Available online at www.sciencedirect.com
ScienceDirect
Mutation Research 618 (2007) 116–129
Fundamental and Molecular Mechanisms of Mutagenesis
www.elsevier.com/locate/molmut
Community address: www.elsevier.com/locate/mutres

Transcription through chromatin by RNA polymerase II: Histone displacement and exchange

Olga I. Kulaeva, Daria A. Gaykalova, Vasily M. Studitsky *

Department of Pharmacology, UMDNJ, Robert Wood Johnson Medical School, 675 Hoes Lane, Room 405, Piscataway, NJ 08854, USA

Received 10 May 2006; accepted 30 May 2006
Available online 21 January 2007

Abstract

The process of transcript elongation by RNA polymerase II (Pol II) involves transcription-dependent exchange and displacement of all core histones and is tightly controlled by numerous protein complexes modifying chromatin structure. These processes can contribute to regulation of transcription initiation and elongation, as well as the chromatin state. Recent data suggest that the histone octamer is displaced from DNA at a high rate of transcription, but can survive less frequent transcription that is accompanied only by partial loss of H2A/H2B histones. Here we propose that critical density of Pol II molecules could be required for displacement of the histone octamer and discuss mechanisms that are most likely involved in the processes of histone exchange.

Keywords: Chromatin; Nucleosome; Histones; Exchange; Transcription; Elongation

1. Introduction

The vast majority of eukaryotic genome is organized into chromatin structure that highly compacts DNA in the nuclei, allows regulated access of various protein complexes to DNA and efficient progression of processive enzymes (such as DNA and RNA polymerases) along the template. Chromatin consists of repeating subunits called nucleosomes. Each nucleosome core includes 147 bp of DNA wrapped 1 2/3 times around a histone octamer containing two each of histones H2A, H2B, H3, and H4 [1]. The core histones are arranged in a tripartite manner: a central $(H3/H4)_2$ tetramer is flanked on each side by an H2A/H2B dimer ([1,2], Fig. 1, inset). One molecule of linker histone, H1, binds to the DNA linking adjacent nucleosomes. Nucleosomes are further compacted into a 30 nm chromatin fiber that most likely is formed by coiled dinucleosomes [3]; these fibers are, in turn, further compacted into structures not fully understood [4].

Compact nucleoprotein organization causes severe problems for processes such as DNA replication, recombination, repair, and transcription *in vitro*. Therefore it is not surprising that many of these processes are accompanied by changes in chromatin structure (chromatin remodeling). Chromatin remodeling is conducted by numerous protein complexes that include multiple ATP-dependent chromatin remodelers, as well as DNA and RNA polymerases [5]. It has become increasingly evident that modulation of chromatin structure plays a central role in numerous intranuclear processes and in their regulation [6]. In particular, in addition to Pol II itself, numerous enzymes involved in modifying chromatin structure (such as ATP-dependent

* Corresponding author. Tel.: +1 732 235 5240; fax: +1 732 235 4073.
E-mail address: studitvm@umdnj.edu (V.M. Studitsky).

0027-5107/$ – see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.mrfmmm.2006.05.040

