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Comment

The chromatin regulatory code: Beyond a histone code

A. Lesne[a]

Institut des Hautes Études Scientifiques, Le Bois-Marie, 35 route de Chartres, 91440 Bures-sur-Yvette, France and Laboratoire de Physique Théorique de la Matière Condensée, Université Pierre et Marie Curie, 4 Place Jussieu, 75252 Paris, France

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Abstract. In this commentary on the contribution by Arndt Benecke in this issue, I discuss why the notion of "*chromatin code*" introduced and elaborated in this paper is to be preferred to that of "*histone code*". Speaking of a code as regards nucleosome conformation and histone tail post-translational modifications only makes sense *within the chromatin fiber*, where their physico-chemical features can be translated into regulatory programs at the genome level, by means of a complex, multi-level interplay with the fiber architecture and dynamics settled in the course of Evolution. In particular, this chromatin code presumably exploits allosteric transitions of the chromatin fiber. The chromatin structure dependence of its translation suggests two alternative modes of transcription initiation regulation, also proposed in the paper by A. Benecke in this issue for interpreting strikingly bimodal micro-array data.

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1 Introduction

Within eukaryotic cells, genomic DNA exhibits higher levels of organization. A central one is the so-called *chromatin fiber*, following from a super-helical three-dimensional ordering of basic units, the nucleosomes, each made of 146 bp of DNA wrapped around a histone octamer. The protein histones forming this octamer are each folded into a globular domain belonging to the nucleosome core and continued on each side with, respectively, C-terminal and N-terminal tails protruding outside the nucleosome. These tails experience numerous specific post-translational modifications (*e.g.* acetylation, phosphorylation or methylation), suggested to behave as a second code, the "histone code", devoted to epigenetic regulation [1]. In his contribution [2], Arndt Benecke argues that these histone tail post-translational modifications rather implement a second *layer* of coding. This second-level code is required in eukaryotic cells to provide the additional information necessary to process their long genomes (compared to prokaryote ones). By sorting a fraction of the genome apt to recognition and binding by transcription factors (TFs), this code delineates the genetic information to be processed at each place and time. The present commentary elaborates further on this essential departure from the histone code paradigm. I will in particular describe how physical properties of the chromatin fiber and their functional implications support this notion of *chromatin code* rather proposed on biological, biochemical and information-theoretic grounds in Benecke's paper [2].

2 Reading histone post-translational modifications

Among other consequences and correlated events, it is well documented [3] that histone post-translational modifications influence the TF recruitment to their binding sites; speaking of a "code" and not only of "specific biochemical interactions" precisely underlines the different *nature* of the regulatory scheme associated with the chromatin code. This scheme involves in an essential way the whole chromatin architecture, through
i) its conformational dynamics (chromatin breathing and hypercycles [2,4]),
ii) the associated topological constraints at the level of the fiber (conservation of the fiber linking number ruling the fiber decondensation [5,6]),
iii) the co-evolved topological and mechanical constraints it generates at the DNA level and ensuing modulation of DNA binding affinities (binding energy landscapes, [7, 6]). Considering histone post-translational modifications

[a] e-mail: lesne@ihes.fr, lesne@lptmc.jussieu.fr

in this integrated and multi-level frame leads to a central property: their embedding in a condensed chromatin fiber can tune and amplify their direct physico-chemical consequences (local charge imbalance, local structural or conformational modifications of the tails, changes in their binding affinities with DNA and proteins). It thus provides complementary ways (in plain words: a kinetic, a topological and a mechanical reading) for interpreting histone modifications in terms of regulatory mechanisms.

The chromatin code hypothesis is thus indissociable with multi-scale and inter-level feedback loops, endowing local histone tail modifications with regulated and regulatory consequences at the transcriptional level, far beyond their own features and physico-chemical meaning. Speaking of a code emphasizes the evolutionary origin of the transcription regulatory scheme within chromatin, beyond the necessary physico-chemical laws and relationships, in a word: its biological specificity. This point illustrates a general caveat to be kept in mind in biological analysis and modeling: physical constraints and mechanisms encountered in biological functions rarely occur in their generic instances; on the contrary, they are most often tuned, differentially enhanced or damped, by their intimate and adapted coupling with specific biological entities, in a context-dependent way.

