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The Allis code

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David Allis (1951–2023) was a leading figure in the field of chromatin biology. He inspired many generations of scientists both through his work and his own personal example as a mentor and colleague. His influential 'histone code' theory remains an important guiding principle to study and understand gene regulation.

In an Obituary in this issue, some of Allis's former students and co-workers pay tribute to his impressive legacy. They describe some of the highlights of his brilliant research career as well as the traits that made him an admired teacher and valued friend. Allis trained a plethora of renowned chromatin biologists and directly or indirectly affected the lives and trajectories of many scientists in other fields. He was the recipient of several prestigious awards, including the Japan Prize for Life Sciences (2014), the Breakthrough Prize in Life Sciences (2015), and the Albert Lasker Basic Medical Research Award (2018).

Perhaps Allis's most famous conceptual contribution to the field of chromatin research was the elaboration of the 'histone code' hypothesis more than 20 years ago. This framework suggested that histone post-translational modifications (PTMs), in different combinations, along with the proteins that can 'write', 'read' or 'erase' them, constitute the basis for a gene regulatory code. In other words, certain histone PTMs could label particular chromatin regions and potentially influence their transcriptional activity. Many of these histone PTMs have been used extensively to characterize or infer a cell state, identity and behavior. For example, methylation marks at H3K27 and H3K9 are mostly associated with gene repression, whereas others, such as H3K4 methylation and H3K27 acetylation, are associated with active regulatory regions.

Although the histone code has been incredibly useful for chromatin biologists and epigeneticists, and is still a valid paradigm, it is a working and evolving model that continues to be refined. Indeed, new histone PTMs, such as H3P16oh, are still being discovered and characterized[1]. Crucially, the exact causal relationship between certain histone PTMs and transcriptional regulation is not yet fully understood. Research using different model organisms and techniques has sometimes offered alternative, or at least thought-provoking, interpretations about the cellular role of specific histone PTMs.

For example, histone acetylation has long been linked to chromatin accessibility and transcriptional activation. H3K27ac is arguably the most widely used acetylation mark for active regulatory regions such as enhancers and promoters. However, a recent paper from Helin and colleagues[2] has reported genetic evidence that H3K27 is largely dispensable for gene activation in mouse embryonic stem cells. So, is H3K27ac a consequence, rather than a cause, of transcriptional activity? Is it a chicken rather than an egg? For instance, Danko and colleagues[3] have shown that transcriptional data can be used to predict histone PTM patterns and indicated that transcription may lie upstream of specific histone PTMs such as H3K27ac. Nonetheless, experiments that manipulate the function of histone acetyltransferases (HAT), including dCas9-p300 recruitment to silent genomic regions, have shown that acetylation can contribute to gene expression. Importantly, HATs can modify other histone residues. The question then emerges: beyond H3K27ac, could other acetylated histone residues have an essential function in gene upregulation?

In an Article in this issue, the Choudhary laboratory reports that the acetylation of histone H2B can be used to identify active enhancers and to predict HAT (CBP/p300) target genes. Although H3K27ac is broadly found on active promoters and enhancers, the authors observe that some H2B acetylated lysine residues show a clear bias towards enhancers. It will be interesting to perform genome-scale histone-editing experiments à la Helin to investigate whether these H2B residues have a causal role in regulating gene expression.

It is worth noting, however, that alternative, or perhaps complementary, interpretations to the histone code have been proposed[4]. Several studies have shown that some histone-modifying complexes can also target non-histone proteins such as transcription factors. Also, those complexes can have key functions that extend beyond their enzymatic roles. For example, in an Article this issue, Ge and colleagues present data indicating that MLL3 and MLL4 have both enzymatic and non-enzymatic roles during mouse development. Therefore, when depleting certain histone-modifying complexes, it is important to not assume that removing those complexes from cells or chromatin is the equivalent of manipulating the levels of their target histone PTMs. In this regard, the Helin paper on H3K27 is a cautionary tale: H3K27ac may be a convenient surrogate for CBP/p300 activity, but the function of these HATs is much broader than modifying this one lysine. The same applies to the Ge paper: depleting MLL3 and MLL4 is not necessarily the same as precluding H3K4me1 deposition; hence the need to study enzymatically dead complexes carefully. This notion may seem obvious to some in the field but it is worth emphasizing.

The histone code has been immensely impactful. However, it is only one part of Allis's remarkable contribution to the scientific community. His passion for science, his kindness, and his mantra that 'every amino acid matters' will be propagated by his mentees. The Allis code will live on.

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