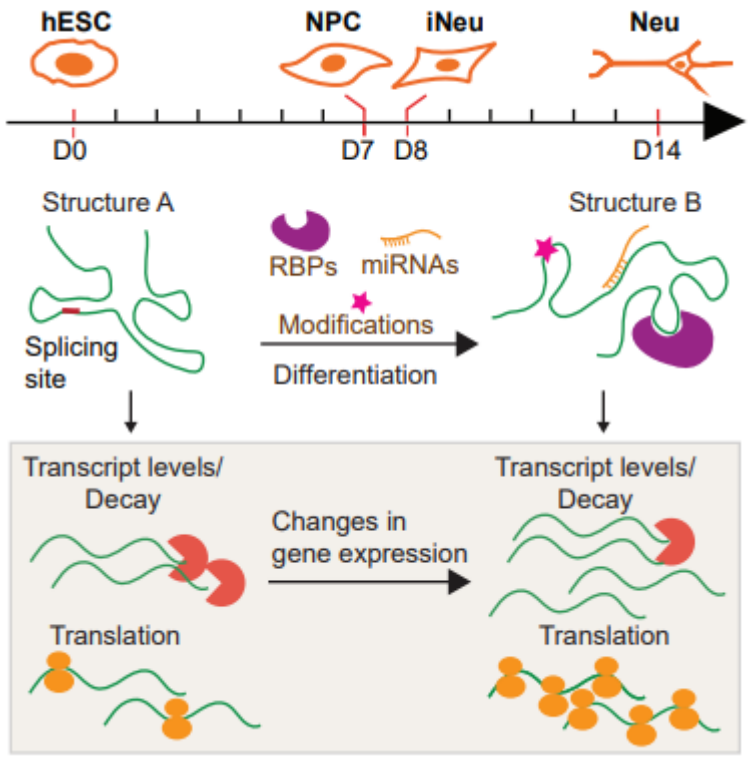
GENOME-WIDE RNA STRUCTURE CHANGES DURING HUMAN NEUROGENESIS MODULATE GENE REGULATORY NETWORKS



Schematic workflow of the study: the RNA shapes, together with their abundance levels, ability to be made into proteins, and speed of being degraded are mapped during neuronal differentiation. We discovered the complex interplay between RNA shapes and their binding partners in governing gene regulation

The human brain is incredibly complex. It controls the expression and regulation of its gene products carefully. One such gene product is a major class of macromolecule in the cell, known as ribonucleic acid (RNA). Similar to proteins, RNA can fold into different shapes to bind to other cellular partners in order to change the gene products in the cell. However, due to the complexity of the human brain, and the extensive amount of processing and regulation that happens in the brain, the shapes of RNA and how they change during brain development is still largely unknown.

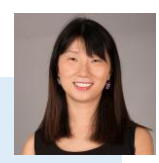
In this research, we developed novel high throughput sequencing technologies to study thousands of RNA shapes at a time during development. The goal was to determine what causes the shape changes and their impact.

We observed that many RNAs change their shapes during neuronal development. This is caused by different cellular partners, such as a class of proteins known as RNA-binding proteins (RBP: protein that can bind to RNAs). Once the RBP binds to an RNA, that RNA can change its shape to either bind with additional partners or to block their binding, hence, changing the fate of the RNA. This complexity deepens our understanding of RNA shape, and their interaction networks in the cell.

Key findings from the research:

- RNA shapes are highly pervasive and dynamic during neuronal differentiation.
- RNA structures in human stem cells are overall more accessible than differentiating neuronal cells, especially for three prime untranslated region (3’-UTR).
- Some of the RNA structures, which continuously changed genes during neurogenesis, are enriched in decay and translation.
- RBPs, microRNAs (miRNA), modifications and splicing are the main factors in influencing structural changes during the various differentiation stages.
- There is an extensive co-regulation between RBP, RNA structure, and RNA-miRNA binding during neuronal differentiation.

This research was published in *Molecular Cell* [insert link] on 15 October 2021.



“To understand how a car operates, we need to understand all of the components within it, and how they fit together and coordinate to enable it to move. RNA is one such important piece in the living cell. Understanding it will enable us to understand how a cell could get sick and how we could treat it.”

Dr Wan Yue, Group Leader of Laboratory of RNA Genomics and Structure, and Associate Director of Epigenetic and Epitranscriptomic Systems, GIS

“The team wanted to understand the extent to which RNA shapes play a role in gene regulation during human neurogenesis, what influences RNA shape changes during this developmental process, and what are the consequences of these shape changes. The findings from this research will help us determine RNA structure based biomarker, and drug target for neurological disease and cancers in the future.”

Prof Patrick Tan, Executive Director, GIS