

Popular summary

Proteins are the building blocks of our cells that are selectively produced from instructions written in our genes under the form of DNA. The process of protein production, known as “protein synthesis” is critical for life. In particular stem cells, a cell type with the potential to self-renew and generate each cell in an organisms or in a specific tissue (a process known as differentiation), rely on tight regulation of protein synthesis. Uncontrolled production of proteins alters the function of stem cells causing severe developmental defects. Similarly, cancer cells hijack the protein synthesis machinery to promote tumor formation and sustain tumor growth. **Still, how stem cells accurately regulate protein production to ensure proper development and prevent cancer formation remains unclear.** In this thesis, I uncovered a novel mechanism that controls protein synthesis in unique population of stem cells, during the earliest steps of embryonic development and the maturation of blood cells. This fail-safe mechanism relies on the chemical modification pseudouridine (Ψ) of specific RNA molecules, which we named mTOG (RNA is a regulatory molecule, transcribed from information encoded in DNA). Intriguingly, in the absence of Ψ -modified mTOGs, stem cells increase protein synthesis rate, augment in cell size and lose their ability to mature into blood cells. Strikingly, I found that mTOGs loss is common in blood cancers and correlates with poorest patient survival. Ultimately, using mTOGs to treat blood stem cells isolated from leukemic patients restores a normal rate of protein synthesis and promotes the production of mature blood cells, which might contribute to eradicate leukemic cells. Overall, this work highlights a novel regulatory network controlling stem cell biology, with broad clinical implications.