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Review:

mRNA quality control at the 5' end*

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Abstract: All eukaryotic mRNAs are capped at their 5' end. Capping of mRNAs takes place co-transcriptionally and involves three steps. The intermediates of the capping process, as well as the uncapped 5' tri-phosphate RNA, are resistant to decapping and degradation by known factors, leading to the assumption that the capping process always proceeds to completion. This view was recently drastically changed. A novel family of enzymes, including the yeast proteins Rai1, Dxo1/Ydr370C, and the mammalian protein DXO/Dom3Z, has been identified. These enzymes catalyze the conversion of the improperly capped mRNAs to 5' mono-phosphate RNA, allowing them to be degraded by 5'-3' exoribonucleases. Several of these enzymes also possess 5'-3' exoribonuclease activities themselves, and can single-handedly clear the improperly capped mRNAs. Studying of these enzymes has led to the realization that mRNA capping does not always proceed to completion, and the identification of an mRNA capping quality control mechanism in eukaryotes. In this paper, we briefly review recent advances in this area.

Key words: mRNA capping, Quality control, Rai1, Dxo1, DXO
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1 Introduction

All eukaryotic mRNAs are capped at their 5' end, shortly after transcription initiation. The cap consists of a guanine nucleotide methylated at the N^7 position, and is linked to the 5' nucleotide of the RNA through an unusual 5'-5' pyrophosphate linkage (m^7GpppN) (Shatkin, 1976; Furuichi and Shatkin, 2000). Capping is crucial for the stability, splicing, polyadenylation, export of mRNA, and their translation efficiency (Merrick, 2004; Meyer *et al*., 2004; Houseley and Tollervey, 2009; Hocine *et al*., 2010). Removal of the cap is a highly regulated process, catalyzed by the decapping enzymes Dcp2 (Dunckley and Parker, 1999; Lykke-Andersen, 2002; Wang *et al*., 2002; Coller and Parker, 2004) and Nudt16 (Song *et al*., 2010; Li *et al*., 2011). These enzymes release a 7-methyl-guanosine diphosphate molecule from the mRNA, leaving a mono-phosphate at its 5' end. Decapping is followed by RNA degradation by the 5'-3' exoribonuclease Xrn1 (Meyer *et al*., 2004; Houseley and Tollervey, 2009), which recognizes the 5' mono-phosphate (Stevens, 1978).

The capping process consists of three steps. First, the tri-phosphate group at the 5' end of the primary transcript is converted to a diphosphate group; second, a GMP molecule is subsequently attached, and finally a mature cap is produced by the methylation of the N^7 atom of the guanosine base (Shuman, 1995; Furuichi and Shatkin, 2000). In yeast, three distinct enzymes catalyze these reactions, whereas in mammals, the first and second reactions are catalyzed by a bifunctional enzyme (Yue *et al*., 1997). The intermediates of the capping process, as well as the uncapped primary transcript, are resistant to degradation by Xrn1, which requires the 5' mono-phosphate (Stevens, 1978). In addition, decapping enzymes Dcp2/Nudt16 recognize

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the mature, methylated cap (Coller and Parker, 2004; Song *et al*., 2010), and cannot convert them to 5' mono-phosphate RNA for degradation. Therefore, the capping process has been thought to always proceed to completion, as the improperly capped mRNA molecules cannot be cleared by known factors.

Recently, this view has drastically changed. Enzymatic activities have been identified for the yeast protein Rai1, which converts the tri-phosphate group, or the unmethylated cap, at the 5' end of RNA to monophosphate, allowing it to be degraded (Xiang *et al*., 2009; Jiao *et al*., 2010). Such discoveries led to the identification of an mRNA capping quality control mechanism (Jiao *et al*., 2010). Thus, we briefly review recent advances in this area.