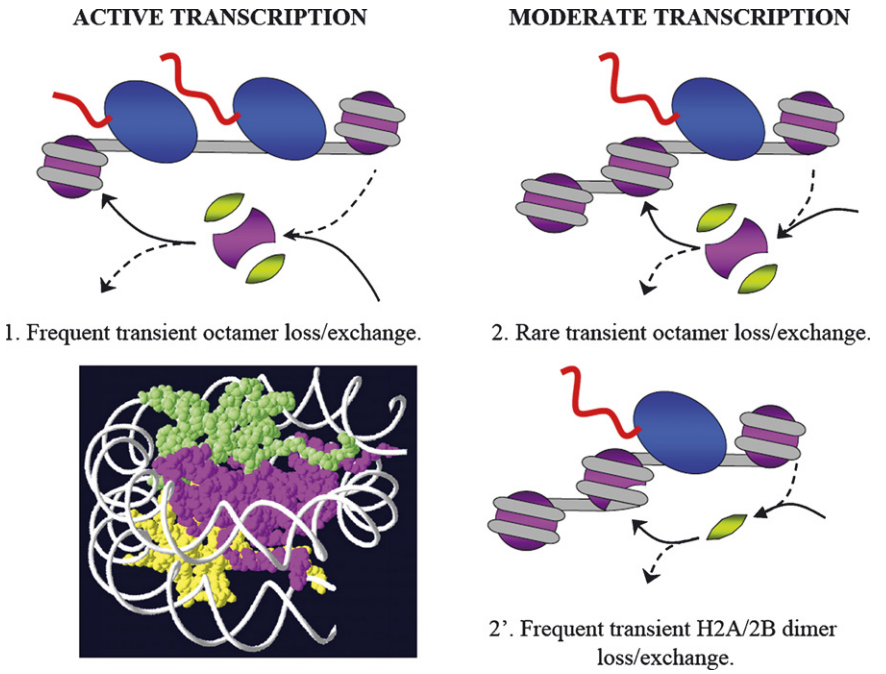

Fig. 1. Possible histone octamer fates during intense and moderate transcription by Pol II *in vivo*. During intense transcription a considerable fraction of the octamers can be displaced from DNA or exchanged (1). The octamer most likely dissociates into chaperone-bound H3/H4 tetramer and two H2A/H2B dimers; the octamers are re-assembled on DNA very soon after the efficiency of transcription is decreased. During moderate transcription the octamer could be transiently displaced from DNA (2); the octamer immediately re-binds to DNA behind the transcribing Pol II. Alternatively, during moderate transcription one H2A/H2B dimer could be transiently displaced by Pol II from the nucleosome or exchanged (2′). Inset: side view of the structure of nucleosome core [1]. DNA is shown in white, the H3/H4 tetramer in purple, and two H2A/H2B dimers in green and yellow. The histone displacement and exchange pathways are indicated by dashed and solid arrows, respectively.

chromatin remodelers, histone-modifying enzymes and histone chaperones) are associated with active genes in transcription-dependent manner (see below) suggesting that at very least chromatin is an ultimate player during transcript elongation. Furthermore, nucleosomes remain associated with transcribed genes unless the level of transcription is extremely high [7–9] and can participate in regulation of the rate of transcript elongation both *in vivo* and *in vitro* [10,11].

This review focuses on the recent progress towards elucidating the mechanistic aspects of transcript elongation by RNA polymerase II (Pol II) through nucleosomal templates. Earlier findings and other aspects of transcription of chromatin by Pol II are covered in several excellent recent reviews [5,12–16].

2. Chromatin transcription by Pol II *in vivo*

2.1. Histone displacement from DNA and nucleosome recovery during transcription in vivo

The structures of the 30 nm chromatin fiber and nucleosome are clearly incompatible with ongoing transcription and have to be disrupted to allow Pol II movement along DNA (reviewed in [12]). Disruption of the higher order chromatin structure is transient and reversible: when Pol II molecules are spaced by more than 200–400 bp, nucleosomal 10 nm and 30 nm filaments are observed between them [17].

Nucleosome structure can also be disrupted during very intense transcription; this can be accompanied by partial loss of all core histones (Fig. 1, model 1). Using chromatin immunoprecipitation technique (ChIP) it has been demonstrated that up to 80% of all core histones can be removed from the transcribed regions of yeast genes [7–9]; the extent of the removal is directly proportional to the efficiency of transcription [8,9]. In earlier studies using micrococcal nuclease (MNase) it has also been shown that some nucleosomes can be lost [18] during very active transcription in yeast. Maximal removal of core histones from the transcribed regions occurs only at high density of Pol II molecules (approximately one molecule per 150 bp [7]). All core histones can be depleted from actively transcribed yeast genes, although in one study it was found that the extent of histone loss is higher for H2A/H2B histones [9]. While the results