# SnapShot: Unconventional miRNA functions

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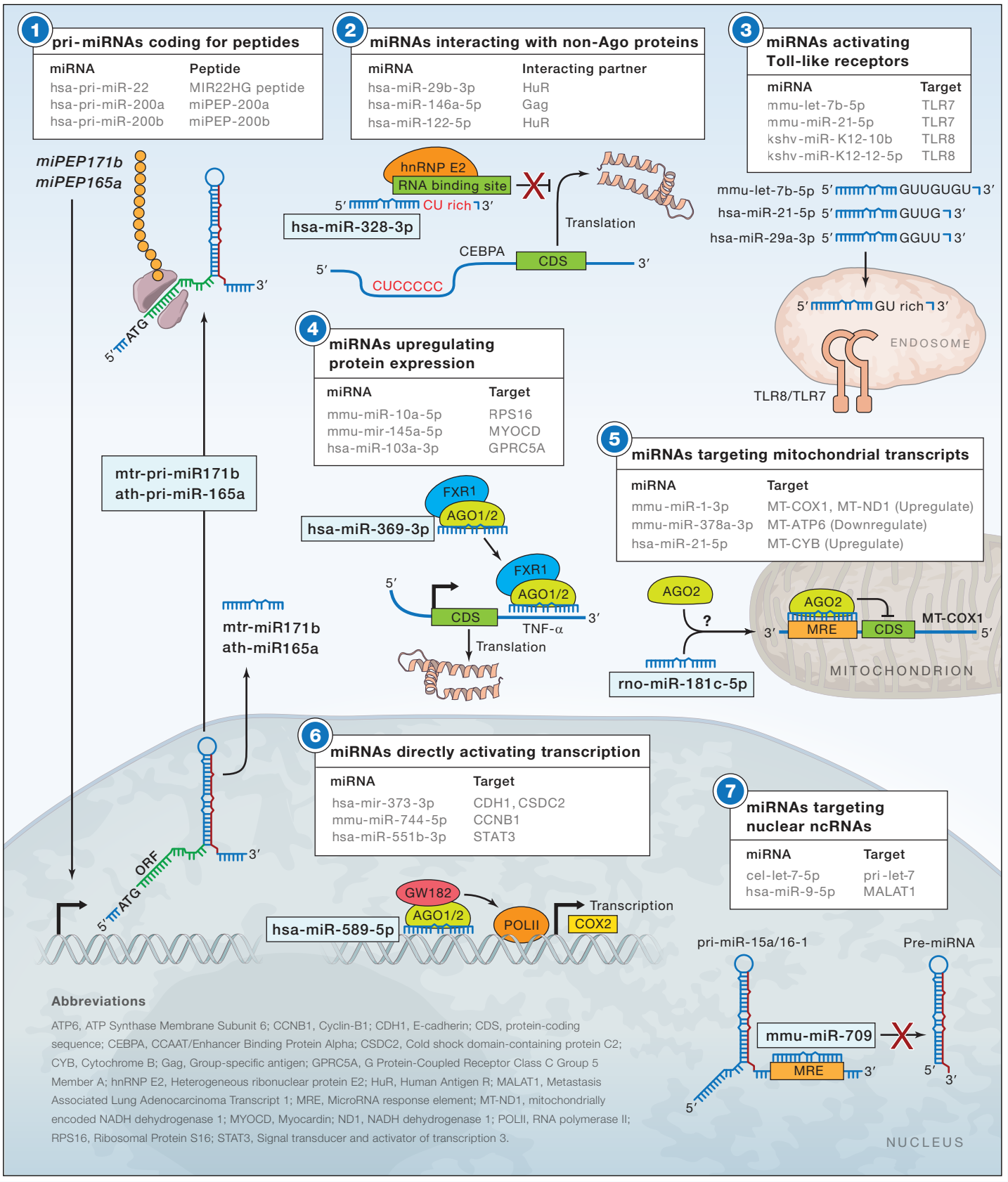




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In the quarter of a century since their initial discovery, interest in miRNAs has exploded, as displayed by the 80,000 PubMed entries and counting focused on miRNAs. The vast majority of these publications have explored how these small non-coding RNAs (ncRNAs) post-transcriptionally reduce the levels of specific target protein coding gene expression by either promoting messenger RNA (mRNA) decay or by dampening translation (Bartel, 2018). A number of studies, however, have reported miRNAs functioning outside this paradigm, and this SnapShot outlines the unconventional ways that miRNAs can exert regulatory functions. Due to space constraints, we highlight initial and prominent examples; however, subsequent studies have implicated additional miRNAs as functioning through these mechanisms (see tables in the figure). This list of arguably heretical mechanisms is also likely not exhaustive and could expand as researchers continue to dive deeper into the versatility of these small ncRNAs.

