

## Falling for the dark side of transcription: Nab2 fosters RNA polymerase III transcription

L. Maximilian Reuter and Katja Sträßer

Institute of Biochemistry, Justus Liebig University Giessen, Giessen, Germany

### ABSTRACT

RNA polymerase III (RNAPIII) synthesizes diverse, small, non-coding RNAs with many important roles in the cellular metabolism. One of the open questions of RNAPIII transcription is whether and how additional factors are involved. Recently, Nab2 was identified as the first messenger ribonucleoprotein particle (mRNP) biogenesis factor with a function in RNAPIII transcription.

### ARTICLE HISTORY

Received 17 February 2016  
Revised 18 March 2016  
Accepted 18 March 2016

### KEYWORDS

gene expression; Nab2;  
ncRNA; RNA polymerase III;  
transcription; tRNA; TFIIB;  
ZC3H14

### RNAPIII transcription and basic transcription factors

RNAPIII synthesizes a rather small set of highly expressed, infrastructural RNAs, such as tRNAs, 5S rRNA, the RNA of the signal recognition particle (*SCR1*), and other small non-coding RNAs.<sup>1</sup> The majority of these RNAPIII transcripts serves as essential components in many cellular processes such as mRNA splicing, tRNA maturation, and translation.<sup>1,2</sup> RNAPIII is the largest DNA-dependent RNA polymerase and comprises 17 sub-units, all of which are essential in *S. cerevisiae*.<sup>3</sup> Four of the RNAPIII sub-units (Rpc34, Rpc37, Rpc53, and Rpc82) are homologous to general RNA polymerase II (RNAPII) transcription factors that are stably associated with the core polymerase, e.g. Rpc34 and Rpc82 show homologies to TFIIE  $\alpha$  and  $\beta$ .<sup>4,5</sup>

The basic mechanism of RNAPIII transcription is well characterized and depends on the three transcription factors TFIIA (for 5S rRNA transcription only), TFIIB, and TFIIC.<sup>2,6</sup> TFIIC binds to the A and B box promoter element in the initial step of RNAPIII transcription and recruits TFIIB.<sup>7,8</sup> At TATA-box containing genes, TFIIB can bind the DNA independently of TFIIC.<sup>3,9</sup> TFIIB function is key to transcription

initiation as it recruits RNAPIII to the promoter. TFIIB is also responsible for opening the double-stranded DNA and thus for establishing a closed pre-initiation complex and the transcription bubble.<sup>10,11</sup> As with other polymerases short, abortive transcripts are initially produced.<sup>12</sup> Once a stable elongation complex is formed, productive transcription proceeds through the gene body until a simple T-rich repeat on the non-template strand is reached. This oligo(dT) stretch has been identified as the universal terminator for RNAPIII at every gene, irrespective of the promoter, other *cis*-elements, or *trans*-acting factors.<sup>13,14</sup> Due to the high need of RNAPIII transcripts, efficient transcription mechanisms had to be evolved. According to a concept known as “facilitated recycling” the transcribing polymerase is committed (tethered) pre-dominantly to reinitiate at the same gene, circumventing the slow steps of initiation. Hence, a new transcription cycle is completed up to 10-fold faster than the initial round of transcription.<sup>15</sup>

### Additional RNAPIII transcription factors

*In vitro* transcription assays reconstituted with RNAPIII, TFIIB, and TFIIC possess a much lower transcriptional activity than transcription active cell

**CONTACT** Katja Sträßer  [katja.straesser@chemie.bio.uni-giessen.de](mailto:katja.straesser@chemie.bio.uni-giessen.de)  Institute of Biochemistry, Justus Liebig University Giessen, Heinrich-Buff-Ring 17, 35392 Giessen, Germany

© 2016 L. Maximilian Reuter and Katja Sträßer. Published with license by Taylor & Francis.

