NIH Public Access
Author Manuscript
Nat Struct Mol Biol. Author manuscript; available in PMC 2007 August 6.

Published in final edited form as:
Nat Struct Mol Biol. 2006 January ; 13(1): 7–9.

More than 1 + 2 in mRNA decapping

Sophie Bail and **Megerditch Kiledjian**
The authors are in the Department of Cell Biology and Neuroscience, Rutgers University, 604 Allison Road, Piscataway, New Jersey, 08854-8082, USA

Abstract

Decapping of messenger RNA was thought to involve a complex of only Dcp1 and Dcp2, but new data suggest that a larger multisubunit decapping complex exists in mammals. The larger complex includes a protein that facilitates the association of the two Dcp proteins and can be recruited by specific factors that promote mRNA decay.

Regulation of mRNA decay is an important step in the control of gene expression, and removal of the 5′ cap is a crucial part of eukaryotic mRNA decay. These mRNAs are not degraded by random processes, but rather undergo decay through two main exonucleolytic pathways that require the removal of the poly(A) tail (deadenylation) as a prerequisite step. The first pathway involves direct decapping and clearing of the mRNA body by the 5′→3′ exonuclease Xrn1. The second pathway proceeds through a continuous degradation by the exosome complex followed by hydrolysis of the resulting cap carried out by the scavenger decapping enzyme DcpS[1].

Two proteins, Dcp1p and Dcp2p, were initially isolated in yeast and shown to be essential for decapping, with Dcp2 being the catalytically active decapping enzyme[2–4]. In yeast, Dcp1p and Dcp2p are thought to form a decapping complex wherein the Dcp1p subunit facilitates decapping by Dcp2p[5]. Although homologs of Dcp1p are present in mammals, a similar stimulatory role has yet to be shown for either of the two human Dcp1p homologs, hDcp1a and hDcp1b. Furthermore, the composition of the decapping complex has also remained unclear.

A recent report by Fenger-Grøn *et al.*[6] now suggests that hDcp1a and hDcp2 are components of a larger decapping complex. Using an affinity purification approach with hDcp1a as bait, three proteins were identified. Two are homologous to previously identified yeast proteins known to enhance decapping, Dhh1p and Edc3p (termed rck/ p54 and hEdc3, respectively, in humans). Consistent with previous results in yeast, both proteins were shown to specifically interact with hDcp1a. The third interacting factor corresponds to a protein of unknown function that was termed Hedls (pronounced "headless"). Hedls enhances mRNA decapping at least in part by facilitating the interaction of hDcp1a with hDcp2. The authors propose that the presence of Hedls promotes formation of a multisubunit decapping complex that can consist of the two Dcp proteins, Hedls, rck/p54 and hEdc3 (Fig. 1). This is an important finding and suggests that Hedls can nucleate a larger decapping complex.

In contrast to yeast Dcp1p and Dcp2p, which can interact with one another[5,7,8], minimal to no interaction was detected between overexpressed hDcp1a and hDcp2 unless Hedls was also expressed. Fenger-Grøn *et al*.[6] also used immunopurified proteins to demonstrate a functional role for Hedls as a stimulator of hDcp2 decapping activity *in vitro*. Whether this is a direct effect of Hedls on hDcp2 or an indirect one via an interaction with hDcp1a associated with rck/p54 and hEdc3 remains to be determined. The lack of Hedls in yeast indicates that yeast and mammals have diverged to use different mechanisms in decapping. Perhaps the more efficient association of Dcp1p with Dcp2p in yeast precludes the need for a Hedls-like protein, whereas the more modest association of mammalian hDcp1a and hDcp2 requires Hedls. This could also account for the previously observed lack of stimulatory activity of hDcp1a for

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

decapping by hDcp2 (refs. 2,3). Therefore, the addition of Hedls might be necessary to observe a decapping-stimulatory phenotype of hDcp1a. Surprisingly, up to 20-fold greater hDcp2 levels were detected upon expression of Hedls. This observation could signify an additional mechanism by which Hedls promotes decapping, perhaps by the stabilization of the hDcp2 protein, as suggested by Fenger-Grøn *et al.*[6].

