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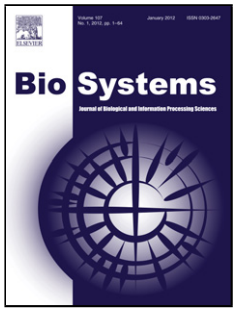

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PII: S0303-2647(17)30368-4
DOI: https://doi.org/doi:10.1016/j.biosystems.2017.11.005
Reference: BIO 3809

To appear in: *BioSystems*

Received date: 17-9-2017
Revised date: 13-11-2017
Accepted date: 15-11-2017

Please cite this article as: Kirti Prakash, David Fournier, Deciphering the histone code to build the genome structure, *<![CDATA[BioSystems]]>* (2017), https://doi.org/10.1016/j.biosystems.2017.11.005

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ACCEPTED MANUSCRIPT

Deciphering the histone code to build the genome structure

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Abstract

Histones are punctuated with small chemical modifications that alter their interaction with DNA. One attractive hypothesis stipulates that certain combinations of these histone modifications may function, alone or together, as a part of a predictive histone code to provide ground rules for chromatin folding. We consider four features that relate histone modifications to chromatin folding: charge neutralisation, molecular specificity, robustness and evolvability. Next, we present evidence for the association among different histone modifications at various levels of chromatin organisation and show how these relationships relate to function such as transcription, replication and cell division. Finally, we propose a model where the histone code can set critical checkpoints for chromatin to fold reversibly between different orders of the organisation in response to a biological stimulus.

Keywords: DNA | nucleosomes | histone modifications | chromatin domains | chromosomes | histone code | chromatin folding | genome structure

Outlook

"The urge to discover secrets is deeply ingrained in human nature; even the least curious mind is roused by the promise of sharing knowledge withheld from others. Most of us are driven to sublimate this urge by the solving of artificial puzzles devised for our entertainment. Detective stories or crossword puzzles cater for the majority; the solution of secret codes may be the hobby of the few."
J. Chadwick, The Decipherment of Linear B [22].
Citation inspired from The Code Book by Simon Singh [113].

From the day/night dichotomy to the genetic code, nature is full of symmetric, antagonistic exemplars and patterns. One such example is the organisation of structurally distinct chromatin states (active, inactive) on a single chromosome. In this article, we try to show how simple combinations of essential elements such as histone modifications can participate in sophisticated cellular features such as the structure of the genome. Here a code is identified, where an input system (histone modifications) is translated into an output system (chromatin states) via adaptors (epigenetic regulators or transcription factors). Such a code has a distinct importance in gene regulation and consequently for the cellular phenotype.

Introduction

The genetic information within chromosomes of eukaryotes is packaged into chromatin, a long and folded polymer of double-stranded DNA, histones and other structural and non-structural proteins. The repeating units of the polymer, the nucleosomes, are 147 base-pairs (1.75 turn) of DNA wrapped around an octamer of 4 histone proteins [74, 3]. Nucleosomes are thought to be further compacted into a higher order 30 nm chromatin fibre by linker histone H1 [135]. The structure of nucleosomes can be altered post-translationally by the small chemical modifications of histone protein [50, 69]. Subsequently, one can characterise the organisation of chromatin into three interrelated categories: (1) the basic building blocks, (2) the functional structure of chromatin and (3) the higher order spatial arrangement of chromatin.

The two classical building blocks (Figure 1A, first column): beads-on-a-string and 30 nm chromatin fibre have been extensively studied previously [62, 102, 74, 61]. Regarding the intermediary level of compaction, chromatin can display several configurations (active, repressed, inactive) depending upon enrichment of a particular histone marks (Figure 1A, second column). At a higher order (Figure 1A, third column), chromatin can be either described as a bimodal heterochromatin/euchromatin model (condensed and open regions, respectively), chromosome territories [76] or as a very condensed structure in the case of the metaphase chromosome. Chromatin fibres indeed present a variety of sizes [95] and of shapes ([39] shows a solenoid model of chromatin), while recent studies attempt to challenge their existence [47], hinting that the hierarchy beads-on-a-string/fibres/domains might be much more complicated and diverse than we currently think.

On the functional side, it has been shown that biochemical changes made to specific histones tails are associated with different condensation levels of chromatin. For instance, trimethylaton of lysine 9 on histone 3 (H3K9me3) is usually associated

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