This is an Open Access article distributed under the terms of the Creative Commons Attribution-Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0/>), which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited. The moral rights of the named author(s) have been asserted.

fractions.<sup>6</sup> This suggested the existence of additional factors that stimulate RNAPIII transcription. Indeed, during the last decade genome-wide studies in a variety of species led to the discovery of several proteins with a function in RNAPIII transcription. To mention but a few, Maf1, Dst1 (TFIIS), Sub1, Myc, Rb, and p53 have been identified to modulate RNAPIII activity (for a review of these proteins see refs. <sup>11,16-18</sup>). Furthermore, chromatin modifying enzymes and remodeling complexes have been proposed to influence RNAPIII transcription.<sup>19</sup> Remodeling enzymes might adapt and maintain the local chromatin in an open state (euchromatin) and thus keep RNAPIII genes free of nucleosomes.<sup>20</sup> Unfortunately, the molecular function of these proteins in RNAPIII transcription often remained elusive.<sup>11</sup> Therefore, the continuous identification of novel factors involved in RNAPIII transcription and the functional characterization of known and novel ones will pave the way toward a true understanding of the RNAPIII transcription mechanisms and its regulation.

### Nab2 and its functions in nuclear mRNP biogenesis

The nuclear polyadenylated RNA-binding protein Nab2 is a member of the poly(A)-binding protein (PABP) family in *S. cerevisiae* and was originally discovered—as its name implies—in a screen for proteins that bind to nuclear polyadenylated RNAs.<sup>21</sup> Since then, Nab2 emerged as a key component in the tightly intertwined system of poly(A) tail length control, mRNP formation, and export of mature mRNPs.<sup>22</sup> In contrast to Nab2's role in these later steps of mRNP biogenesis, its function in RNAPII transcription is less clear. *NAB2* mutant cells show reduced transcription of the heterologous *lacZ* gene, which is badly transcribed and processed in yeast. However, the *NAB2* allele used, *nab2-1(-GFP)*, causes very slow growth, and transcription of the endogenous yeast gene *PHO5* is not affected.<sup>23</sup> Thus, the effects observed for the *lacZ* gene might be non-specific. This is in line with the observation that neither RNAPII processivity nor nascent *HSP104* mRNA levels are affected by nuclear depletion of Nab2 using the anchor-away technique.<sup>24</sup> Thus, Nab2 probably does not play a role in RNAPII transcription, but rather in mRNA stability.<sup>24</sup>

Orthologues of Nab2 have been identified in many organisms, e.g., human, mouse, and fly. Human

ZC3H14 can functionally substitute dNab2 in fly neuronal tissue.<sup>25</sup> Furthermore, Nab2 is required for correct poly(A) tail length in *D. melanogaster* and probably *H. sapiens*.<sup>25,26</sup> Thus, Nab2's functions are probably conserved as well.

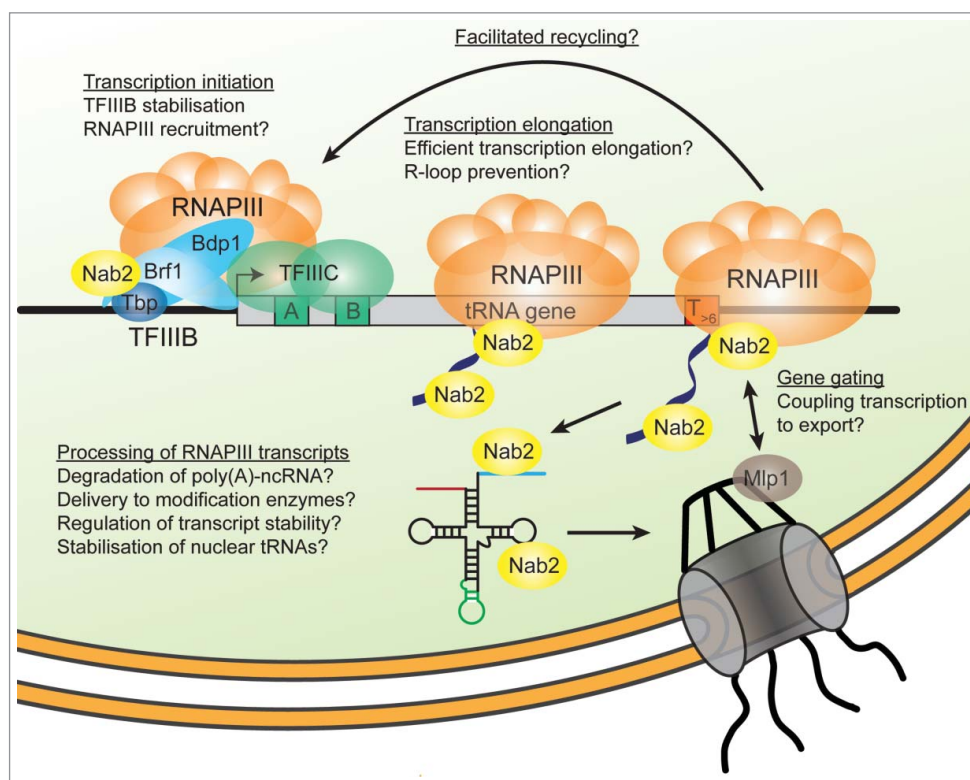
### Nab2 functions in RNAPIII transcription initiation

