Editorial

“Histones and Chromatin” Review series

Wrapping up histone regulation

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Histones and Chromatin”, a new review series in *EMBO Reports* and *The EMBO Journal* on histones, the chief protein components of chromatin, provides a state-of-the-art focus on molecular mechanistic understanding of the regulation of chromatin. The review series is centered on the histone code hypothesis, rather than the epigenetic code—i.e. excluding DNA modifications. Since the histone code concept was first proposed, the field has assembled a large catalogue of histone modifications and a broad range of regulatory outputs. The series focuses on histones, including the often neglected H1 linker histones, on histone variants and chaperones, and on the structural basis of their interactions. It covers writers, readers and erasers of histone modifications and their role in nuclear organization. Throughout, the aim is to integrate the functional roles of all these components in chromatin compaction and regulation, transcription and DNA repair. While there is no dedicated analysis of the role of histone modification in disease, the reviews are relevant in this context, given the profound links to human disorders such as cancer.

In this issue of *EMBO Reports*, Sonja Hergeth and Robert Schneider assess new functions of H1 linker histones that go beyond a structural role. Notably, it is still unclear how exactly H1 histones bind to the nucleosomal core particle and mediate higher-order chromatin structure. The review discusses the whole spectrum of H1 subtypes and their post-translational modifications from yeast to human and their roles in heterochromatin formation, transcriptional regulation, DNA repair and embryogenesis. Surprisingly, writers, erasers and readers of H1 modifications are still unknown.

A second review by Francesca Mattiroli, Sheena D’Arcy and Karolin Luger focuses on the molecular determinants of histone variant–histone chaperone interactions. It remains unclear whether the structural features of histone variants and chaperones are sufficient to account for their specificity or if other determinants contribute. The review discusses effects of histone variants on chromatin structure, the regulation of histone variant dynamics by histone chaperones, and lists known functions of histone variant–chaperone pairs. The future will show how histone variants are chaperoned and/or exchanged at the molecular and atomic level.

Two reviews from Neil Brockdorff’s and Robert Klose’s laboratories assess histone code writers, readers and erasers. Zhang, Cooper and Brockdorff discuss mechanisms underlying the formation, reinforcement and maintenance of histone mark patterns associated with active and repressed transcriptional states, and review the crosstalk between these modifications. While histone modifications clearly correlate with gene expression states, it remains to be determined whether they are a cause or consequence of these states. It is becoming increasingly clear that existing histone modifications can influence writer activity and recruitment and that they might interplay with DNA sequence-based recruitment. Dimitrova, Turberfield and Klose focus on histone demethylases a decade after their initial discovery and crystallize molecular principles by which they recognize their substrates, control gene expression, reprogram chromatin and protect genome integrity. As histone code writers, erasers also have or interact with reader domains to identify their substrates; again, it remains unclear what the relative contributions of reader domains, DNA sequence-specific binding activity and non-coding RNAs are in this context. Histone demethylases also target non-histone proteins, they can hydroxylate substrates and exhibit demethylase-independent functions as molecular scaffolds. These differential roles will need to be dissected in the future to determine the primary function of the demethylases and the underlying basis for phenotypes caused by their deletion.

Two upcoming reviews by Titia Sixma & Andrea Mattevi (*The EMBO Journal*) and Susan Gasser (*EMBO Reports*) and colleagues will discuss technical advances for the study of chromatin-associated proteins and mechanisms in substrate recognition and the roles of histone modifications in nuclear organization.

Together, this review series provides a synthesis of the current state of the field without skirting the open questions. With our increasing knowledge of the variety of specific histone subtypes, modifications, chaperones and their specific functions in chromatin biology and therefore nearly all cellular processes, the picture becomes increasingly complex. Importantly, parallels can be drawn within this growing complexity and recurrent themes and principles emerge, and this is where we advance our understanding of fundamental and basic cellular and molecular processes.

While we have gained much insight into the roles of histones, their marks and associated enzymes in cellular processes such as transcription, reprogramming, replication, cell cycle and DNA repair, it is less clear how cellular processes impact on the activity of chromatin-modifying enzymes themselves and thus how chromatin integrates with other cell biological mechanisms. A case in point is cell metabolism, in particular the regulation of chromatin-modifying enzyme activity by specific cellular metabolites. We are looking forward to learn more about it and to see a holistic picture emerge on this fascinating new layer of chromatin regulation.

This series aims to provide an overview by leaders in the field for the general reader and to share with those in the field the latest updates, concepts and projections. We will add chapters to the series as the scene develops.

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EMBO reports Vol 16 | No 11 | 2015 | 1409