2 Discovery of the mechanism

The yeast protein Rai1 (Rat1 interacting protein 1) has been known to bind and stimulate the activity of the 5'-3' exoribonuclease Rat1/Xrn2 (Xue *et al*., 2000), which has an important role in polymerase II (Pol II) transcription termination (Kim *et al*., 2004). The first 3D structure of Rai1 was determined in complex with Rat1/Xrn2. However, the structure of Rai1 indicated that it possesses some sort of enzymatic activity. A large pocket is found on its surface, away from the Rat1/Xrn2 interacting region (Fig. 1a). Many conserved residues are concentrated in this region, suggesting that this pocket may serve as an active site. Consistently, subsequent work revealed Rai1 possesses pyrophosphatase activity, which can be attributed to this active site. This activity converts 5' tri-phosphate RNA to 5' mono-phosphate RNA. Like Xrn1, the Rai1 associating exoribonuclease Rat1/Xrn2 specifically recognizes a 5' mono-phosphate on RNA substrates (Poole and Stevens, 1995; Stevens and Poole, 1995), and cannot degrade a 5' tri-phosphate RNA. The identified Rai1 enzymatic activity allows such RNAs to be degraded by the Rai1-Rat1/Xrn2 complex (Xiang *et al*., 2009).

The Rai1-Rat1/Xrn2 complex associates with the Pol II mRNA transcription machinery (Kim *et al*., 2004). In eukaryotes, the tri-phosphate group at the 5' end of a primary transcript is rapidly converted to an m^7GpppN cap. These considerations led to the proposal that Rai1 plays a role in mRNA capping quality control, by processing primary transcripts that failed to be capped for degradation (Xiang *et al*., 2009).

Following up this clue, subsequent work demonstrated that Rai1 could also convert a capping intermediate, RNAs with an unmethylated cap, to 5' mono-phosphate RNAs for degradation. In a strain defective in cap methylation, knocking out of *Rai1* significantly increased the half-life of mRNAs, indicating that inside of the cell Rai1 also plays a central role in clearing improperly capped mRNAs. Importantly, additional work demonstrated that contrary to what was thought, mRNA capping is a regulated

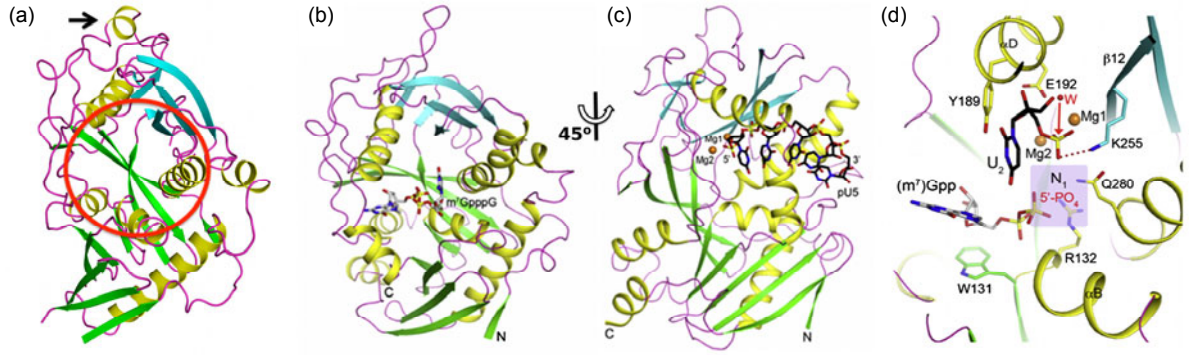

Fig. 1 Structural basis of the catalysis by Rai1 and its homologues

(a) Structure of Rai1 (produced by PyMOL via http://www.pymol.org). The active site is indicated by the red cycle, and the arrow indicates the region that interacts with Rat1/Xrn2. (b) Structure of DXO/Dom3Z in complex with the cap analogue m^7GpppG. (c) Structure of DXO/Dom3Z in complex with an oligonucleotide. (b) and (c) are roughly related by a 45°-rotation along the vertical axis. (d) Active site of DXO/Dom3Z. The positions of the cap and the second nucleotide are shown and the pink box indicates the position of the first nucleotide. The red letter "W" indicates the attacking water or hydroxyl ion and the red arrow indicates the nucleophilic attack. (b)–(d) are adopted from Jiao *et al.* (2013) (Note: for interpretation of the references to color in this figure legend, the reader is referred to the web version of this article)

process and does not always proceed to completion. Under nutrient starvation conditions, the relative amounts of improperly mRNAs were significantly increased in a *Rai1* knock-out strain, despite the fact that the capping machinery was intact. Together, all these evidences identified a quality control mechanism of mRNA capping (Jiao *et al*., 2010).

