m^5U54 tRNA hypomodification induces the generation of tRNA-derived small RNAs

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Abstract:

Transfer RNAs (tRNAs) are the effector molecules of translation and are also a known source of small non-coding RNAs collectively known as tRNA-derived small RNAs (tsRNAs). tsRNAs have regulatory functions that range from translation regulation to gene expression control and cellular stress response, but what exactly triggers their formation is still under discussion.

Both tRNAs and tsRNAs bear several modifications catalyzed by tRNA modifying enzymes. These modifications are essential for tRNA stability, translational efficiency and fidelity, and constitute the tRNA epitranscriptome. Although different enzymes, such as Dicer and Angiogenin (ANG), catalyze the formation of different classes of tsRNAs, the biological role of the tRNA epitranscriptome and whether it plays a role in tRNA fragmentation is only now beginning to be uncovered.

Here, we describe how disruption of the 5-methyluridine (m^5U) modification at position 54 of cytosolic tRNAs - one of the most common and conserved tRNA modifications among species - induces the generation of tsRNAs. Knockdown of the tRNA modifying enzyme TRMT2A in a human cell line induces m^5U54 tRNA hypomodification, cellular stress and ANG up-regulation. The increase in ANG levels due to TRMT2A known-down results in tRNA cleavage near the anticodon, and accumulation of 5'tRNA-derived stress-induced RNAs (5'tiRNAs). Additionally, we demonstrate that exposure to oxidative stress conditions induces TRMT2A down-regulation and tiRNAs formation in mammalian cells.

Our results unravel m^5U54 as a tRNA cleavage protective mark, adding a further layer to the mechanisms associated with tsRNA generation upon stress. It also identifies TRMT2A as an important player in the cellular response to stress, and demonstrates that disruption of tRNA methylation is a trigger for tRNA fragmentation.

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