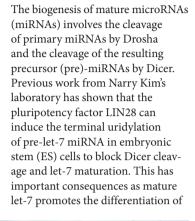
## RESEARCH HIGHLIGHTS

## SMALL RNAS

## Keeping let-7 young

ZCCHC11 ... is the TUTase that regulates LIN28-mediated pre-let-7 uridylation.



ES cells and development. Because LIN28 does not posses uridylyl transferase activity, how it is involved in inducing pre-let-7 uridylation was unknown. Three studies now reveal that the mammalian terminal uridylyl transferase (TUTase) zinc finger CCHC domain-containing protein 11 (ZCCHC11; also known as TUT4), and its *Caenorhabditis elegans* orthologue poly(U) polymerase 2 (PUP-2), is the TUTase that regulates LIN28-mediated pre-let-7 uridylation.

Studies by Heo et al. and Hagan et al. identify ZCCHC11 as the only one of seven mammalian TUTases that can uridylate pre-let-7 in mouse ES cells. Heo et al. show that small interfering RNA-mediated knockdown of ZCCHC11 or LIN28 reduces the level of pluripotency markers in mouse ES cells, which is consistent with the role of mature let-7 in promoting ES cell differentiation. They also present data suggesting that LIN28 recruits ZCCHC11 to pre-let-7 by recognizing a GGAG motif in the terminal loop of this pre-miRNA. Several additional miRNAs that contain the GGAG motif, including other let-7 family members and miR-107, miR-143 and miR-200c, also undergo uridylation in a LIN28-dependent manner. This suggests that the ability of LIN28 and ZCCHC11 to repress pre-miRNA processing by inducing uridylation may not be specific to let-7.

Hagan *et al.* show that knockdown of ZCCHC11 or LIN28, using small interfering RNA, stops the inhibition of let-7 processing, leads to the accumulation of mature let-7 miRNA and results in the repression of reporter genes that are inhibited by mature let-7.

Finally, Lehrbach *et al.* examined the post-transcriptional regulation of let-7 in *C. elegans*. They found that LIN-28 also binds to pre-let-7 and prevents its processing by Dicer, and that this is dependent on the ZCCHC11 orthologue, PUP-2. Furthermore, LIN-28 stimulates the uridylation of pre-let-7 by PUP-2 in vitro.

Together, these studies show that the newly defined let-7–LIN28–TUTase pathway is evolutionarily conserved to control the processing of let-7. However, as the terminal loop of pre-let-7 is not conserved in *C. elegans*, the exact mechanistic details might differ between organisms. Future studies are likely to confirm whether this pathway regulates the processing of other miRNAs in *C. elegans* and mouse ES cells.

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ORIGINAL RESEARCH PAPERS Heo. I. et al. TUT4 in concert with Lin28 suppresses microRNA biogenesis through pre-microRNA uridylation. Cell 138, 696-708 (2009) | Hagan, J. P. et al. Lin28 recruits the TUTase Zcchc11 to inhibit let-7 maturation in mouse embryonic stem cells. Nature Struct. Mol. Biol. 27 Aug 2009 (doi:10.1038/nsmb.1676) | Lehrbach, N. J. et al. LIN-28 and the poly(U) polymerase PUP-2 regulate let-7 microRNA processing in Caenorhabditis elegans. Nature Struct. Mol. Biol 27 Aug 2009 (doi:10.1038/nsmb.1675) FURTHER READING Vamsi, K. & Lin, H. MicroRNAs: key regulators of stem cells. Nature Rev. Mol. Cell Biol. 10, 116-125 (2009) | Kim, V. N. et al. Biogenesis of small RNAs in animals. Nature Rev. Mol. Cell Biol. 10, 126-139 (2009)