The recent identification of cytoplasmic foci termed processing bodies (P-bodies, also referred to as GW bodies and Dcp bodies) that contain the decapping enzymes has raised a great deal of interest. In general, many of the proteins that are directly or indirectly involved in the 5′→3′ decay pathway can localize within the P-bodies[9]. In addition, the deadenylase Ccr4, the translation initiation factor eIF4E and its transporter, and the RNA-induced silencing complex (RISC) proteins Argonaute 1 and 2 are also in P-bodies[2,3,10–12]. As would be expected for a decapping-complex protein, Fenger-Grøn *et al.*[6] found that Hedls colocalizes with hDcp1a in P-bodies[6]. Overexpression of Hedls leads to the formation of aberrant P-bodies and accumulation of deadenylated mRNAs. This is a common theme for proteins involved in the 5′→3′ decay pathway, as similar enlargements of P-bodies also occur in yeast and mammalian cells upon disruption of Dcp1p and Xrn1 (refs. 10,13).

mRNA turnover can be stimulated by adenine-uracil–rich elements (AREs) found in many unstable mRNAs. One mechanism by which the AREs can promote rapid mRNA decay is by recruitment of the exosome[14,15]. Moreover, the recent demonstration that the tristetraprolin (TTP) ARE-binding protein interacts with hDcp2 (ref. 16) suggests that ARE-binding proteins can also function to recruit decapping factors. Using an *in vitro* decapping assay, Fenger-Grøn *et al.*[6] now show that immunopurified TTP can significantly enhance the decapping of an ARE-containing RNA but has a minimal effect on an RNA that does not contain any AREs. Furthermore, the N-terminal domain of TTP, which contains the hDcp2-interaction region[16], was required for this stimulation. Therefore, TTP seems to be a multifunctional protein that can promote the decay of mRNA by a variety of mechanisms (Fig. 2). Although TTP can directly facilitate decapping in the above-mentioned *in vitro* decay assay[6], it seems also to require the miR16 microRNA to promote overall decay of a reporter RNA containing a different ARE, the tumor necrosis factor-α mRNA[17]. In this case, TTP was shown to interact with Argonaute 2, suggesting that miR16 functions with TTP to promote decapping. Whether a microRNA is required for all ARE-mediated mRNA decay or just that of a subset of ARE-containing mRNAs still remains to be determined, as does the mechanism by which it promotes decay.

The demonstration that the Dcp proteins can be part of a larger complex opens new avenues for investigation. Although such a complex can be immunopurified, further work is needed to determine whether this complex is the functional decapping unit or simply one of multiple different decapping complexes that are used in cells. The ability of yeast Edc3p to promote general decapping[18] as well as decapping of a specific transcript without prior deadenylation[19] supports the notion of multiple decapping complexes. Furthermore, the role of rck/p54 in decapping is still unclear. The association of rck/p54 with hDcp1a might serve as an active stimulator of decapping, or it might represent a means for recruiting translationally repressed RNAs to the decapping machinery. This question is posed in light of the recent demonstration by Coller and Parker[20] that the rck/p54 homolog in yeast, Dhh1p, is a translational repressor that promotes movement of mRNA into P-bodies and P-body aggregation. Numerous additional factors have also been proposed to promote decapping[9], although their mechanisms still need to be clarified. Finally, even though a great deal of emphasis has been placed on the decapping enzymes and the promoters of decapping, it seems likely that regulation of decapping will also involve inhibitors of decapping that have yet to be identified. It is clear that regulation of decapping is an intricate process, and the identification of Hedls adds one more piece toward completion of the mRNA decapping puzzle.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