In a recent study, we unraveled a function of Nab2 in RNAPIII transcription in the model organism *S. cerevisiae* (Fig. 1).<sup>27</sup> Serendipitously, we observed in a genome-wide approach that Nab2 is present at all RNAPIII-transcribed genes. Nab2's occupancy is independent of RNAPII occupancy, but dependent on active RNAPIII transcription. Using a novel temperature-sensitive mutant, *nab2-34*, we showed that Nab2 is required for the occupancy of RNAPIII at its target genes. Importantly, impairment of Nab2 function causes an RNAPIII transcription defect *in vivo* and *in vitro* that can be rescued by the addition of recombinant Nab2 to the *in vitro* assay. Interestingly, Nab2 interacts directly with RNAPIII and RNAPIII transcript precursors. Finally, Nab2 interacts with TFIIB *in vivo* and increases the occupancy of TFIIB at the promoter—Independently of TFIIC. Thus, Nab2 functions in RNAPIII transcription initiation by enhancing the stability of TFIIB at RNAPIII genes and is thus most likely required for efficient assembly and stability of the RNAPIII transcription initiation complex in *S. cerevisiae*.

As Nab2 functions in nuclear mRNA biogenesis (poly(A)-tail length control, mRNP formation, and nuclear mRNP export)<sup>22,28</sup> as well as RNAPIII transcription<sup>27</sup> the question arises whether the effects observed for one process might be indirect, i.e. caused by a defect in another process. However, since the evidence for the function of Nab2 in all of these processes is quite direct, we believe that Nab2 functions directly in nuclear mRNP biogenesis as well as RNAPIII transcription.

### Potential additional functions of Nab2 in RNAPIII metabolism

We analyzed the function of Nab2 in RNAPIII transcription initiation and TFIIB occupancy in more detail. However, based on our data, one can envision that Nab2 also functions in a variety of additional steps in RNAPIII transcription and transcript biogenesis.



**Figure 1.** Known function and potential roles of Nab2 in RNAPIII transcription. Nab2 functions in RNAPIII transcription initiation by stabilizing TFIIB and possibly RNAPIII at the promoter.<sup>27</sup> In addition, preliminary evidence suggests several additional functions of Nab2 in RNAPIII transcript biogenesis.<sup>27</sup> Besides initiation, Nab2 might play a role in elongation, facilitated recycling, processing, and nuclear export of RNAPIII transcripts. Different steps of the transcription cycle / RNAPIII transcript processing are depicted with a tRNA gene as an exemplary gene. The major steps of gene expression are underlined, and the potential functions of Nab2 are listed below. Proteins/protein complexes are colored as follows: orange, RNAPIII; blue, TFIIB sub-units; green, TFIIC; yellow, Nab2; gray, NPC; brown, Mlp1. The double layer of the nuclear envelope is shown in orange, the nucleoplasm is indicated in green above and the cytoplasm in white below the nuclear envelope, and a nuclear pore complex is depicted in grey. See text for details.

### Boosting of the RNAPIII transcription cycle by Nab2

As Nab2 not only interacts with and stabilizes TFIIB at the promoter but also interacts directly with RNAPIII, it could enhance the recruitment of RNAPIII to the promoter (Fig. 1). This would increase the probability of the gene to be transcribed. Nab2 could also be needed for transcription elongation as it is present along the whole coding sequence of *SCR1*, the longest RNAPIII-transcribed gene in *S. cerevisiae* (Fig. 1).<sup>27</sup> Here, Nab2 might increase transcription fidelity or processivity of the transcribing polymerase. Specifically, similar to the function of mRNA-binding proteins in RNAPII transcription, Nab2 could prevent the formation of DNA-RNA hybrids, so-called R-loops, and thus maintain genome stability.<sup>29</sup> Alternatively, but not mutually exclusively, Nab2 may be involved in the process of “facilitated recycling”, a process in which the transcribing polymerase is pre-dominantly committed to repetitive transcription of the same gene

(Fig. 1).<sup>15</sup> This mechanism is thought to be required for the efficient synthesis of RNAPIII transcripts to meet the high cellular demand of RNAPIII transcripts.<sup>15</sup> Nab2 could facilitate recycling by pre-initiation complex stabilization and recruitment of the terminating polymerase.

