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Biochimie 87 (2005) 827–834
BIOCHIMIE
www.elsevier.com/locate/biochi

Expression of metazoan replication-dependent histone genes

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Received 31 December 2004; accepted 18 March 2005

Available online 12 April 2005

Abstract

Histone proteins are essential components of eukaryotic chromosomes. In metazoans, they are produced from the so-called replication-dependent histone genes. The biogenesis of histones is tightly coupled to DNA replication in a stoichiometric manner because an excess of histones is highly toxic for the cell. Therefore, a strict cell cycle-regulation of critical factors required for histone expression ensures exclusive S-phase expression. This review focuses on the molecular mechanisms responsible for such a fine expression regulation. Among these, a large part will be dedicated to post-transcriptional events occurring on histone mRNA, like histone mRNA 3′ end processing, nucleo-cytoplasmic mRNA export, translation and mRNA degradation. Many factors are involved, including an RNA-binding protein called HBP, also called SLBP (for hairpin- or stem-loop-binding protein) that binds to a conserved hairpin located in the 3′ UTR part of histone mRNA. HBP plays a pivotal role in the expression of histone genes since it is necessary for most of the steps of histone mRNA metabolism in the cell. Moreover, the strict S-phase expression pattern of histones is achieved through a fine cell cycle-regulation of HBP. A large part of the discussion will be centered on the critical role of HBP in histone biogenesis.

Keywords: Cell cycle-dependent histone; Replication-dependent histone; Histone mRNA metabolism; Histone biogenesis

1. Introduction

DNA in chromatin is organized in arrays of nucleosomes. Two copies of each histone, H2A, H2B, H3 and H4, are assembled in an octamer that has 146 ± 1 bp of DNA wrapping around it to form a so-called nucleosome core. The repeating nucleosomes further assemble into higher-order structures, which are stabilized by the linker histone H1. The nucleosome in its role as the principal packaging element of DNA within the nucleus is the primary determinant of DNA accessibility [1]. RNAi experiments in *Caenorhabditis elegans* showed that inhibition of histone expression in embryos lead to decondensed chromosomes and chromosome bridges inducing an early arrest of cell proliferation [2]. Inhibition of histone expression at post-embryonic stages causes sterility and multivulval phenotypes of the animals that reached adulthood [3]. In addition, over-expression of one subtype of histone led to severe troubles in transcription [4] or even to chromosomal loss appearing after several cell cycles [5]. These experiments have shown that expression of all the histone subtypes has to be absolutely stoichiometric. Therefore regulation of histone expression is critical for proper DNA packaging and for normal life cycles during cell proliferation. In metazoans, histones are produced from two gene families. First, the replication-independent genes that are constitutively expressed at a basal level throughout the whole cell cycle in order to provide the required histones necessary for putative chromatin lesion repair. Second, the replication-dependent histone genes are coupled to DNA biosynthesis

Abbreviations: bp, base pair; CHO, Chinese hamster ovary; eIF3, eukaryotic initiation factor 3; eIF4E, eukaryotic initiation factor 4E or cap binding protein; eIF4G, eukaryotic initiation factor 4G; HBP, hairpin binding protein; HDE, histone downstream element; 3′hExo, human 3′ exonuclease; NPC, nuclear pore complex; NTPs, ribonucleotides; ORF, open reading frame; PABP, polyA binding protein; RBD, RNA-binding domain; SLBP, stem-loop binding protein; TAP, tip associated protein; 3′ UTR, 3′ untranslated region.

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doi:10.1016/j.biochi.2005.03.012

during replication. This class of genes provides the large amounts of histones required for genome duplication during S-phase. This review is focused on the molecular mechanisms involved in the massive biogenesis of histones encoded by the replication-dependent histone genes. These genes are unique in eukaryotes in that they do not contain any introns. They are exclusively expressed during the S-phase of the cell cycle. The massive expression of histones is tightly regulated at different levels of the biosynthesis process in order to ensure exclusive S-phase expression (Fig. 1). Indeed, the production of histones during G1-, G2-, or M-phase is highly toxic for the cell [6].

