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Stem cell proteostasis disruption in ribosomopathy-associated bone marrow failure and cancer

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Scientific Abstract:

Ribosomopathies are congenital human diseases linked to mutations in genes encoding factors that influence ribosome biogenesis. Patients with ribosomopathies typically present with cytopenias, bone marrow failure andan increased incidence of hematological malignancies. These disorders suggest that hematopoietic stem cells (HSCs) are particularly sensitive to ribosomal mutations, as defects in HSC maintenance can lead to anemia and bone marrow failure, and over-activation of HSC self-renewal programs leads to hematopoietic neoplasms. The effects of ribosomal mutations on HSCs have, understandably, been thought to disrupt cellular function by reducing ribosome biogenesis and protein synthesis. However, emerging data in model organisms suggests thatribosomal mutations can cause broad disruptions in protein homeostasis (proteostasis), marked by an accumulation of misfolded proteins, impaired protein degradation and activation of proteotoxic stress response pathways. We recently discovered that HSCs contain fewer misfolded and unfolded proteins than restricted progenitors, and even modest disruptions in proteostasis impair HSC self-renewal. Furthermore, we found that proteostasis disruption can activate proto-oncogenic transcription factors within HSCs. Based on these data, we hypothesize that loss of proteostasis impairs HSC function in ribosomopathy patients, and proteostasis disruption may create a selective pressure that alters gene expression and promotes cancer initiation later in life. We will test this by assessing HSC function, proteostasis and gene expression within primary human HSCs isolated frompediatric ribosomopathy patients. Our goal is to unravel the mechanisms that contribute to ribosomopathy- associated bone marrow failure and hematological malignancies to identify actionable therapeutic targets to treatthese patients.

Lay Abstract:

In diseases called ribosomopathies, kids are born with genetic errors that disrupt ribosomes, which are the machines our cells use to make protein. This causes problems in multiple organ systems, especially the blood. Patients often develop reduced blood cell counts and are at increased risk for developing leukemia and other cancers that respond poorly to chemotherapy and treatment. Thus, further research is needed to determine thefactors that cause these blood disorders so that we can develop new treatments to help these patients and decrease the likelihood that they develop cancer. Recent findings suggest that genetic errors that disrupt ribosomes can cause cells to make faulty proteins that fold into the wrong shape and work incorrectly. This stresses our cells and makes them function poorly. We discovered that blood-forming stem cells, which are cells in our bone marrow that produce blood cells throughout our lives, are very sensitive to accumulation of misfoldedproteins. This raises the possibility that protein stress in ribosomopathy patients makes their stem cells malfunction leading to blood disorders and cancer. Using new technology, we will investigate if blood-forming stem

cells in children with ribosomopathies have defective proteins, and whether this impairs their stem cells' ability to make blood. We will also test if these protein changes make stem cells more likely to become cancerous. Our approach will provide critical new information about how these diseases occur, and could provide new strategies for treating these children and preventing their development of cancer.