

## INTEGRATIVE APPROACH TO MINOR SPLICEOSOME REGULATORY NETWORKS



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In multicellular organisms the flow of genetic information from DNA to proteins is tightly regulated. In this process the genetic information is initially transcribed to mRNA precursor (pre-mRNA) that gives rise to mRNA molecules which in turn serves a template for protein synthesis. Each of these steps in the gene expression pathway are regulating the flow of genetic information. Our objective is to investigate one of these steps, an ancient post-transcriptional regulatory pathway that controls cellular growth and differentiation. The foundation of this research is our earlier research where we sought to understand why a small subset of genes (~700 in humans), specifically those involved in e.g. cellular growth, have a unique layer of regulation orchestrated by a molecular machine called as the minor spliceosome.

This regulatory layer operates at post-transcriptional level during nuclear mRNA processing and is evolutionarily extraordinary conserved – it is present in the same (orthologous) genes from plants to humans and has hence withstand at least 900 million years of evolutionary pressure. Human diseases that compromise the integrity of this regulatory system lead to widespread defects in multiple tissues,

particularly in neuronal system (causing for example microcephaly, cerebellar ataxia) and immune system (myelodysplastic syndrome). Very recent data has shown that minor spliceosome defects affect specifically cell growth and differentiation and its dysregulation leads to formation of multinuclear cells.

In the present work we have identified a novel component of the minor spliceosome that is mutated in a certain rare human diseases. The patient cells show significantly increased levels of chromosome segregation errors during cell division. At the same time our gene expression analyses have revealed that a clearly defined subset of genes targeted of by the minor spliceosome show abnormal processing of pre-mRNA molecules. Among these are many genes that encode protein factors involved in chromosome segregation during cell division. Our aim is to investigate how the defect in minor spliceosome function propagates to the protein level and affects the global gene expression network both at the mRNA and protein level. Our integrative analysis will help to refine the mechanistic model of minor spliceosome regulation, but will also help to understand the diseases caused by the dysfunction of this regulatory system.

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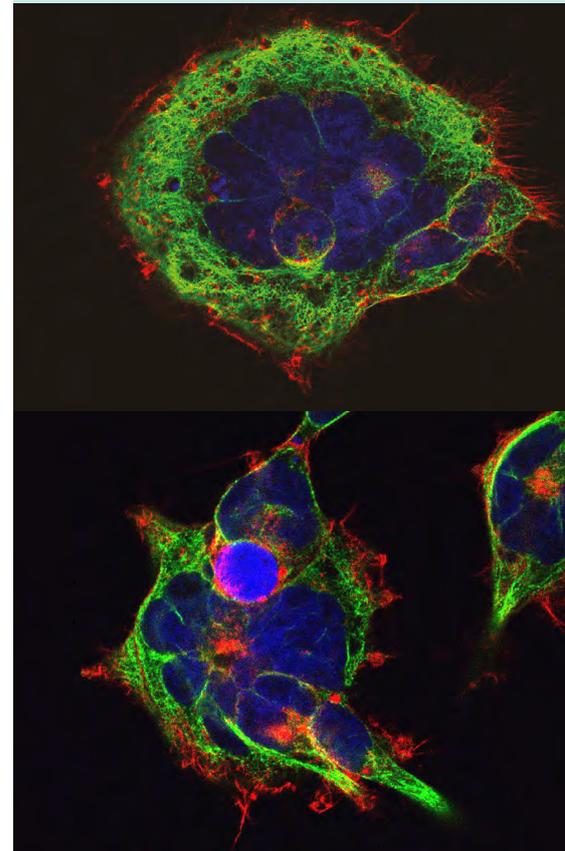
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