References

1. Parker R, Song H. Nat Struct Mol Biol 2004;11:121–127. [PubMed: 14749774]
2. Lykke-Andersen J. Mol Cell Biol 2002;22:8114–8121. [PubMed: 12417715]
3. van Dijk E, et al. EMBO J 2002;21:6915–6924. [PubMed: 12486012]
4. Wang Z, Jiao X, Carr-Schmid A, Kiledjian M. Proc Natl Acad Sci USA 2002;99:12663–12668. [PubMed: 12218187]
5. Steiger M, Carr-Schmid A, Schwartz DC, Kiledjian M, Parker RA. RNA 2003;9:231–238. [PubMed: 12554866]
6. Fenger-Grøn M, Fillman C, Norrild B, Lykke-Andersen J. Mol Cell 2005;20:905–915. [PubMed: 16364915]
7. Dunckley T, Parker R. EMBO J 1999;18:5411–5422. [PubMed: 10508173]
8. She M, et al. Nat Struct Mol Biol 2004;11:249–256. [PubMed: 14758354]
9. Coller J, Parker R. Annu Rev Biochem 2004;73:861–890. [PubMed: 15189161]
10. Cougot N, Babajko S, Seraphin B. J Cell Biol 2004;165:31–40. [PubMed: 15067023]
11. Liu J, Valencia-Sanchez MA, Hannon GJ, Parker R. Nat Cell Biol 2005;7:716–723.
12. Sen GL, Blau HM. Nat Cell Biol 2005;7:633–636. [PubMed: 15908945]
13. Sheth U, Parker R. Science 2003;300:805–808. [PubMed: 12730603]
14. Chen CY, et al. Cell 2001;107:451–464. [PubMed: 11719186]
15. Mukherjee D, et al. EMBO J 2002;21:165–174. [PubMed: 11782436]
16. Lykke-Andersen J, Wagner ER. Genes Dev 2005;19:351–361. [PubMed: 15687258]
17. Jing Q, et al. Cell 2005;120:623–634. [PubMed: 15766526]
18. Kshirsagar M, Parker R. Genetics 2004;166:729–739. [PubMed: 15020463]
19. Badis G, Saveanu C, Fromont-Racine M, Jacquier A. Mol Cell 2004;15:5–15. [PubMed: 15225544]
20. Coller J, Parker R. Cell 2005;122:875–886. [PubMed: 16179257]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

