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Molecular biology Mediating transcription and RNA export

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Abstract

The finding that the Mediator protein complex contributes to messenger RNA export from the nucleus in yeast adds to a growing list of roles for the complex in regulating transcriptional processes.

Gene transcription is fundamental for all major physiological processes, and defects in its regulation underlie myriad human diseases. Transcription culminates in the export of messenger RNA transcripts from the nucleus to the cytoplasm, where they are translated into proteins. In a paper published in *Cell*, Schneider *et al.*[1] use a combination of structural and cell biology, biochemistry, yeast genetics and transcript analyses to describe how this process is regulated by cooperation between the mRNA export machinery and a large, multi-subunit protein complex called Mediator, which is best known for regulating the activity of the enzyme RNA polymerase II (pol II) to mediate early stages of transcription[2].

Many factors converge on nascent mRNA transcripts to facilitate their export from the nucleus. One such factor, the TREX-2 protein complex, regulates export through interactions with other complexes, including pol II and the nuclear pore complex (NPC)[3], a protein complex that acts as a gateway for cellular components to exit the nucleus and enter the cytoplasm. However, the mechanisms by which TREX-2 acts are still uncertain.

Schneider *et al.* investigated TREX-2 in the brewer's yeast, *Saccharomyces cerevisiae*. In yeast cells lacking the TREX-2 subunit Sac3, the composition of the Mediator complex changed. Specifically, components of the Mediator 'kinase module' failed to associate with the rest of the complex. The authors demonstrated that TREX-2 physically associated with Mediator, and that their association depended on Sac3 and a Mediator subunit implicated in activation of transcription, Med31.

A series of experiments then showed a functional interdependence between Mediator and TREX-2. In yeast, genes that are in the process of being transcribed have been shown to associate with the NPC, presumably to facilitate mRNA export to the cytoplasm[4]. Schneider and colleagues demonstrated that, similar to Sac3 (ref. 1), Med31 is required for gene targeting to the NPC, implying that the Mediator complex plays a part in mRNA export. However, in contrast to cells lacking Sac3, mRNA export seemed normal in cells lacking Med31 or the Mediator kinase Cdk8. Thus, although the authors' data support a role for Mediator in mRNA export, the precise molecular mechanism remains unclear.

The link between Mediator and mRNA export is an addition to a long list of regulatory roles for Mediator (Fig. 1). Schneider and colleagues' work adds to a growing set of studies[5-7] suggesting that Mediator regulates late stages of transcription, such as mRNA processing, in addition to its role in transcription initiation[2].

It should be noted, however, that indirect effects could also contribute to the mRNA export or gene NPC association defects reported by the authors. Consistent with a previous study[8], Schneider *et al.* found decreased expression of genes involved in the sulfur amino acid biosynthesis pathway in both Sac3-lacking and Med31-lacking cells. An end product of this biosynthetic pathway is S-adenosyl methionine (SAM), which is an essential cofactor for methyltransferase enzymes. A reduction in SAM levels would be expected to inhibit methyltransferase activity, which, in *S. cerevisiae*, regulates mRNA processing and export[9,10].

An array of future research avenues derive from Schneider and colleagues' study. For example, the study's relevance to human Mediator remains to be determined. Although the authors demonstrated that TREX-2 interacts with Mediator in *S. cerevisiae*, existing studies of human Mediator-interacting proteins are largely devoid of human versions of the TREX-2 subunits. The functional link between *S. cerevisiae* Mediator and mRNA export will probably be evolutionary conserved in some way, but the mechanisms by which Mediator acts in human cells are likely to be distinct. Most *S. cerevisiae* mRNAs are not spliced into different versions of the transcript, for instance, in contrast to human mRNAs. Active genes in human cells do not typically associate with the nuclear periphery or the NPC, unlike in yeast. Instead, data suggest[11] that active genes are found in the nuclear interior in human cells, and that they preferentially associate with structures called PML bodies or with 'mobile' NPC proteins such as NUP98 (ref. 4).

