

# Alternate Endings: A New Story for mRNA Decapping

Sarah Geisler<sup>1</sup> and Jeff Collier<sup>1,\*</sup>

<sup>1</sup>Center for RNA Molecular Biology, Case Western Reserve University, Cleveland OH 44106, USA

\*Correspondence: [jmc71@case.edu](mailto:jmc71@case.edu)

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With most of the important players identified, the process of decapping is thought, for the most part, to be well understood. In this issue of *Molecular Cell*, Song et al. (2010) challenge this notion with the identification of a previously uncharacterized mRNA decapping enzyme.

All messenger RNA transcripts bear distinctive features at their extremities, i.e., a cap at one end and a tail at the other. The 5' 7-methylguanosine cap structure and 3' polyadenosine tail shunt the transcript through the appropriate metabolism of a message and ultimately drive its association with ribosomes. Because for some messenger RNA, the regulated removal of the cap (i.e., decapping) irreversibly influences expression of the transcript, decapping is a critical regulatory event (Franks and Lykke-Andersen, 2008). Specifically, decapping silences expression of the message by removing the ability of translation initiation factors to bind and, perhaps most importantly, commits the transcript to destruction by exposing the 5' end to exonucleases that voraciously degrade the transcript body. In this way, decapping can affect the overall level of protein synthesis within the cell.

Since its identification just over a decade ago, it has generally been assumed that a single polypeptide, Dcp2, is responsible for the majority of eukaryotic mRNA decapping (Franks and Lykke-Andersen, 2008). Dcp2 is a member of the Nudix family of pyrophosphatases and was originally discovered in yeast through a genetic screen (Dunckley and Parker, 1999). Characterization of Dcp2 over the years has shown that this enzyme is the major and perhaps only decapping enzyme in yeast. Parallel studies have shown that Dcp2 is conserved and functions as a decapping enzyme in flies, worms, plants, mice, and humans (Franks and Lykke-Andersen, 2008). By strict analogy to yeast, it has been generally assumed that Dcp2 was also the sole decapping activity in more complex eukaryotes, so it is with great interest that Song et al. (2010) now demonstrate that mice have a second decapping

enzyme, Nudt16, that has an effect on decapping equal to and perhaps slightly greater than Dcp2.

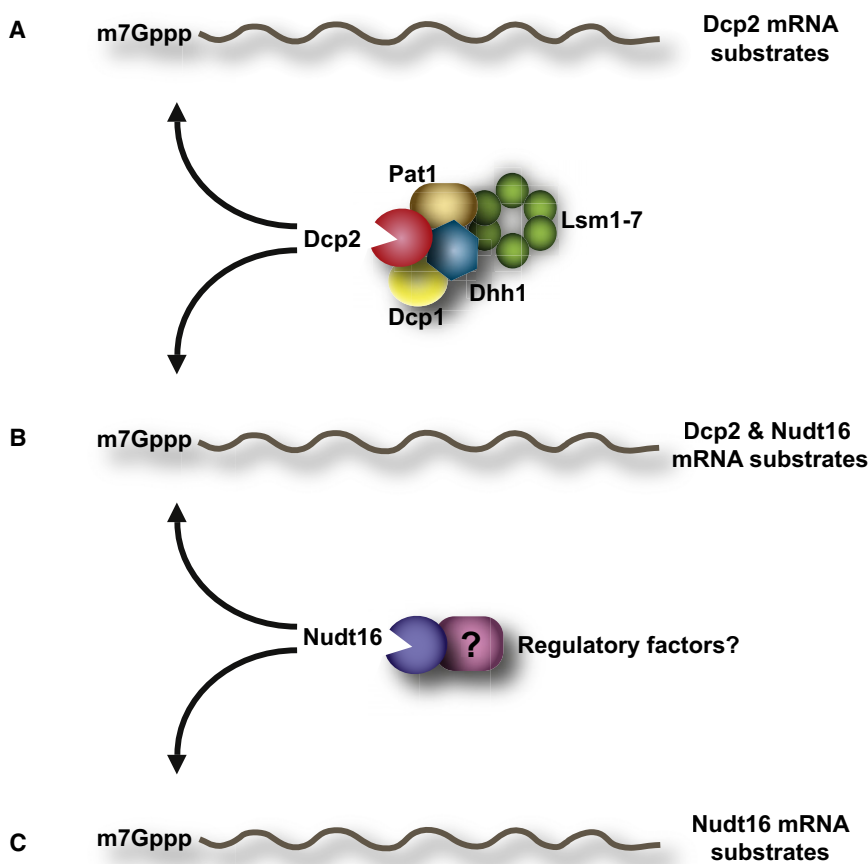
Song et al. embarked on a search for additional decapping enzymes based on two surprising observations. First, in the adult mouse, they found that Dcp2 was expressed in only a limited number of tissues and that in the embryo, Dcp2 was developmentally regulated. An enzyme responsible for bulk mRNA turnover would be expected to be more ubiquitous. Second, MEF cells without measurable Dcp2 expression still decap electroporated RNA substrates. These results point to the existence of a second decapping enzyme in mammalian cells. Song et al. surveyed a number of recombinant Nudix-containing proteins for in vitro decapping activity and identified Nudt16 as a bona fide decapping enzyme. Although Nudt16 was previously implicated in *Xenopus* as a nucleolar decapping enzyme (Ghosh et al., 2004), in mice it is expressed predominantly in the cytoplasm. Moreover, unlike Dcp2, Nudt16 expression is much more ubiquitous in adult tissues. Lastly, microarray analysis indicated that both Dcp2 and Nudt16 influence decay to similar extents. Importantly, they find some transcripts are specifically decapped by Dcp2 and some by Nudt16, and a few transcripts are regulated by both (Figure 1).

