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Review

Ubiquitin and assembly of export competent mRNP☆

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ABSTRACT

The production of mature and export competent mRNP (mRNA ribonucleoprotein) complexes depends on a series of highly coordinated processing reactions. RNA polymerase II (RNAPII) plays a central role in this process by mediating the sequential recruitment of mRNA maturation and export factors to transcribing genes, thereby establishing a strong functional link between transcription and export through nuclear pore complexes (NPC). Growing evidence indicates that post-translational modifications participate in the dynamic association of processing and export factors with mRNAs ensuring that the transitions and rearrangements undergone by the mRNP occur at the right time and place. This review mainly focuses on the role of ubiquitin conjugation in controlling mRNP assembly and quality control from transcription down to export through the NPC. It emphasizes the central role of ubiquitylation in organizing the chronology of events along this highly dynamic pathway. This article is part of a Special Issue entitled: Nuclear Transport and RNA Processing.

1. mRNA export pathway: actors and mechanisms

mRNA export is an evolutionarily conserved process essential for gene expression in all eukaryotic cells. mRNA export is tightly coupled to upstream events including transcription and processing as well as downstream events, such as mRNA localization and translation. The mRNA biogenesis pathway involves a myriad of factors that interact either transiently with the mRNA to promote its maturation or remain associated with the transcript along the export path facilitating its translocation through nuclear pores or protecting it from degradation before its translation in the cytoplasm.

mRNA processing involves the addition of a 5′ cap structure, excision of introns by the splicing machinery and 3′ end cleavage and polyadenylation by the 3′ processing complex composed of CPF, CFIA and CFIB [1,2]. All these maturation steps are tightly coordinated by RNA polymerase II, which triggers the sequential recruitment of these processing machineries to nascent transcripts as a function of the phosphorylation of its C-terminal domain (CTD) [3]. Co-transcriptional mRNP assembly is highly dynamic and involves the association and dissociation of multiple processing and export factors with the transcription machinery and/or the nascent transcript, which ultimately result in the release of mature mRNPs from the transcription site (Fig. 1).

mRNA export is mediated by the evolutionarily conserved shuttling heterodimeric export receptor Mex67-Mtr2 (TAP-p15 or NXF1-Nxt1 in higher eukaryotes) which promotes mRNP translocation into the cytoplasm through direct interaction with FG-nucleoporins lining the central channel of the NPC [4]. The association of Mex67 with mature mRNPs is mediated by adaptor proteins. The first and best-characterized adaptor is the conserved mRNA binding protein Yra1/REF (Aly/REF in higher eukaryotes) (Table 1) [4–6]. Although essential in yeast, Aly/REF is not absolutely required for mRNA export in metazoan systems suggesting the existence of additional export adaptors [7]. Indeed the shuttling SR (serine/arginine rich) proteins SRp20 and 9G8 in mammals [8,9] and the SR-like protein Npl3 essential for yeast mRNA export [10] have been identified as Mex67/NXF1 adaptors. Finally, the yeast hnRNP protein Nab2, involved in polyA tail length control and mRNA export [11–13] was recently described as an additional export adaptor able to simultaneously interact with Mex67 and Yra1 [14]. An early study suggested that Nab2 and Npl3 may define distinct export pathways as they were found to interact with overlapping but distinct classes of transcripts [15]. However, more recent studies based on RNA deep sequencing indicate that Nab2 binds most transcripts and may therefore represent a general mRNA export factor [16]. Importantly, while Npl3 and Nab2 are shuttling mRNA binding proteins, Yra1 appears to dissociate from mRNPs before export and may therefore not represent a *bona fide* export adaptor [5,6,17].

The export receptor Mex67 and its adaptors Yra1, Nab2 and Npl3 are all recruited during transcription, via independent and specific interactions with the transcription machinery. While Nab2 associates with transcribing genes via a yet unknown interaction [18,19], Npl3 directly interacts with RNA polymerase II at the 5′ end of

