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Histone profiles in cancer

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ABSTRACT

While DNA abnormalities have long been recognized as the cause of cancer, the contribution of chromatin is a relatively recent discovery. Excitement in the field of cancer epigenetics is driven by 3 key elements: 1. Chromatin may play an active and often critical role in controlling gene expression, DNA stability and cell identity. 2. Chromatin modifiers are frequent targets of DNA aberrations, in some cancers reaching near 100%. Particularly in cancers with low rates of DNA mutations, the key "driver" of malignancy is often a chromatin modifier. 3. Cancer-associated aberrant chromatin is amenable to pharmacologic modulation. This has sparked the rapidly expanding development of small molecules targeting chromatin modifiers or reader domains, several of which have shown promise in clinical trials. In parallel, technical advances have greatly enhanced our ability to perform comprehensive chromatin/histone profiling. Despite the discovery that distinct histone profiles are associated with prognostic subgroups, and in some instances may point towards an underlying aberration that can be targeted, histone profiling has not entered clinical diagnostics. Even eligibility for clinical trials targeting chromatin hinges on traditional histologic or DNA-based molecular criteria rather than chromatin profiles.

This review will give an overview of the philosophical debate around the role of histones in controlling or modulating gene expression and discuss the most common techniques for histone profiling. In addition, we will provide prominent examples of aberrantly expressed or mutated chromatin modifiers that result in either globally or locally aberrant histone profiles, and that may be promising therapeutic targets.

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1. Introduction

In 2000, Strahl and Allis put forth the histone code hypothesis. It stated that "multiple histone modifications, acting in a combinatorial or sequential fashion on one or multiple histone tails, specify unique downstream functions" (Strahl & Allis, 2000). In the 15 years since, our understanding of the involvement of histone modifications in development and cancer has exploded, yet, several key questions remain highly debated: Are histone modifications active determinants of transcriptional activity or do they just reflect the execution of a process that is determined by a different mechanism? And if histone modifications actively govern the transcriptional status, do they truly consist of a code? These are critical questions to consider as both histone profiling

Abbreviations: ac, acetyl; ATRA, all-trans retinoic acid; BrD, bromodomain; FL, follicular lymphoma; H, histone; HAT, histone acetyltransferase; HDAC, histone deacetylase; HMT, histone methyltransferase; K, lysine; KMT, lysine methyltransferase; me, methyl; me1, mono-methyl; me2, di-methyl; me3, tri-methyl; PcG, polycomb group; PTM, post translational modification; RA, retinoic acid; RARα, retinoic acid receptor-α; TF, transcription factor; Trx, trithorax; TSS, transcription start site.

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and the pharmacologic modulation of histone modifications are entering clinical practice in oncology.

2. Chromatin and transcriptional regulation

The nucleosome consists of 147 bp of DNA wrapped around a histone octamer that is composed of histones H2A, H2B, H3 and H4 with two copies of each. Post translational modifications (PMTs) on histone proteins are associated with distinct chromatin structures; regions of condensed heterochromatin or open euchromatin. In addition, combinations of PMTs are associated with specific genomic elements such as enhancers, transcription start sites or gene bodies, and correlated with the transcriptional status of the respective gene. Most modifications occur on the N-terminal histone tails, which are unstructured and protrude from the nucleosome core (Kornberg, 1974; Luger et al., 1997). Three different models have emerged that attempt to capture the relationship between chromatin and transcription (Fig. 1).

1. In a transcription factor (TF) centered model, specific TFs respond to environmental or developmental signals by occupying enhancers or promoters through binding to consensus sequences. Depending on the binding of activating or repressing TFs, coactivator or corepressor

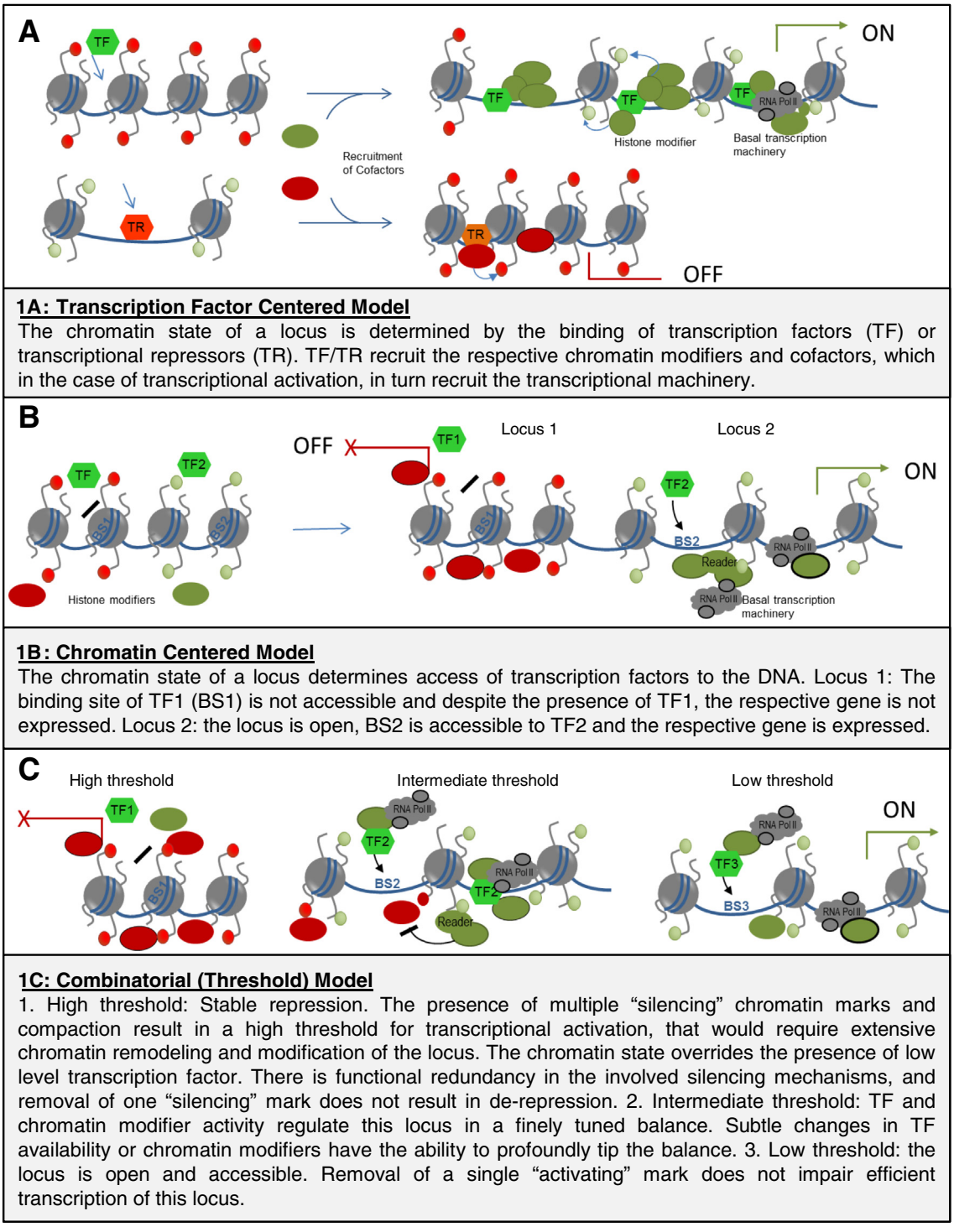

Fig. 1. The role of histones in modulating transcription.

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