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POINT OF VIEW

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Non-coding RNAs, the cutting edge of histone messages

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ABSTRACT

In metazoan the 3′-end processing of histone mRNAs is a conserved process involving the concerted action of many protein factors and the non-coding U7 snRNA. Recently, we identified that the processing of histone pre-mRNAs is promoted by an additional ncRNA, the Y3-derived Y3** RNA. U7 modulates the association of the U7 snRNP whereas Y3** promotes recruitment of CPSF (cleavage and polyadenylation specific factor) proteins to nascent histone transcripts at histone locus bodies (HLBs) in mammals. This enhances the 3′-end cleavage of nascent histone pre-mRNAs and modulates HLB assembly. Here we discuss new insights in the role of ncRNAs in the spatiotemporal control of histone synthesis. We propose that ncRNAs scaffold the formation of functional protein-RNA complexes and their sequential deposition on nascent histone pre-mRNAs at HLBs. These findings add to the multiple roles of ncRNAs in controlling gene expression and may provide new avenues for targeting histone synthesis in cancer.

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Introduction

Histone mRNAs encode for one of the most essential classes of chromatin-associated proteins in eukaryotes. The histone proteins H2A, H2B, H3 and H4 assemble into higher order complexes, which condense the chromosomal DNA into functional units, the nucleosomes. Histone H1 acts as linker connecting distinct nucleosomes. Accordingly, histone proteins are an integral component of eukaryotic chromatin and serve essential regulatory roles in transcription. Replication-dependent (canonical) histone mRNAs encode for the majority of histone proteins. Their expression is precisely controlled in a cell-cycle dependent manner with a precisely timed upregulation in S-phase when newly synthesized DNA has to be packed into nucleosomes.[1] In contrast to bulk mRNAs, histone-encoding transcripts usually lack introns and a poly(A)-tail at their 3′-end. Instead they contain a conserved stem-loop structure in the 3′-UTR, which is essential to control the life-cycle of these mRNAs including 3′-end processing, nuclear export and most importantly their translation. Consistent with their none typical 3′-end, a specialized processing machinery has evolved to ensure proper mRNA processing (Fig. 1).

NPAT (nuclear protein, ataxia-telangiectasia locus) and its insect homolog Mxc (multi sex combs) are considered to be the major transcriptional regulators of histone expression in higher eukaryotes. Upon S-phase entry, NPAT is phosphorylated by cyclin-dependent kinases (CDKs) leading to the initiation of histone transcription.[2] The FLASH-protein (FLICE-associated huge) associates with NPAT and is considered to be essential for connecting histone mRNA synthesis to 3′-end processing by modulating the recruitment of processing factors to nascent histone pre-mRNAs (Fig. 1).[3-5] The stem-loop binding protein (SLBP) is a specialized RNA-binding protein associating with the conserved stem-loop structure of metazoan histone mRNAs. SLBP is a key regulator of histone mRNA fate modulating histone mRNA processing, nuclear export and translation in the cytoplasm.[6-8] The U7 snRNP complements the histone specific processing complex. This ribonucleoprotein-(RNP)-complex nucleates on the small non-coding RNA (ncRNA) U7. The U7 snRNP subunit LSM11 mediates association with the FLASH-protein and thus recruitment of the U7 snRNP to the DNA-associated transcription/processing-complex. The multiprotein cleavage and polyadenylation specificity factor (CPSF) is utilized by both, bulk as well as histone mRNAs to mediate the 3′-end processing of pre-mRNAs. The cleavage of histone mRNAs is facilitated by the CPSF-associated nuclease CPSF-73 (CPSF3) typically targeting nascent histone pre-mRNAs in the proximity of CA/UA-dinucleotides located downstream of the stem-loop. Furthermore, additional processing factors (PFs), for instance CstF64 and Symplekin, complement the histone 3′-end