3 mRNA capping quality control in yeast and mammals

Homologues of Rai1 are found in most eukaryotes (Xue *et al*., 2000). Although they only share a moderate sequence similarity, residues corresponding to these in the Rai1 active site are highly conserved (Xiang *et al*., 2009; Chang *et al*., 2012; Jiao *et al*., 2013). This suggests Rai1 homologues also possess similar enzymatic activities, and the mRNA capping quality control mechanism is conserved in eukaryotes. To date, two such Rai1 homologues have been studied, leading to a further understanding of mRNA capping quality control in yeast, and the confirmation and characterization of such a mechanism in mammals.

Unlike most eukaryotes, which contain only one copy of the Rai1 homologue, in several fugal species including *S. cerevisiae*, another protein homologous to Rai1 exists (Xue *et al*., 2000). This protein, Ydr370C, shares 20% sequence identity with Rai1. Like Rai1, it possesses decapping activities towards RNAs with unmethylated caps. In addition, Ydr370C also has a 5'-3' exoribonuclease activity. These activities enable Ydr370C to degrade RNA molecules with an unmethylated cap single-handedly, and prompted the change of its name to decapping exoribonuclease 1 (Dxo1). Dxo1/Ydr370C does not have any detectable pyrophosphatase activity, unlike Rai1. In normal growth conditions, knocking out either *Rai1* or *Dxo1/Ydr370C* did not cause any detectable changes in mRNA levels. However, knocking them out simultaneously caused a significant increase in the amount of improperly capped mRNA, indicating that both proteins play essential roles in mRNA capping quality control in yeast, and their functions can compensate for each other to some degree (Chang *et al*., 2012).

The mammalian Rai1 homologue is Dom3Z. It was found to be a hybrid of Rai1 and Dxo1/Ydr370C, possessing both pyrophosphatase and decapping activities towards RNAs with 5' tri-phosphates or unmethylated caps, as well as a 5'-3' exoribonuclease activity, and its name was subsequently changed to DXO. These activities enable DXO/Dom3Z to single-handedly degrade uncapped RNAs and RNAs with an unmethylated cap. Knocking down *DXO/Dom3Z* in cells caused a significant increase in the amount of improperly capped pre-mRNAs, without affecting the levels of mature mRNAs. All these evidences indicate the existence of an mRNA capping quality control mechanism in mammals, in which DXO/Dom3Z plays a central role (Jiao *et al*., 2013).

The cellular locations of the Rai1-Rat1/Xrn2 complex, Dxo1/Ydr370C, and DXO/Dom3Z are different. The Rai1-Rat1/Xrn2 is distributed exclusively in the nucleus (Johnson, 1997), DXO/Dom3Z is mainly found in the nucleus (Zheng *et al*., 2011), whereas Dxo1/Ydr370C primarily resides in the cytoplasm (Huh *et al*., 2003; Chang *et al*., 2012). The differences in the cellular localization of these proteins suggest that mRNA capping quality control in mammals takes place inside the nucleus, whereas in yeast, it takes place both inside the nucleus and in the cytoplasm. This difference is probably related to the difference in mRNA export in yeast and mammals. In both organisms, a conserved TREX (transcription/export) complex plays a central role in mRNA export to the cytoplasm. In yeast, TREX recruitment is coupled to the transcription machinery, whereas the recruitment of the TREX complex is splicing and 5' cap-dependent in mammals (Hocine *et al*., 2010). The mammalian mRNA export process therefore acts as an additional checkpoint for mRNA capping, and prevents improperly capped mRNA from entering the cytoplasm. Yeast lacks such a mechanism, which might make additional surveillance for proper capping in the cytoplasm by Dxo1/Ydr370C necessary.