One or a combination of the above mentioned mechanisms could be mediated by Nab2 and/or other proteins leading to the observed, higher transcription rates *in vivo*. Hence, it will be of great interest to unravel all of Nab2's functions in RNAPIII transcription and to analyze their molecular mechanism.

### Nab2 could regulate RNAPIII transcript stability and RNA modification

Nab2 has an established role in mRNA processing and nuclear mRNA export and binds directly to all RNAPIII transcript precursors.<sup>27</sup> Thus, Nab2 could play a similar role for RNAPIII transcript biogenesis. First, Nab2 might

guide these precursors to modifying enzymes (Fig. 1). Second, Nab2 might regulate the stability of RNAPIII transcript precursors (Fig. 1). It is known that Nab2 can be displaced from defective or improperly processed mRNAs by the Rrp6 sub-unit of the nuclear exosome complex in *S. cerevisiae*, a process that leads to mRNA degradation.<sup>30</sup> Likewise, Nab2 could function in recognizing 3'-adenylated and/or defective tRNAs and cause their degradation via its interaction with Rrp6 (or other subunits of the exosome) or the nuclear surveillance pathway. This possible function of Nab2 could be crucial for cellular fitness, as it would prevent the release or export of defective RNAs.

### **Nab2 and gene gating of RNAPIII-transcribed genes**

It was recently shown that tDNAs relocate to the nuclear pore complexes (NPCs) during their peak expression in M phase of *S. cerevisiae* dependent on Los1, the major tRNA exportin.<sup>31</sup> This relocalization connects RNAPIII transcription with pre-tRNA export, but does not affect RNAPIII-gene association nor transcriptional activity. Moreover, it was hypothesized that the relocalization of the transcribing RNAPIII machinery to NPCs is a mechanism to prevent collisions of DNA replication forks.<sup>31</sup> Relocalization of actively transcribed genes to the NPC is also known for RNAPII-transcribed genes to efficiently link transcription to mRNA export; a process called gene gating.<sup>32,33</sup> Interestingly, Nab2 interacts with the NPC-associated protein Mlp1 and is thought to be important for linking mRNA processing to nuclear export.<sup>34</sup> Hence, Nab2 could also facilitate gene gating of RNAPIII-transcribed genes (Fig. 1). Having in mind that Nab2 interacts with TFIIB and RNAPIII and stabilizes TFIIB binding to DNA, Nab2 could also interact with Mlp1 when bound to RNAPIII and/or TFIIB. Thus, Nab2 could function in linking active transcription of RNAPIII to export of tRNAs and other RNAPIII transcripts by relocating actively transcribed genes to the NPC and recruiting RNAPIII transcripts to their nuclear exporters Los1 or Msn5.

### **Nab2 might link RNAPII and RNAPIII transcription in *S. cerevisiae***

As Nab2 is the first mRNP biogenesis factor identified to play a role in RNAPIII transcription, it will be of great interest to investigate whether more proteins involved in mRNP biogenesis or export have a second function in

RNAPIII transcription. Furthermore, RNAPII transcription factors were shown to function in RNAPIII transcription, such as Dst1 or Sub1 in yeast.<sup>16,17</sup> Interestingly and in contrast to yeast, RNAPII and RNAPIII and their respective transcription factors are not only present at their classical set of genes they transcribe, but also at genes transcribed by the other polymerase in higher eukaryotes.<sup>35,36</sup> Thus, gene expression by RNAPII and RNAPIII might be interconnected both at the level of transcription and the level of downstream processes (processing, export, and quality control of transcripts); although by slightly different mechanisms in *S. cerevisiae* versus higher eukaryotes. Nab2 and potentially its orthologues could play a pivotal role for this interconnection. Communication between RNAPII and RNAPIII gene expression pathways might guarantee correct and coordinated expression of all genes, but remains to be shown to exist in the future.