Another intriguing implication of the current study is the potential involvement of Mediator in regulating transcriptional memory, in which re-activation of specific genes, such as those induced by stress, occurs faster in cell progeny whose parents have previously experienced that stress[10]. This behaviour has been demonstrated in both yeast and mammalian cells[4], although the underlying mechanisms remain incompletely understood. In *S. cerevisiae*, maintenance of gene–NPC associations following cell division correlates with maintenance of transcriptional memory[4]. Schneider *et al.* showed that gene–NPC association required Med31, suggesting a potential role for Mediator in this process.

An interesting aspect of transcriptional memory in yeast is its apparent dependence on a looped genomic DNA architecture that juxtaposes the 5' end (the start site for transcription) and 3' end (the site of transcriptional termination) of the gene[12]. Although DNA architecture at active genes is different in humans, it is noteworthy that Mediator seems to be involved in the formation and stabilization of these loops in both species[7,13]. It will be interesting to see whether Mediator, perhaps through its Med31 subunit, contributes to such 'epigenetic' mechanisms of transcriptional memory. For these and other reasons, Schneider and colleagues' study represents an important advance, with mechanistic implications that remain to be explored.

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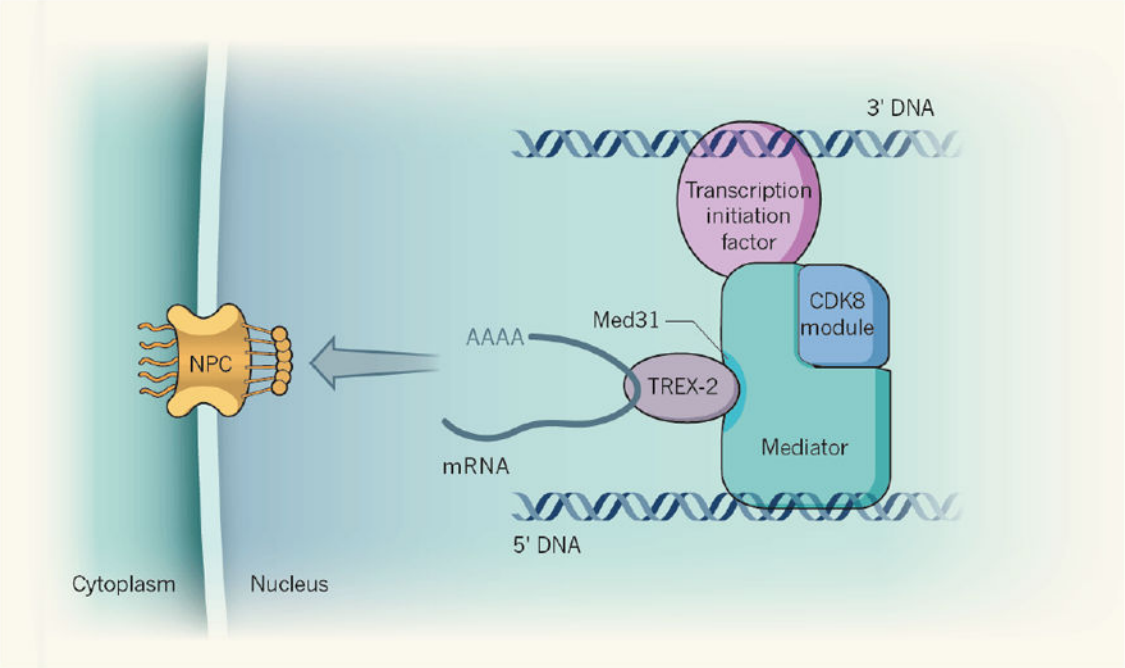

Figure 1. Complex interactions in mRNA export

Following gene transcription, messenger RNA transcripts are poly-adenylated (adenine (A) bases are added to the 3' end of the transcript) and disassociate from the transcribing enzyme RNA polymerase II (pol II).During and after transcription, factors involved in export of mRNA from the nucleus, such as the TREX- 2 protein complex, can associate with the mRNA. Schneider *et al.*[1] report that mRNA export is regulated by interactions between TREX-2 and another protein complex, Mediator. In yeast, the Mediator–TREX-2 interaction seems to stabilize Mediator's association with its Cdk8 kinase module — possibly through the TREX-2 subunit Sac3 and a subunit of Mediator called Med31. Mediator–TREX-2 interactions help ensure that genes undergoing transcription are close to the nuclear pore complex (NPC), thus facilitating mRNA export to the cytoplasm.