UC San Diego
MOORES CANCER CENTER

2023 MCC Structural and Functional Genomics Pilot Project Award

Charting the RNA processing landscape in pediatric B-cell ALL using long-read sequencing

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Scientific Abstract:

This research seeks to explore RNA processing dysregulation in pediatric B-cell Acute Lymphoblastic Leukemia (ALL) with iAMP21, a high-risk subtype characterized by chromothripsis in chromosome 21, using long-read sequencing. We hypothesize that the oncogene SON, amplified and overexpressed in iAMP21, plays a critical role in downregulating ADAR2, a highly site-specific RNA editing enzyme. We propose to study how SON- ADAR2 interplay may confer a selective advantage to cancer cells by altering RNA processing, including alternative splicing, RNA editing, and circular RNA formation, thus affecting the transcriptome's composition and complexity. Our rationale stems from observation that SON overexpression in iAMP21 leads to disproportionate downregulation of RUNX1, a key factor in hematopoiesis often disrupted in leukemia, and ADAR2 compared to their copy number changes. We aim to experimentally confirm this interplay in human pre-B cell lines (NALM-6 and REH), focusing on SON's influence on ADAR2 expression and their joint impact on RNA processing. Our goals include confirming the SON-ADAR2 interplay, characterizing the impact of SON-upregulation on the mRNA-isoform landscape, and exploring the RNA-editing and circular-RNA landscape with ADAR2- downregulation. This will involve RNA-seq, ChIP-seq and long-read cDNA sequencing in SON-overexpressing cells. We will also validate our results in a pilot set of iAMP21 samples through long-read sequencing. We expect our research to modify our understanding the role of dysregulated SON and ADAR2 genes in pediatric hematological cancers. Ultimately, this study will provide significant insights and methodologies for future research in this field, with potential clinical implications for iAMP21 and similar pediatric cancers.

Lay Abstract:

Our study is focused on understanding a particular type of childhood blood cancer called B-cell cancer, specifically a high-risk form known as iAMP21. This form of leukemia involves shattering of chromosome 21 in B cells of the patients. We believe this shattering has functional consequences not only on DNA sequences but also on proper RNA processing of the cell. To get a better understanding of this condition, we propose to use high-throughput techniques coupled with state-of-the-art long-read sequencing, which will allow us to look closely at how the genetic information is processed in these cancer cells. We hypothesize that a gene called SON, which is overly active in iAMP21, plays a significant role in reducing the activity of another important gene, ADAR2. ADAR2 is usually implicated in preventing cancer development, so its decrease might be helping the leukemia cells to thrive. We believe that the interaction between these two genes, SON and ADAR2, changes the way genetic information is used in the cells, especially in how it affects the creation of different RNA molecules, a key step in the flow of genetic information. Our goal is to confirm this interaction in cell line models for this type of leukemia and repeat similar experiments using patient samples. By comparing cells with

and without these changes, we hope to better understand the complex interaction between these genes. This research could significantly improve our understanding of iAMP21 and potentially lead to new ways of managing and treating this challenging subtype of childhood leukemia.