in promoting transcriptional and phenotypic plasticity in diseases such as cancer [37,52]. Based on this example, it is possible that the distinct and evolutionarily conserved biophysical sensitivities of histone variants to oxidation underpins an important new mechanism connecting cellular metabolism (i.e., production of ROS by mitochondria) to the regulation of gene expression. The studies highlighted here lead to important new questions in the field (see Outstanding questions).

In summary, we propose the hypothesis that PTMs that resulted from histones protecting the genome from oxidizing metabolites were captured over evolutionary time to serve essential roles in the determination of nucleosome structure and chromatin accessibility, thereby coupling gene transcription to the metabolism-dictated redox state of the cell.

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Declaration of interests

N.K. is a consultant for Thermo Fisher Scientific on proteomics and biological mass spectrometry applications.

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