### **Conservation of Nab2 and potential involvement in diseases**

The mechanisms suggested above would lead to the correct and fine-tuned expression of RNAPIII transcripts, which is crucial for cell metabolism, by Nab2 and possibly other proteins. As outlined above, Nab2 is highly conserved from yeast to human. Although all of its orthologues and their isoforms differ in size and domain composition some basic features are the same in all analyzed organisms. For example, most orthologues contain a nuclear localization sequence (NLS) and all Nab2 orthologues and splice variants contain an array of C-terminally localized C<sub>3</sub>H<sub>1</sub>-zinc fingers of variable length, some of which were shown to bind RNA.<sup>26,37</sup> Interestingly, point mutations in the human ortholog ZC3H14 that only yield the cytoplasmically localized protein but none of its nuclear isoforms are associated with non-syndromic autosomal recessive intellectual disability (NS-ARID).<sup>26</sup> In line with this is the finding that Nab2 is required for normal behavior and correct axon projection from the Kenyon neurons into the mushroom bodies during neural development in *Drosophila melanogaster*.<sup>26,38</sup> On the other hand, evidence exists that tRNAs and tRNA fragments (tRFs) function in a variety of cellular pathways, such as stress response, gene expression, and the regulation of apoptosis.<sup>39,40</sup> Furthermore, tRNA levels are often upregulated in cancer cells, and impaired aminoacylation causes neurological or mitochondrial diseases like

Charcot–Marie–Tooth syndrome or ataxia.<sup>40,41</sup> Conversely, reduced tRNA levels can lead to neonatal death or hypoplasia, especially during development.<sup>41</sup> Taken together, these findings point out the importance of tightly-regulated tRNA levels during the development and life of metazoans.

Thus, it will be of great importance to assess, whether the function of Nab2 in RNAPIII transcription is conserved in higher eukaryotes as Nab2's function in poly(A) tail length control. If so, the impaired function of ZC3H14 in RNAPIII transcription could be the cause for the observed human diseases (see above). Which contribution to disease development the different functions of Nab2 have remains to be determined. In summary, Nab2 could play a central role in the homeostasis of RNAPII as well as RNAPIII transcripts and consequentially disease development, a field that still holds many secrets.

## Summary

In addition to its long-known functions in gene expression, i.e., poly(A) tail length control, mRNP biogenesis, and nuclear mRNA export, Nab2 is important for efficient RNAPIII transcription initiation. Based on the high conservation of Nab2 in other organisms and its conserved function in poly(A) tail length control, Nab2 will probably emerge as a central player in the regulation of gene expression. Given the medically relevant implications of human and *Drosophila* Nab2, it will be important to fully uncover the functions of Nab2 in yeast and higher eukaryotes and to assess their contribution to disease mechanisms.

## Abbreviations

mRNA	messenger RNA
mRNP	Messenger ribonucleoprotein particle
Mlp1	Myosin-like protein 1
Nab2	Nuclear polyadenylated RNA-binding protein 2
ncRNA	Non-coding RNA
NLS	Nuclear localization sequence
NPC	Nuclear pore complex
PABP	Poly(A)-binding protein
PIC	Pre-initiation complex
RNAPII	RNA polymerase II
RNAPIII	RNA polymerase III
rRNA	ribosomal RNA
TF	Transcription factor

tRNA	transfer RNA
tRF	tRNA fragment

## Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

## Acknowledgments

We thank Peter Friedhoff (Institute of Biochemistry, JLU Gießen) for critical reading of the manuscript.

## Funding

This work was supported by grants from the German Research Foundation (DFG) and the European Union (ERC Starting Grant).