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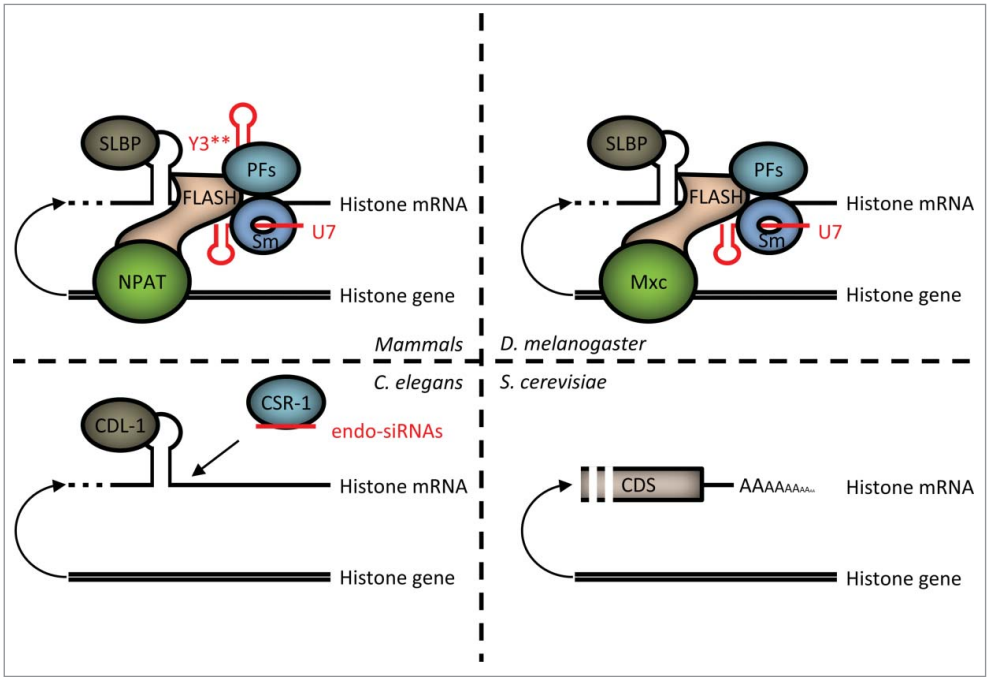

Figure 1. Eukaryotic histone mRNA processing pathways. The proposed histone mRNA processing mechanisms are shown for mammals, *D. melanogaster, C. elegans* and yeast. Involved ncRNAs are indicated in red. The indicated involved protein factors are explained in the main text. PFs – Processing factors (e.g. CPSF, CstF64, Symplekin).

processing machinery by associating with FLASH and/or the U7 snRNP.[9-12] We recently demonstrated that the Y3** ncRNA associates with the CPSF and promotes the recruitment of this processing factor to histone pre-mRNAs.[13] Consistently, Y3** enhances the 3′-end processing of canonical histone pre-mRNAs. In conclusion this indicates that besides the well-established role of U7, another medium-sized ncRNA modulates the 3′-end processing of mammalian histone mRNAs.

The U7 snRNA

U7 was first cloned from sea urchin, where it was shown that this ncRNA promotes the 3′-end processing of histone mRNAs upon partial hybridization to the 3′-UTR of nascent pre-mRNA.[14] Like other snRNAs, the ~60–70 nts long U7 is synthesized from individual genes by RNA Polymerase II. It is assumed that this ncRNA consists of a mostly single stranded 5′-end, whereas the 3′-end folds into a stem-loop structure. Consistent with the biogenesis of spliceosomal snRNAs, U7 is cycled through the cytoplasm for maturation involving the addition of a trimethyl cap and Sm-ring association.[15] In contrast to other snRNAs, U7 contains a variant Sm-binding site, which also explains the unusual composition of the U7-associated Sm-ring. Accordingly, it was shown that SmD1 and SmD2, components of the usual heptameric Sm-ring, are replaced by the U7-specific Lsm10 and Lsm11 proteins.[16,17] The N-terminus of Lsm11 associates with FLASH, one of the most important interactions within the histone pre-mRNA cleavage complex (HCC).[11] The association of U7-associated complexes with nascent histone pre-mRNAs is assumed to essentially rely on RNA-RNA hybridization. This was shown to involve the conserved histone downstream element (HDE) located downstream of the histone stem-loop in nascent histone transcripts and the 5′-end of the U7 ncRNA.[18-20]

The Y3** ncRNA

Y RNAs are medium-sized ncRNAs (83–112 nts in human) transcribed by RNA polymerase III from individual genes.[21,22] These ncRNAs mainly associate with the Ro60-protein and other RNA-binding proteins like IGF2BP1 in cytoplasmic RNPs.[23,24] It was reported, that the Y3 RNA can be processed into a smaller 60nt-long RNA, termed Y3**.[25] We found that Y3 and Y3** directly bind to proteins of the CPSF-complex suggesting their involvement in the 3′-end processing of mRNAs.[13] This was confirmed by the depletion of Y RNAs using chimeric anti-sense oligonucleotides (ASOs). The knockdown of Y3/Y3** selectively impaired the 3′-end processing of canonical histone but not bulk mRNAs. The characterization of the Y3**-CPSF interaction revealed that Y3** directly associates with the CPSF-associated FIP1L1 protein and promotes the cooperative association of CPSF4 in cell lysates. In contrast to Y3, Y3** associates with histone mRNAs near the HDE. This was supported by