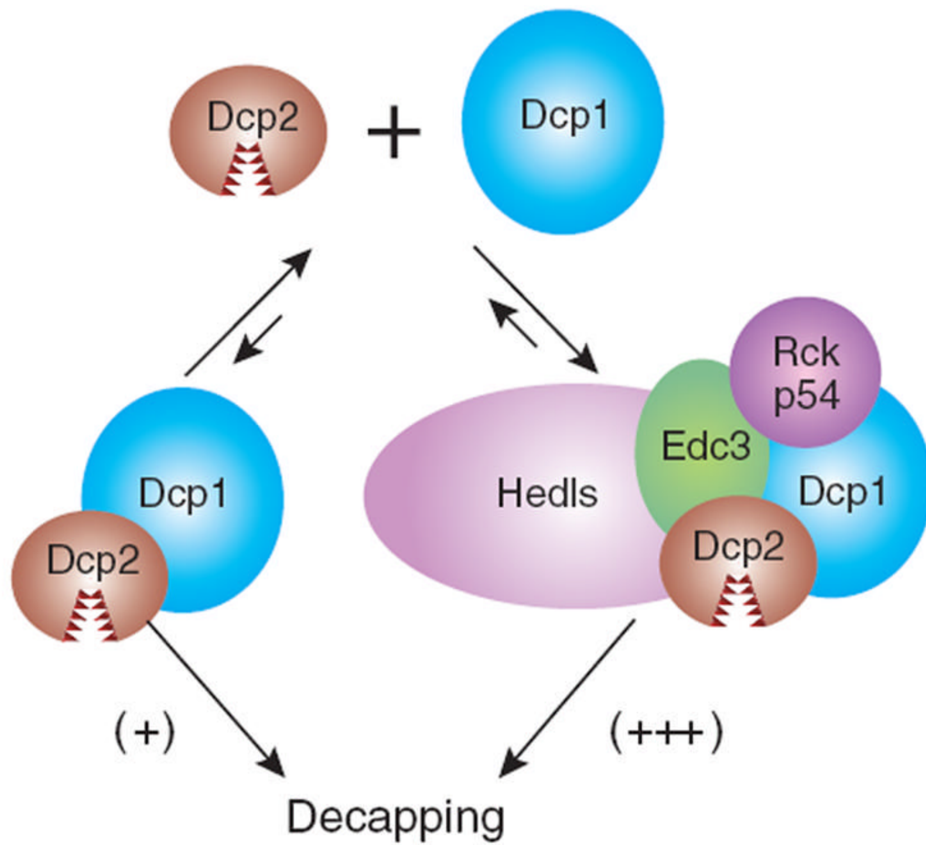

Figure 1.

Model of potential Dcp2 decapping complexes. Top arrows represent the equilibrium of Dcp1 and Dcp2 association/dissociation in the presence or absence of Hedls. The decapping activity of Dcp2–Dcp1 complex (+) may be enhanced (+++) in the presence of the other decapping-complex components. The Dcp2 catalytic component is shown with teeth. Not shown are potential intermediates with only a subset of the proteins.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

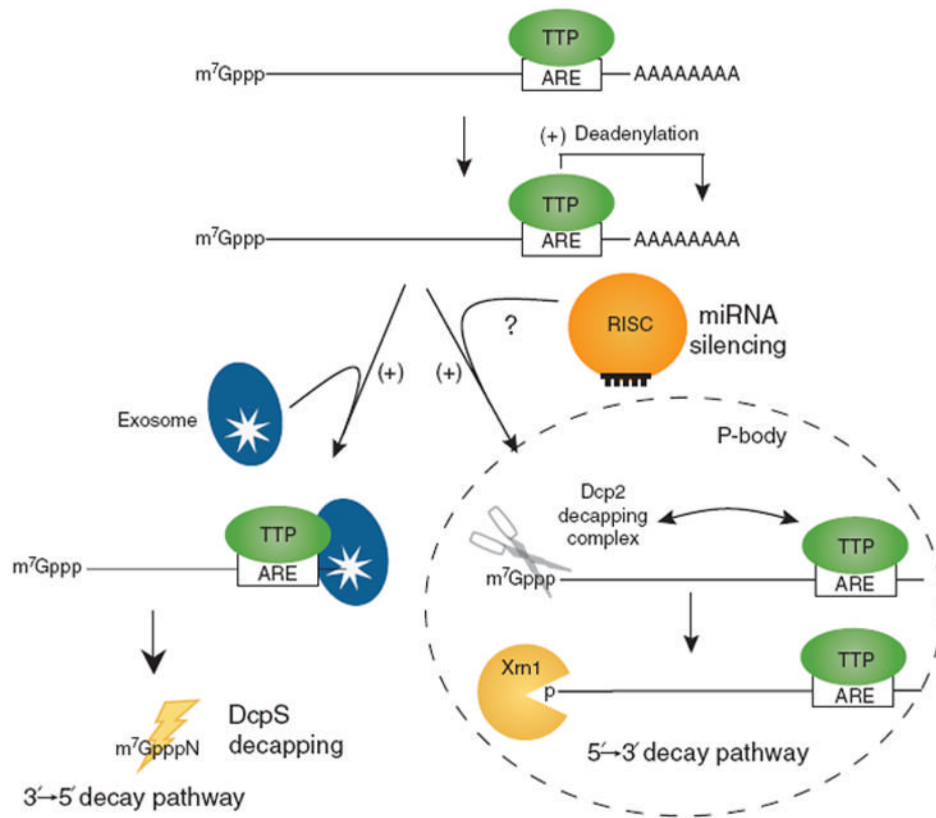

Figure 2.
Activation of ARE-containing mRNA decay by TTP. To facilitate rapid decay of the ARE-containing mRNA, TTP is known to promote both the 5′→3′ and the 3′→5′ decay pathways as well as to function with miR16, at least in the case of the tumor necrosis factor-α ARE.