## References

- [1] Dieci G, Fiorino G, Castelnuovo M, Teichmann M, Pagano A. The expanding RNA polymerase III transcriptome. *Trends Genet* 2007; 23:614–622.
- [2] Ciganda M, Williams N. Eukaryotic 5S rRNA biogenesis. *Wiley Interdiscip Rev RNA* 2011; 2:523–533.
- [3] Geiduschek EP, Kassavetis GA. The RNA Polymerase III Transcription Apparatus. *J Mol Biol* 2001; 310: 1–26.
- [4] Carter R, Drouin G. The Increase in the Number of Subunits in Eukaryotic RNA Polymerase III Relative to RNA Polymerase II Is due to the Permanent Recruitment of General Transcription Factors. *Mol Biol Evol* 2010; 27:1035–1043.
- [5] Cramer P, Armache KJ, Baumli S, Benkert S, Brueckner F, Buchen C, Damsma GE, Dengl S, Geiger SR, Jasiak AJ et al. Structure of eukaryotic RNA polymerases. *Annu Rev Biophys* 2008; 37:337–352.
- [6] Ducrot C, Lefebvre O, Landrieux E, Guirouilh-Barbat J, Sentenac A, Acker J. Reconstitution of the yeast RNA polymerase III transcription system with all recombinant factors. *J Biol Chem* 2006; 281:11685–11692.
- [7] Kassavetis GA, Geiduschek EP. Transcription factor TFIIB and transcription by RNA polymerase III. *Biochem Soc Trans* 2006; 34:1082–1087.
- [8] Male G, von Appen A, Glatt S, Taylor NM, Cristovao M, Groetsch H, Beck M, Muller CW. Architecture of TFIIC and its role in RNA polymerase III pre-initiation complex assembly. *Nat Commun* 2015; 6:7387.
- [9] Kassavetis GA, Braun BR, Nguyen LH, Geiduschek EP. *S. cerevisiae* TFIIB is the transcription initiation factor proper of RNA polymerase III, while TFIIA and TFIIC are assembly factors. *Cell* 1990; 60:235–245.
- [10] Kassavetis GA, Letts GA, Geiduschek EP. The RNA polymerase III transcription initiation factor TFIIB participates in two steps of promoter opening. *EMBO J* 2001; 20:2823–2834.