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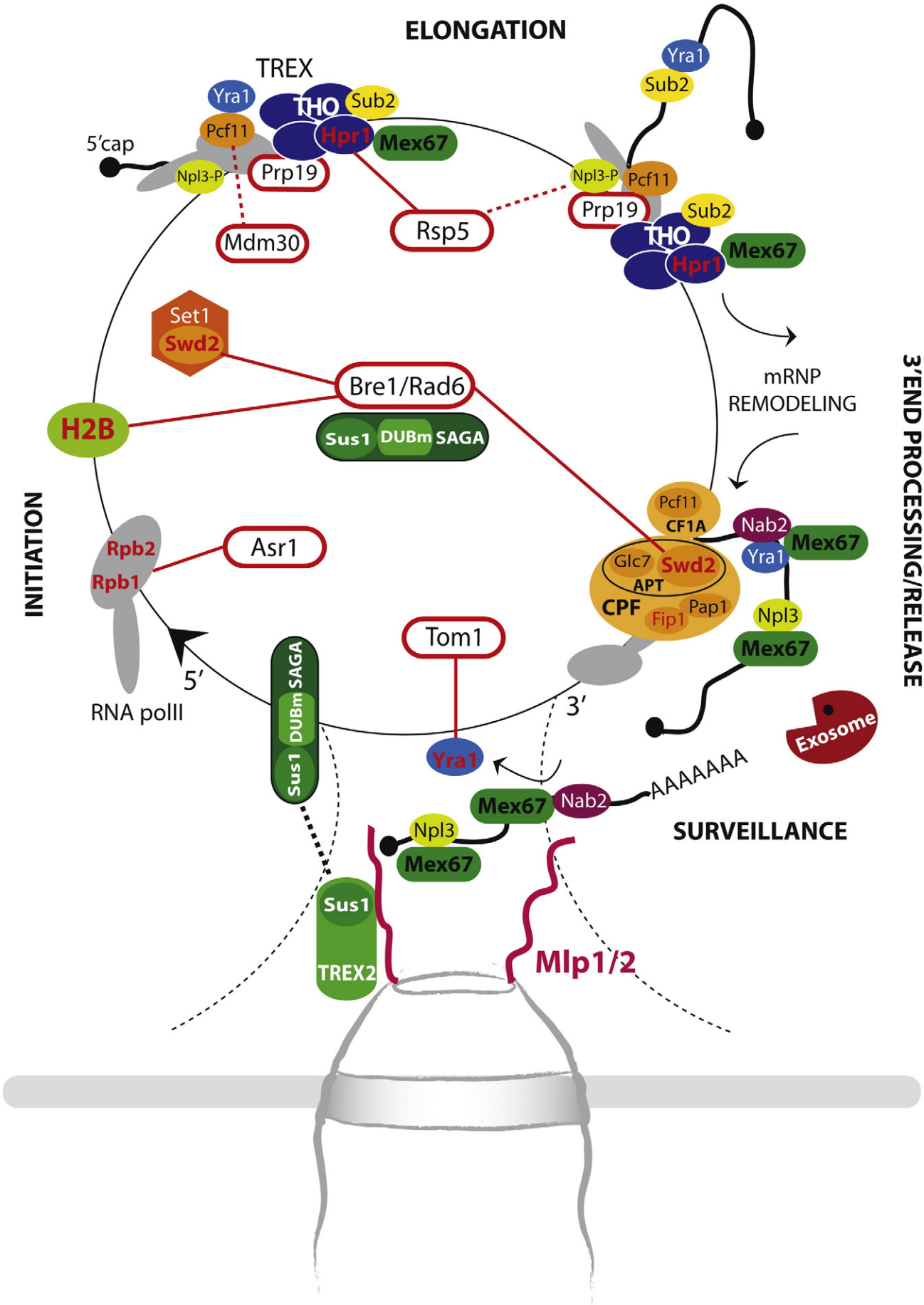
ELONGATION
TREX
Yra1
THO
Sub2
Pcf11
Hpr1
Mex67
5'cap
Npl3-P
Prp19
Mdm30
Rsp5
Yra1
Sub2
Npl3-P
Pcf11
Prp19
Sub2
THO
Hpr1
Mex67
Set1
Swd2
Bre1/Rad6
H2B
Sus1
DUBm
SAGA
mRNP
REMODELING
3'END PROCESSING/RELEASE
INITIATION
Pcf11
CF1A
Nab2
Mex67
Yra1
Rpb2
Rpb1
Asr1
Glc7
Swd2
APT
CPF
Pap1
Fip1
Npl3
Mex67
Tom1
5'
RNA polII
3'
Exosome
DUBm
SAGA
Sus1
Yra1
AAAAAAA
Mex67
Nab2
SURVEILLANCE
Npl3
Mex67
Sus1
TREX2
Mlp1/2