While Rai1 has a minimum decapping activity with regard to mRNAs with mature methylated caps, both Dox1/Ydr370C and DXO/Dom3Z have appreciable decapping activities with regard to this substrate *in vitro* (Chang *et al*., 2012; Jiao *et al*., 2013). However, inside cells such activity is countered by cap-binding proteins, which preferentially bind to the mature cap and protect it. Consistently, both the nuclear and cytoplasmic cap-binding proteins, CBP20 and elF4E, effectively block this decapping activity of DXO/

Dom3Z *in vitro* (Jiao *et al*., 2013). In addition, DXO/Dom3Z also possesses a decapping activity towards tri-methylated $m^{2,2,7}$GpppN capped RNAs, and may modulate the tri-methyl capped uridylate-rich small nuclear RNAs inside the cell (Jiao *et al*., 2013).

4 Structural insights into the catalysis by Rai1 and its homologues

The structures of Rai1 and its homologues contain two highly twisted β-sheets and several α-helices that cover up some of the exposed surfaces of the β-sheets. The active site is located in the middle of the protein, at the interface between the β-sheets (Xiang *et al*., 2009; Chang *et al*., 2012; Jiao *et al*., 2013) (Fig. 1a). Four highly conserved sequence motifs are located in the active site, and in DXO/Dom3Z they correspond to residues Arg132 (motif I), Gly188-Tyr-Lys-Phe-Glu192 (motif II, GΦXΦE, where Φ is an aromatic or hydrophobic residue and X is any residue), Glu234-Val-Asp236 (motif III, EhD, where h is a hydrophobic residue), and Glu253-Leu-Lys255 (motif IV, EhK) (Chang *et al*., 2012; Jiao *et al*., 2013). The structures of Rai1 and its homologues are not homologous to any other known protein structures, but have a remote relationship with the structures of D-(D/E)XK nucleases. However, little sequence conservation exists between Rai1 homologues and these nucleases, and the similarity is limited primarily to the aspartate residue in motif III (EhD) and motif IV (EhK), which contribute to the binding of a metal ion in all these enzymes (Chang *et al*., 2012).

Mutagenesis studies indicate that the single active site is responsible for all three activities of Rai1 and its homologues: decapping, pyrophosphatase, and 5'-3' exoribonuclease (Xiang *et al*., 2009; Jiao *et al*., 2010; Chang *et al*., 2012; Jiao *et al*., 2013). Unlike the decapping enzyme Dcp2, which removes the m^7Gpp cap from the mRNAs, the decapping activities of Rai1 and its homologues hydrolase the phosphodiester linkage between the first and second nucleotides, releasing methylated or unmethylated GpppN (Jiao *et al*., 2010; 2013; Chang *et al*., 2012).

Structural studies of DXO/Dom3Z provided molecular insights into the catalysis by Rai1 and its homologues. Structures of DXO/Dom3Z in complex with the cap analogue m^7GpppG (Fig. 1b) and oligonucleotides (Fig. 1c) indicate that a capped mRNA molecule binds across the active site pocket, with the cap and the first nucleotide (m^7GpppN) at one side and the rest of the RNA molecule at the opposite side, and the catalytic machinery consists of two metal ions, located in the middle. The side-chain of Arg132 (motif I) recognizes a phosphate group on the cap and the catalytic metal ions are coordinated by side-chains of residues in motifs II, III, and IV, the phosphate group between the first and second nucleotides, as well as the main chain carbonyl of Leu254 in motif IV. Based on the structural information, it was proposed that one of the metal ions activates a water molecule or a hydroxyl ion, which subsequently attacks the scissile phosphate between the first and second nucleotides, making a cleavage 5' to this group and releasing GpppN. The side-chain of Lys255 (motif IV) stabilizes the oxyanion intermediate in the catalysis (Jiao *et al*., 2013) (Fig. 1d). This two-metal-ion catalysis is also widely employed by many nucleases (Yang, 2011).