- [11] Acker J, Conesa C, Lefebvre O. Yeast RNA polymerase III transcription factors and effectors. *Biochim Biophys Acta* 2013; 1829:283-295.
- [12] Bhargava P, Kassavetis GA. Abortive initiation by *Saccharomyces cerevisiae* RNA polymerase III. *J Biol Chem* 1999; 274:26550-26556.
- [13] Arimbasseri AG, Maraia RJ. Mechanism of Transcription Termination by RNA Polymerase III Utilizes a Non-template Strand Sequence-Specific Signal Element. *Mol Cell* 2015; 58:1124-1132.
- [14] Arimbasseri AG, Rijal K, Maraia RJ. Transcription termination by the eukaryotic RNA polymerase III. *Biochim Biophys Acta* 2013; 1829:318-330.
- [15] Dieci G, Sentenac A. Facilitated recycling Pathway for RNA Polymerase III. *Cell* 1996; 84:245-252.
- [16] Tavenet A, Suleau A, Dubreuil G, Ferrari R, Ducrot C, Michaut M, Aude JC, Dieci G, Lefebvre O, Conesa C et al. Genome-wide location analysis reveals a role for Sub1 in RNA polymerase III transcription. *Proc Natl Acad Sci U S A* 2009; 106:14265-14270.
- [17] Ghavi-Helm Y, Michaut M, Acker J, Aude JC, Thuriaux P, Werner M, Soutourina J. Genome-wide location analysis reveals a role of TFIIS in RNA polymerase III transcription. *Genes Dev* 2008; 22:1934-1947.
- [18] White RJ. RNA polymerases I and III, growth control and cancer. *Nat Rev Mol Cell Biol* 2005; 6:69-78.
- [19] Bhargava P. Epigenetic regulation of transcription by RNA polymerase III. *Biochim Biophys Acta* 2013; 1829:1015-1025.
- [20] Kumar Y, Bhargava P. A unique nucleosome arrangement, maintained actively by chromatin remodelers facilitates transcription of yeast tRNA genes. *BMC Genomics* 2013; 14:402.
- [21] Anderson JT, Wilson SM, Datar KV, Swanson MS. NAB2: a yeast nuclear polyadenylated RNA-binding protein essential for cell viability. *Mol Cell Biol* 1993; 13:2730-2741.
- [22] Soucek S, Corbett AH, Fasken MB. The long and the short of it: the role of the zinc finger polyadenosine RNA binding protein, Nab2, in control of poly(A) tail length. *Biochim Biophys Acta* 2012; 1819:546-554.
- [23] Gallardo M, Luna R, Erdjument-Bromage H, Tempst P, Aguilera A. Nab2p and the Thp1p-Sac3p complex functionally interact at the interface between transcription and mRNA metabolism. *J Biol Chem* 2003; 278:24225-24232.
- [24] Schmid M, Olszewski P, Pelechano V, Gupta I, Steinmetz LM, Jensen TH. The Nuclear PolyA-Binding Protein Nab2p Is Essential for mRNA Production. *Cell Rep* 2015; 12:128-139.
- [25] Kelly SM, Leung SW, Pak C, Banerjee A, Moberg KH, Corbett AH. A conserved role for the zinc finger polyadenosine RNA binding protein, ZC3H14, in control of poly(A) tail length. *RNA* 2014; 20:681-688.
- [26] Pak C, Garshasbi M, Kahrizi K, Gross C, Apponi L, Noto JJ, Kelly SM, Leung SW, Tzschach A, Behjati F et al. Mutation of the conserved polyadenosine RNA binding protein, ZC3H14/dNab2, impairs neural function in *Drosophila* and humans. *Proc Natl Acad Sci U S A* 2011; 108:12390-12395.
- [27] Reuter LM, Meinel DM, Strasser K. The poly(A)-binding protein Nab2 functions in RNA polymerase III transcription. *Genes Dev* 2015; 29:1565-1575.
- [28] Meinel DM, Strasser K. Co-transcriptional mRNP formation is coordinated within a molecular mRNP packaging station in *S. cerevisiae*. *Bioessays* 2015; 37:666-677.
- [29] Aguilera A, Garcia-Muse T. R loops: from transcription byproducts to threats to genome stability. *Mol Cell* 2012; 46:115-124.
- [30] Schmid M, Poulsen MB, Olszewski P, Pelechano V, Saguez C, Gupta I, Steinmetz LM, Moore C, Jensen TH. Rrp6p controls mRNA poly(A) tail length and its decoration with poly(A) binding proteins. *Mol Cell* 2012; 47:267-280.
- [31] Chen M, Gartenberg MR. Coordination of tRNA transcription with export at nuclear pore complexes in budding yeast. *Genes Dev* 2014; 28:959-970.
- [32] Blobel G. Gene gating: a hypothesis. *Proc Natl Acad Sci U S A* 1985; 82:8527-8529.
- [33] Burns LT, Wentz SR. From hypothesis to mechanism: uncovering nuclear pore complex links to gene expression. *Mol Cell Biol* 2014; 34:2114-2120.
- [34] Fasken MB, Stewart M, Corbett AH. Functional significance of the interaction between the mRNA-binding protein, Nab2, and the nuclear pore-associated protein, Mlp1, in mRNA export. *J Biol Chem* 2008; 283:27130-27143.
- [35] Raha D, Wang Z, Moqtaderi Z, Wu L, Zhong G, Gerstein M, Struhl K, Snyder M. Close association of RNA polymerase II and many transcription factors with Pol III genes. *Proc Natl Acad Sci U S A* 2010; 107:3639-3644.
- [36] Barski A, Chepelev I, Liko D, Cuddapah S, Fleming AB, Birch J, Cui K, White RJ, Zhao K. Pol II and its associated epigenetic marks are present at Pol III-transcribed noncoding RNA genes. *Nat Struct Mol Biol* 2010; 17:629-634.
- [37] Kelly SM, Pabit SA, Kitchen CM, Guo P, Marfatia KA, Murphy TJ, Corbett AH, Berland KM. Recognition of polyadenosine RNA by zinc finger proteins. *Proc Natl Acad Sci U S A* 2007; 104:12306-12311.
- [38] Kelly SM, Bienkowski R, Banerjee A, Melicharek DJ, Brewer ZA, Marenda DR, Corbett AH, Moberg KH. The *Drosophila* ortholog of the Zc3h14 RNA binding protein acts within neurons to pattern axon projection in the developing brain. *Dev Neurobiol* 2015; 76:93-106.
- [39] Raina M, Ibba M. tRNAs as regulators of biological processes. *Frontiers in Genetics* 2014; 5:171.
- [40] Anderson P, Ivanov P. tRNA fragments in human health and disease. *FEBS Lett* 2014; 588:4297-4304.
- [41] Kirchner S, Ignatova Z. Emerging roles of tRNA in adaptive translation, signalling dynamics and disease. *Nat Rev Genet* 2015; 16:98-112.