Irrespective of the turf war between Dcp2 and Nudt16, one important point is that together these two enzymes regulate only a fraction of total transcripts. This implies that decapping is a minor aspect of mRNA decay and/or that it is an extremely redundant process (i.e., involving multiple enzymes that catalyze similar reactions). An important caveat to these experiments is that they were conducted in a Dcp2 knockdown mouse that

only reduces expression rather than eliminates it. Since the mouse still expresses Dcp2, albeit at a reduced level, the full effect of decapping on global turnover cannot be convincingly stated. Irrespective, the identification of Nudt16 shows us that decapping is redundant in metazoans. In the end, perhaps even more decapping enzymes will be discovered. Indeed, very recently, the Kiledjian group showed that Rai1 has a unique decapping activity in yeast (Jiao et al., 2010). Thus, it is tantalizing to imagine that a number of distinct decapping complexes exist, each with their own substrate specificities, cellular regulation, and expression profiles.

So does redundancy in decapping enzymes diminish the importance of Dcp2 in metazoans? Probably not. We imagine, rather, that Dcp2 and perhaps other similar enzymes will turn out to be exquisitely specific regulators of gene expression in animals. Indeed, Song et al. show that Dcp2 is appreciably expressed in the embryonic heart, but its levels quickly ebb after birth and are virtually undetectable in the adult. These findings indicate that Dcp2 might have important developmental roles. This hypothesis is supported by the recent discovery that Not3, a regulator of deadenylation, is required for heart development in flies and mouse (Neely et al., 2010). Perhaps the "yeast-like" decay system represents an ancient and now highly differentiated machine that is used exclusively for special circumstances. It will be exciting to determine how message, cellular, and tissue specificities are achieved for the distinct metazoan decapping enzymes.

Finally, with the discovery of a new mRNA decapping enzyme comes a new set of questions. For instance, much is known about Dcp2-dependent events.



**Figure 1. Decapping Enzymes Have Overlapping but Sometimes Distinct Substrates**  
(A–C) For certain transcripts, Dcp2 is the major decapping enzyme. These might include developmentally regulated messages or those having specific Dcp2 binding elements (Li et al., 2009). Other mRNAs can be recognized by both enzymes (B). In these cases, the overall half-life of the mRNA would be predicted to be a consequence of the relative expression and activity of Dcp2 versus Nudt16. Lastly, transcripts can be decapped solely by Nudt16 (C). The features that distinguish substrate specificity are not clear but will be an area of great interest in the near future.

There are over 14 regulatory proteins that enhance or impede Dcp2-dependent decapping, such as Dcp1, Dhh1 (RCK/p54), PAB1, and eIF4E. What about Nudt16? Like Dcp2, does Nudt16 require accessory factors? Is translation an important determinant of Nudt16 activity, as it is for Dcp2? Is Nudt16 activity closely associated with polyribosomes? Are Dcp2 and Nudt16 differentially used in other decapping pathways such as nonsense-mediated decay and/or ARE-mediated decay? Time will tell, as we open a new chapter in the complex story of mRNA decay. And like those “choose your own adventure” books of our youth, we think it seems likely that the mRNA ending one chooses to follow will have unique and interesting outcomes.

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