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Pseudouridine-driven programmes in stem cells and cancer

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Pseudouridylation (Ψ) is the most abundant and widespread type of RNA epigenetic modification in living organisms; however, the biological role of Ψ remains poorly understood. Recently, we have uncovered a Ψ-driven posttranscriptional program that steers translation control to impact stem cell commitment during early embryogenesis and in cancer. Mechanistically, the Ψ "writer" PUS7 modifies and activates a novel network of tRNA-derived small fragments (tRFs) targeting the translation initiation complex. That keeps in check mRNA translation levels during differentiation and in cancer.

Specifically, PUS7 inactivation in embryonic stem cells impairs tRF-mediated translation regulation, leading to increased protein biosynthesis and defective germ layer specification. Remarkably, dysregulation of this posttranscriptional regulatory circuitry impairs hematopoietic stem cell commitment and is common to aggressive subtypes of human myelodysplastic syndromes. We further show that PUS7-tRFs axis selectively inhibits aberrant protein synthesis programmes, thereby promoting engraftment and differentiation of haematopoietic stem and progenitor cells in patients with myelodysplastic syndromes. Loss of this regulatory node promotes malignant phenotypes in acute myeloid leukemias.

Collectively, our findings unveil a critical function of Ψ in directing translation control in stem cells with important implications for development and disease.