Structures of DXO/Dom3Z indicate the active site region that binds the cap and the first nucleotide can also accommodate a 5' end nucleotide (pN_1) or a pyrophosphate group, and the catalysis on 5' monophosphate or 5' tri-phosphate RNAs releases pN_1 or the pyrophosphate group, giving rise to the 5'-3' exoribonuclease and pyrophosphatase activities. Therefore, the three seemingly distinct activities of Rai1 and its homologues all utilize the same catalytic machinery, and the outcome of the catalysis is dictated by the different binding modes of different substrates (Jiao *et al*., 2013).

5 Concluding remarks

Contrary to what had been thought, it is now known that the eukaryotic mRNA capping process does not always proceed to completion. Improperly capped mRNAs might be caused by sporadic errors in the capping process, and the capping quality control mechanism corrects these errors. And/or, as emerging evidence suggests, this is the result of active regulation to mRNA capping. For instance, it has been reported that importin-α stimulates general cap methylation (Wen and Shatkin, 2000), Myc regulates the cap methylation of many mRNAs (Cowling and Cole,

2007; 2010; Cowling, 2010), and nutrient starvation caused a general decrease in cap methylation (Jiao *et al*., 2010). The regulatory factors of mRNA capping, together with the capping quality control mechanism, might provide yet another layer of regulation to gene expression.

Recent studies have greatly advanced our understanding of mRNA capping quality control in eukaryotes. However, our current understanding of this process is far from complete. For instance, the molecular basis for the differences in the substrate specificities of Rai1, Dxo1/Ydr370C, and DXO/Dom3Z remains obscure; whether a 5' di-phosphate RNA, another intermediate generated in the capping process, can be cleared by currently known capping quality control factors remains to be seen. Importantly, little is known about how Rai1 and its homologues interact with other factors, to coordinate capping quality control with other cellular processes. For instance, in yeast it has been shown that the Rai1-Rat1/Xrn2 complex associates with the Pol II transcription machinery (Kim *et al*., 2004), and Rat1/Xrn2 degrades the improperly capped nascent transcripts co-transcriptionally (Jimeno-Gonzalez *et al*., 2010). It remains to be seen whether in mammalian cells DXO/Dom3Z also associates with the transcription machinery and, if so, what factors are responsible for its recruitment. Further studies are necessary to answer these questions.

The mRNA cap has important functions in many cellular processes, and the identification of the capping quality control mechanism provides a novel method to perturb the cap structure and to probe the function of the cap in these processes. This is exemplified by the knocking down studies of *DXO/Dom3Z*, which has led to the realization that in mammalian cells the mRNA cap is more intimately linked to mRNA splicing and polyadenylation than previously thought (Jiao *et al*., 2013). Further studies in this direction will bring a better understanding of the physiological role of the mRNA cap.

Compliance with ethics guidelines

Li-ting ZHAI and Song XIANG declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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中文概要：

本文题目：mRNA 5'端的质量控制

mRNA quality control at the 5' end

本文概要：所有真核生物的 mRNA 都在 5'端被加帽，正确的加帽对 mRNA 的稳定性、出核及翻译调控具有重要意义。近年来，随着对 Rai1 及其同源蛋白的酶活性的发现，引出一个对 mRNA 加帽过程质量控制机制的发现。研究表明，Rai1 及其同源蛋白可以将未被加帽（含 5'端三磷酸基团）或未被正确加帽的 mRNA 转化成 5'端含单磷酸基的 RNA，使得它们可以被 5'–3' RNA 外切酶降解。某些 Rai1 的同源蛋白也具有 5'–3' RNA 外切酶的活性，可以同时完成降解 RNA 的工作。Rai1 的同源蛋白在真核生物中广泛保守，提示这一机制普遍存在于真核生物中。

关键词组：mRNA 加帽；质量控制；Rai1；Dxo1；DXO