PCL/23/07 - The minor spliceosome in health and disease.

Defects in RNA processing are associated with diverse human diseases including cancers, immunodeficiency and neurological degeneration. Understanding the mechanisms underlying these associations can be challenging because many RNA pathways are essential, and so it is often not possible to study knockout model systems. Monogenic diseases with extreme phenotypes offer an opportunity to address these questions. Here, I propose to investigate defects in minor splicing, a conserved pathway that removes minor introns from about 700 of the 500,000 spliced human RNA transcripts. Patients with mutations in a non-coding RNA component of the minor spliceosome have exceptionally impaired growth leading to perinatal lethality, together with immunological dysfunction. I hypothesise that minor splicing and the cell cycle are co-regulated, and that disease-linked mutations impair cell proliferation. Based on potential shared mechanisms with other growth disorders, I also hypothesise that disrupted minor splicing reduces organism-level cell number by causing genomic instability, impaired ribosome synthesis or dysregulated innate immunity. I will test these hypotheses using genetically-engineered cell lines and patient-derived fibroblasts. This work will lay the foundation for future research investigating minor splicing defects in diseases such as acquired blood dyscrasias and early-onset cerebellar ataxia, as well broader questions related to growth disorders and immunodeficiency.