NUS National University of Singapore | Department of Anatomy
Yong Loo Lin School of Medicine

NUHS National University Health System

ORAL PQE

ADARs regulate alternative splicing and backsplicing

Human transcriptome is greatly expanded by alternative splicing (AS) which produces multiple functional linear mRNAs and recently uncovered backsplicing which generates circular RNAs (circRNAs) from any given gene. The causal relationship between dysregulation of these two processes and tumorigenesis has been proved in many cancers. Adenosine deaminases acting on RNA, ADARs (ADAR1 and ADAR2)-mediated adenosine-to-Inosine (A-to-I) RNA editing also contributes to transcriptome diversity and has been found aberrant in some cancers. However, it remains unclear how these post-transcriptional processes interplay with the other during cancer progression. To this end, ADARs expression was modulated in an esophageal squamous carcinoma cell line EC109 by either overexpression using a lenti-viral system or shRNA-mediated silencing, followed by total RNA sequencing (RNA-seq) and circRNA sequencing (circRNA-seq) analysis.

Project 1: As detected by RNA-seq, approximately a hundred of high-confidence splicing events affected by ADARs were identified. Among these events, exon 3 inclusion of RELL2 (Receptor Expressed in Lymphoid Tissues like 2) gene was found repressed by ADAR2, independent of RNA editing. A novel mechanism through which ADAR2 functions as a common splicing factor by binding to dsRNA formed between GA-rich sequences and Py-tract and precluding access of U2AF65 to 3'splicing site for exon recognition was unraveled. Furthermore, I found that exon 3 skipping of RELL2 produces a nonsense-mediated decay (NMD)-sensitive isoform which manipulated transcript balance of RELL2, thus contributing to tumorigenesis.

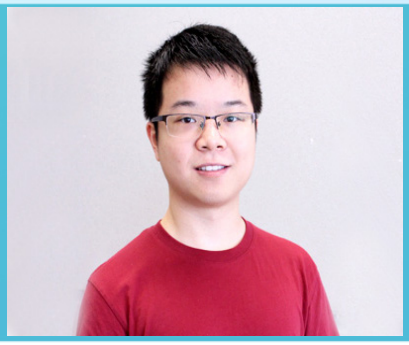
Project 2: The circRNA-seq analysis showed hundreds of circRNAs were affected by ADARs and for the first time uncovered that ADARs regulate circRNA biogenesis bi-directionally. Editing sites have no significant overlap with circRNA flanking introns, suggesting circRNAs could be regulated by ADARs through editing-dependent and independent mechanisms, which can also be experimentally validated. These findings provide novel insights into the role of ADARs in regulating circRNAs. Future work will be focusing on the underlying mechanisms of ADARs-regulated circRNA biogenesis and biological importance of these affected circRNAs in cancer.

In sum, successful completion of these two projects will provide a profound understanding on the interplay and crosstalk between different post-transcriptional RNA processing and their contributions to cancer development.

Wednesday
19 June 2019
3.30pm – 5.00pm
Seminar Room, MD10
Level 2, Anatomy Museum

Shen Hao Qing

Graduate Student
Anatomy, NUS Medicine



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