chromatin-immunoprecipitation (CHIP) of a Mini-FLASH reporter protein reported to localize to histone locus bodies (HLBs), the site of histone mRNA transcription and processing.[5,26] Like the U7 snRNA, Y3** associates with chromatin-bound Mini-FLASH supporting the role of both ncRNAs in the 3′-end processing of histone transcripts at HLBs. In contrast to U7, however, Y3** modulates the morphology and dynamic recruitment of proteins to HLBs. This suggests that Y3** modulates HCC-assembly at HLBs presumably by enhancing the recruitment of CPSF-components to nascent histone mRNAs. Surprisingly, however, Y3** is not observed in mouse-like rodents (*muroidea*) suggesting that yet to identify ncRNAs direct the recruitment of the CPSF to HLBs in these species.

Other ncRNAs involved in the processing of histone mRNAs

In contrast to metazoan, yeast histone mRNAs lack a stem-loop structure and become polyadenylated like bulk mRNAs. It is assumed that the cell-cycle dependent timing of histone synthesis in yeast is regulated by the control of transcriptional activation and poly(A)-tail length.[27,28] Up to date no ncRNAs involved in histone mRNA metabolism could be identified in unicellular eukaryotes like yeast (Fig. 1). The architecture of histone mRNA 3′-ends in *C. elegans* is similar to mammalian histone transcripts including a stem-loop but lacking polyadenylation. Consistently, an SLBP-homolog (CDL-1) modulating the translation of histone mRNAs was identified (Fig. 1).[29,30] Interestingly, however, until now no U7-homolog was identified in *C. elegans*. Instead, the 3′-end processing of histone pre-mRNAs is considered to rely on other small ncRNAs (endo-siRNAs) associating with the Argonaute-protein CSR-1 at the 3′-UTR of nascent histone transcripts in proximity to the stem-loop.[31] Accordingly, *C. elegans* histone pre-mRNAs are presumed to be processed by an RNAi-like mechanism. Although the pathway of histone mRNA 3′-end processing differs significantly from worm to mammals, the involvement of ncRNAs seems to be conserved in all metazoan histone mRNAs. Along these lines it has to be noted that also spliceosomal ncRNAs (U2 and U12) were reported to promote the 3′-end processing of mammalian histone mRNAs.[32] In contrast to U7 or Y3**, these snRNAs associate with a 22nt-element located upstream of the stem-loop, mostly within the coding region. Consistently it was shown, that components of the U2 snRNP associate with histone messages as well. It is therefore tempting to speculate that additional ncRNAs control the expression and 3′-end processing of histone mRNAs.

The role of ncRNAs in HLB formation

Metazoan histone genes are mainly organized in genomic clusters. In mammals dozens of functional histone genes have been identified, which mainly cluster at 2 genomic regions (on chromosomes 1 and 6 in human). Although substantially different, a clustered genomic organization of tandemly repeated histone genes is also observed in *D. melanogaster*. Thus, the expression of histones is not just coordinated in a temporal cell-cycle dependent manner but obviously requires the spatial coordination of histone genes in genomic clusters. These can even be visualized as compact nuclear bodies, the so-called histone locus bodies (HLBs) considered to indicate the site of histone transcript synthesis and processing. Consistent with previous studies, we observed that the NPAT protein is associated with HLBs throughout the cell-cycle.[33] To characterize the role of ncRNAs in modulating histone mRNA processing at HLBs, we analyzed how mammalian HLB morphology and the dynamic recruitment of processing factors to HLBs is modulated by the depletion of ncRNAs and processing factors.[13] Based on these studies our data supports the view that the FLASH protein is an integral component of HLBs ensuring proper HLB formation and maintenance (Fig. 2A).[34-36] The depletion of FLASH in human cells leads to a severe impairment of HLB assembly and the displacement of NPAT. Upon cell-cycle dependent activation by NPAT-phosphorylation histone mRNA synthesis initiates in HLBs (Fig. 2A). Subsequently processing factors (PFs) like the CPSF are recruited to HLBs, which is promoted by Y3** (Fig. 2B). This notion is supported by the strongly reduced size of HLBs upon the depletion of all analyzed CPSF-associated proteins (CPSF1, CPSF2, CPSF3, CPSF4, SYMPK and FIP1L1) as well as the Y3** ncRNA. This indicates that the Y3**-directed recruitment of PFs is dispensable for the initial formation of HLBs but modulates the dynamic assembly of the processing machinery at HLBs and thus HLB maturation. Interestingly, HLB morphology remained essentially unchanged by the depletion of U7 or its associated proteins Lsm10 and Lsm11 although these components serve essential roles in the processing of nascent histone transcripts and are associated with HLBs throughout the cell cycle (Fig. 2).[36-38] These findings strongly suggest that the Y3**-directed recruitment of PFs enhances HCC-assembly at HLBs in S-phase to assist in histone mRNA 3′-end processing (Fig. 2C). This hypothesis is consistent with earlier reports in *Drosophila* suggesting a hierarchically ordered assembly of the processing machinery at HLBs.[39] Notably in this respect is that neither the depletion of Y3** nor U7 abolished proper 3′-end processing suggesting that both ncRNAs only