The above-mentioned kinetic and physical "interpretation" of histone modifications not only enlightens the evolutionary design of the chromatin code; it also accounts for its establishment during the stem cell life prior to differentiation commitment, as detailed in the Benecke paper on a model system (myeloid differentiation upon retinoic acid treatment) [2].

3 Chromatin allosteric transitions

The notion of allostery is associated with the presence of a "concerted transition": concerted binding events and structural changes as a control parameter varies, yield a sharp transition, with a threshold ensuring that intermediary states are not observed. The chromatin fiber might exhibit various allosteric transitions, generalizing those proposed for DNA long ago by Pohl and Jovin [8]. Cooperativity, typically reflecting in a sigmoidal shape of the transition extent (or any other reaction coordinate) as a function of time or control parameter, means that an all-or-none transition is achieved, at a free-energy cost increasing more slowly than the transition extent (or even constant, associated with the initial barrier, in perfectly cooperative cases). It is mainly ensured by the symmetries of the fiber structures or by topological constraints propagating the effects of local modifications in a whole chromatin loop [6, 9]. When their effectors are histone modifications, chromatin allosteric transitions are of great relevance to the notion of chromatin code, for at least the two following reasons:

– they explain how local histone modifications might code for major structural reorganizations of the chromatin fiber;
– allosteric transitions delineate *discrete states* for the chromatin fiber; this allows to establish one-to-one relations with the discrete histone modifications, as required to get a *bona fide* code.

4 House-keeping vs. regulated transcription

The chromatin code viewpoint leads to distinguish
i) plain physico-chemical interactions between elementary ingredients (*e.g.* TFs and histone tails) that occur outside any regulatory code and with no need of supplementary information;
ii) on the other hand, coordinated regulation schemes not imposed as a physico-chemical necessity but on the contrary slowly assembled, adapted and settled in the course of Evolution.

Both modalities presumably coexist as alternative mechanisms, respectively direct or regulated, controlling transcription initiation. A working hypothesis is that the first scenario (basically the scheme at work in procaryote cells) is the typical one in euchromatin, with a plain stochastic initiation and no need of a fine-tuned, specific regulation. It would control the transcription of housekeeping genes, *i.e.* genes devoted to maintain the basic cell life and transcribed at a roughly constant level in all instances.

By contrast, the second one would be the rule in functionally organized heterochromatin, where it allows to regulate the specific activation of highly transcribed genes according to an expression pattern adapted to each situation. Such a regulated transcription initiation monitored by a chromatin-coded program is basically the major step in cell differentiation. Due to the inter-level couplings and feedbacks described in Section 2, the chromatin architecture would itself evolve in the course of differentiation commitment, hence the program would undergo a dynamic and adaptive change. Such an adaptive dynamic feature of the chromatin-coded regulatory scheme gives a possible account of the "point of no return" observed in the differenciation pathway: it would occur once the targeted and active chromatin reorganization pathway following from the time-extended implementation of such a program has a negligible probability to be traveled backward (*e.g.* due to a prohibitive free-energy cost or irreversible reaction steps).

This coexistence of direct physico-chemical consequences of histone tail post-translational modifications i) and their evolutionary adapted regulatory interpretation ii) is to be confronted with the observation by Benecke of markedly bimodal transcriptional profiles extracted from high-sensitivity micro-array data. Our distinction recovers its interpretation: the existence of two gene populations, associated with different levels of transcriptional activity, reflects alternative instances of transcription initiation, namely a purely stochastic one and a specifically regulated one [10].

5 Conclusion

Benecke's paper [2] leads to a simple but essential message: only the chromatin fiber architecture, its physical and topological properties, and its dynamics might endow the histone post-translational modifications and their combinatorics with an information contents going beyond their direct physico-chemical consequences. Joint experimental and theoretical work should now validate the integrated regulatory schemes following from the chromatin code hypothesis and their predictions about transcription initiation. Within a wider scope, this paper offers a new view on the "genetic program" not restricted to the symbolic and static genomic sequence level. On the contrary, gene regulatory programs are predicted to be *essentially coordinated with the cell cycle and metabolism*, through enzymatic hypercycles and signalling ruling chromatin dynamics. Last but not least, it introduces a new information-theoretic paradigm: a *two-level code*.

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