2. Transcription

At the beginning of S-phase the transcription of the replication-dependent histone genes by RNA polymerase II increases from three to five-fold ([7] and references therein). Although the transcription of each histone subtype is regulated in a coordinate manner, there are no obvious sequence elements in the promoters of histone genes responsible for such a coordinate transcription. However, common elements for a particular histone gene can be found like the Octamer-binding Transcription Factor OTF-1, which binds to all the H2b promoter regions [8]. Another element named CRAS

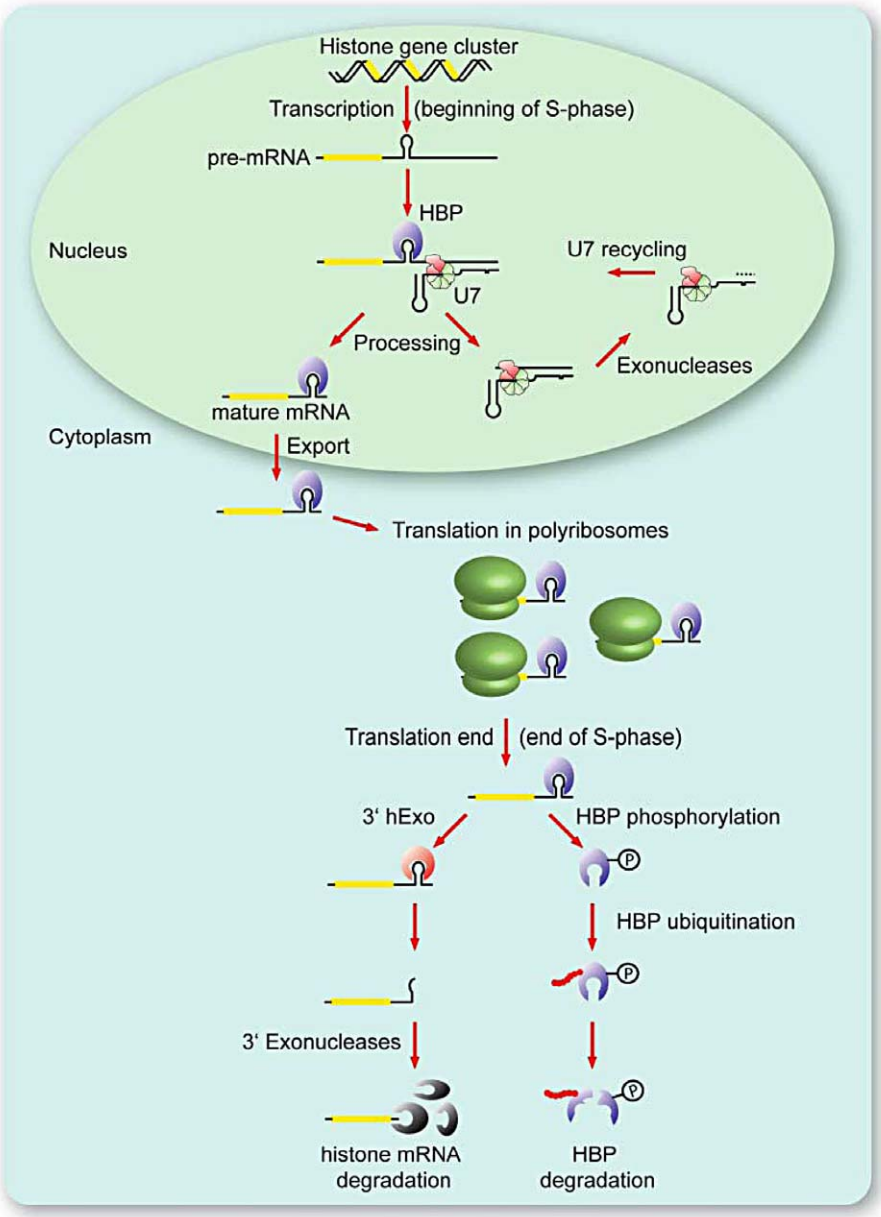

Fig. 1. Schematic representation of the replication-dependent histone mRNA metabolism. At the beginning of the S-phase, histone precursor mRNAs are transcribed from clustered genes that are located close to the Cajal Bodies. Following 3′ end processing in the nucleus, HBP accompanies the mature histone mRNA to the cytoplasm where it is required for efficient translation and histone mRNA stability. At the end of the S-phase, HBP is phosphorylated and ubiquitinated leading to its rapid degradation via the proteasome pathway. The naked histone mRNAs are first partially degraded by a specific 3′ hExo and then by the canonical mRNA decay exonucleases.