Scanning for a unified model for translational repression by microRNAs

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**MicroRNAs (miRNAs) silence target mRNAs by inhibiting translation and subsequently initiating mRNA decay. The mechanism by which miRNAs silence translation is still poorly understood, with a number of competing models proposed. In this issue of *The EMBO Journal*, Kuzuo glu-Öztürk *et al* (2016) investigated miRNA silencing in human and insect cells. Their data support a model whereby miRNAs inhibit translation initiation. However, in contrast to several recent reports, their data suggest that translational inhibition is independent of 43S ribosomal subunit scanning, eIF4A translation factor activity, and 5’UTR secondary structure.**

Several early studies pointed to miRNAs inhibiting cap-dependent translation at the initiation step via an unknown mechanism (Humphreys *et al*, 2005; Pillai *et al*, 2005). Translation initiation depends on a number of factors, including the eIF4F complex, which is composed of three subunits: eIF4E, which binds to the mRNA 5’-cap structure; eIF4A, an RNA helicase; and eIF4G, a scaffold that binds both eIF4E and eIF4A and helps recruit the small ribosomal subunit 43S pre-initiation complex (PIC) (Gingras *et al*, 1999). eIF4A activity is essential for unwinding highly structured 5’UTRs to allow for 43S PIC scanning.

A number of mechanisms have recently been proposed to explain how miRNAs suppress translation (reviewed in Jonas & Izaurralde, 2015). The authors show that the W-binding pockets in AGO1 utilize its W-binding pockets to interact with the CCR4–NOT complex (Meijer *et al*, 2013). However, this model has been questioned based on the observation that (i) eIF4AII is vertebrate-specific and (ii) eIF4AII knockout cells display no defects in miRNA silencing (Galicia-Vazquez *et al*, 2015). Other groups have reported that miRNAs inhibit 43S ribosomal scanning, with miRNA reporters harboring unstructured 5’UTRs being refractory to miRNA silencing (Ricci *et al*, 2013). Several laboratories have also reported that translational repression somehow intersects with eIF4AI (Fukao *et al*, 2014; Fukaya *et al*, 2014) by showing that eIF4A depletion in *Drosophila melanogaster* (Dm) S2 cells impairs miRNA-mediated translational repression. Furthermore, experiments carried out in Dm and human cell-free extracts showed that eIF4A is displaced from miRNA-targeted reporters. Finally, it has also been reported that Dm AGO1 can facilitate eIF4A dissociation and repress translation in GW182-depleted S2 cells (Fukaya & Tomari, 2012).

In this issue of *The EMBO Journal*, Kuzuo glu-Öztürk *et al* (2016) investigate miRNA-mediated translational repression in human and *Dm* cells to determine whether parallel and potentially species-specific mechanisms exist. They use a multitudes of reporter RNAs that cannot be deadenylated in order to investigate “pure” translational repression mediated by miRNAs, AGOs, GW182, and the CCR4–NOT complex. The authors show that the W-binding pockets in AGO proteins, which bind GW182, are critical for it to silence miRNA targets in human cells. However, they also found this to be the case in *Dm* S2 cells, where AGO1 has been reported to silence a target mRNA in the absence of GW182 protein (Fukaya & Tomari, 2012). It is possible, as Kuzuo glu-Öztürk *et al* (2016) propose, that the *Dm* AGO1 utilizes its W-binding pockets to interact with another protein in the absence of GW182 in *Dm* that also mediates gene silencing. However, the identity of this protein and the biological significance of its interaction with AGO1 remain to be determined.

Kuzuo glu-Öztürk and colleagues provide evidence that miRNAs, AGO, GW182, and the CCR4–NOT complex engender a common

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miRNA machinery may interact with eIF4A, directly or indirectly, in order to repress eIF4F-mediated translation. Thus, the miRISC could silence a mRNA whose translation is less dependent on eIF4A activity (i.e. scanning-independent), as long as eIF4A is present and accessible.

References