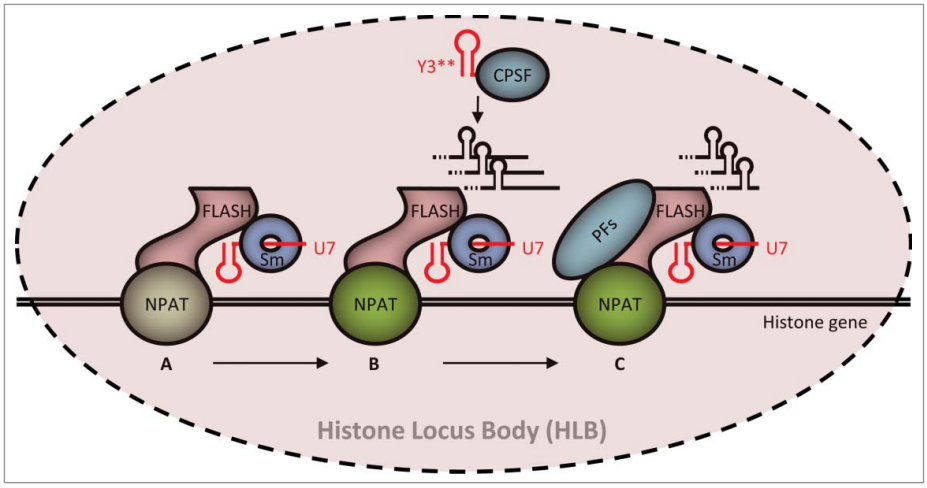

Figure 2. Schematic model of the sequential assembly of factors involved in the synthesis and processing of histone mRNAs at HLBs. It is assumed that NPAT, FLASH and the U7 snRNP associate with histone genes throughout the cell-cycle (A). Following the phosphorylation-directed activation of NPAT, histone mRNA synthesis is initiated. The Y3** ncRNA recruits the CPSF-complex to nascent histone transcripts at HLBs (B). After the completion of HCC assembly (including processing factors (PFs) like the CPSF), histone mRNAs are processed and released from HLBs to foster the export to the cytoplasm and histone protein synthesis (C).

expedite processing to ensure the efficient and timely release of matured histone mRNAs from HLBs.

Perspective

NcRNAs promote the assembly and spatially controlled deposition of processing complexes on nascent histone transcripts at HLBs. These mechanisms add to the multiple roles of ncRNAs in the synthesis and processing of RNAs in the nucleus. To provide a holistic view on the involvement of ncRNAs in the 3′-end processing of RNAs FLASH- and/or CPSF-associated ncRNAs need to be identified in a systematic manner. Moreover, the molecular mechanisms underlying the apparently tightly controlled assembly of processing factors on nascent transcripts in discrete nuclear foci need to be addressed in further detail. For instance, little is known about the signaling events involved in the hierarchal assembly of HLBs and release of matured transcripts. These aspects are important to understand how histone synthesis is controlled in highly proliferative tumor cells, frequently characterized by an amplification of histone gene loci.[26,40] Intriguingly, the transcriptional regulator MYC localizes to HLBs suggesting an involvement of this potent oncogene in the expression of histones.[41] In support of this, Y RNA abundance is increased in cancer cells suggesting that elevated histone synthesis observed in some cancers, for instance MYCN-amplified neuroblastoma, is sustained by enhanced 3′-end processing.[42] The analyses of molecular mechanisms underlying histone synthesis in cancer cells might thus provide novel avenues for pursuing therapeutic strategies aiming at the impairment of uncontrolled excessive proliferation.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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