## Pri-miRNAs Coding for Peptides

miRNAs are transcribed as much longer pri-miRNAs that are subsequently processed to yield the mature ~22 nt miRNA. It has been found that these pri-miRNAs can actually encode for regulatory peptides, which have been termed miRNA encoded peptides (miPEPs). This initial finding by Lauressergues et al. (2015) discovered that, in plants, several pri-miRNAs, including pri-miR-171b of *Medicago truncatula* and pri-miR-165a of *Arabidopsis thaliana*, produce short peptides. These short peptides initiate from ATG start codons within the pri-miRNA. miPEP-171b is a mere 9 amino acids, and miPEP-165a is only slightly longer at 18 amino acids. Curiously, these miPEPs ultimately function by increasing transcription of their own pri-miRNA, which subsequently enhances the accumulation of their corresponding mature miRNAs (Lauressergues et al., 2015).

## miRNAs Interacting with Non-AGO Proteins

miRNAs are loaded into Argonaute (AGO) protein-containing complexes to exert canonical repression mechanisms. Eiring et al. (2010), however, reported an example of a miRNA that can act as a decoy for another RNA binding protein and, in doing so, interferes with its function. Specifically, miR-328 contains a polyU/C stretch that is very similar to the binding site for hnRNP E2 within the CEBPA mRNA. Binding of miR-328 leads to a release of CEBPA mRNA from hnRNP E2-mediated translational inhibition. Interestingly, CEBPA is a hematopoietic transcription factor, and through a canonical miRNA role, miR-328 suppresses the survival factor Pim-1 Proto-Oncogene, Serine/Threonine Kinase (PIM1). This dual ability, therefore, rescues differentiation and impairs survival of leukemic blasts in chronic myelogenous leukemia when miR-328 is reintroduced (Eiring et al., 2010).

## miRNAs Activating Toll-like Receptors

Although the direct physical interaction has not yet been proven, an exciting unconventional role for miRNAs with great therapeutic potential involves activation of Toll-like receptors (TLRs). Fabbri et al. (2012) discovered that both miR-21 and miR-29a activate TLR7 (in humans, and TLR8 in mice). This agonist effect causes a prometastatic inflammatory response in lung cancers (Fabbri et al., 2012). Lehmann et al. (2012) found that let-7 activates TLR7 and causes neurodegeneration (Lehmann et al., 2012). Blocking these effects could have therapeutic implications in patients with cachexia (microvesicular miR-21) and sepsis (Kaposi Sarcoma-associated Herpesvirus miRNAs).

## miRNAs Upregulating Protein Expression

Vasudevan et al. (2007) identified that the direction of a miRNAs effect on protein expression can be cell-cycle dependent, in that specific miRNAs induce translation of target mRNAs upon cell cycle arrest, yet they repress translation in proliferating cells. Specifically, human miR-369 directs association of AGO2 and fragile X mental-retardation-related protein 1 (FXR1) with AU-rich elements (AREs) in tumor necrosis factor-alpha (TNF-$\alpha$) mRNA to activate translation (Vasudevan et al., 2007).

## miRNAs Targeting Mitochondrial Transcripts

Although no miRNAs have been identified within the mitochondrial genome, Das et al. (2012) showed that miR-181c translocates into the mitochondria and inhibits mitochondrially encoded cytochrome *c* oxidase subunit 1 (MT-COX1) protein expression but at the same time increases MT-COX2 mRNA expression and protein content (Das et al., 2012). mitomiRs such as miR-181c could be targeted therapeutically to restore normal mitochondria function or used as drugs.

## miRNAs Directly Activating Transcription

Hwang et al. (2007) demonstrated that a distinctive hexanucleotide terminal motif of miR-29b acts as a transferable nuclear localization element that directs nuclear enrichment of small ncRNAs to which it is attached (Hwang et al., 2007). Further studies have shown that miRNAs together with AGO1 or AGO2 can be imported into the nucleus by Importin 8. Matsui et al. (2013) found that miR-589, in complex with AGO2 and GW182, bound the promoter RNA of cyclooxygenase-2 (COX2), which led to induction of transcription of COX2 as well as Phospholipase A2 Group IVA (PLA2G4A) though gene looping (Matsui et al., 2013).

## miRNAs Targeting Nuclear ncRNAs

Tang et al. (2012) identified that nuclearly localized miR-709 inhibited maturation of miR-15a and miR-16-1 via a direct interaction with the primary transcript. Importantly, miR-15a and miR-16-1 are part of a miRNA cluster known to induce apoptosis. By inhibiting their maturation, miR-709 thereby restricted cells from going into apoptosis (Tang et al., 2012).

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