Base-resolution quantitative sequencing methods for functional investigation of RNA modifications in gene expression regulation

Dr. Li-Sheng ZHANG

Assistant Professor,

Division of Life Science and Department of Chemistry,

Hong Kong University of Science and Technology

Abstract

The reversible N^6-methyladenosine (m^6A) methylation regulates messenger RNA (mRNA) fate and metabolism in various biological processes. Functional characterization of other mRNA modifications, such as pseudouridine (Ψ), 2'-*O*-methylation (Nm), 5-methylcytidine (m^5C), and internal N^7-methylguanosine (m^7G), has been hampered by the lack of the sensitive and quantitative methods that can map these RNA modifications transcriptome-wide. In this talk, based on chemical approaches and enzyme engineering, I will introduce the quantitative sequencing tools to uncover multiple mRNA modifications at base resolution, and to monitor their modification fraction change through misincorporation and deletion signatures, including BID-seq, Nm-Mut-seq, m^7G-quant-seq, etc. These methods accurately assigned the specific 'writer' protein for the modified sites and facilitated the discovery of 'reader' proteins that reveal the functional roles of these RNA modifications. Besides the RNA modifications on steady-state RNA, I will introduce DAMM-seq to site-specifically detect and quantify multiple RNA methylations simultaneously within mitochondrial nascent RNA, which demonstrated ALKBH7-mediated reversible RNA methylation to regulate the processing and structural dynamics of polycistronic mitochondrial RNAs. These new technologies set the stage to investigate the roles and mechanisms of multiple RNA modifications in gene expression regulation and diverse biological processes.

Biography

Professor Li-Sheng ZHANG is an Assistant Professor in Department of Life Sciences and in Department of Chemistry at HKUST. In 2009, He entered Peking University, majoring in Materials Chemistry, and won the highest academic award for undergraduate graduates. After the undergraduate training, in 2013, Li-Sheng entered the Department of Chemistry at The University of Chicago to start his Ph.D. training in Prof. Chuan He's Lab. Li-Sheng Zhang earned his Ph.D. in 2019, with the HHMI International Student Research Fellowship award. During Ph.D. training, Li-Sheng discovered ALKBH7-mediated reversible RNA methylation in mitochondrial RNA and demonstrated mRNA internal N^7-methylguanosines *via* base-resolution sequencing. Li-Sheng

continued working as a postdoctoral scholar in Professor Chuan He's lab upon the completion of his Ph.D., where he developed multiple base-resolution quantitative sequencing methods to investigate diverse RNA modifications in mammals, including BID-seq for pseudouridine, Nm-Mut-seq for 2′-*O*-methylation (Nm), DAMM-seq for $m^1A/m^3C/m^1G/m^2{}_2G$, m^7G-seq/m^7G-quant-seq for internal m^7G, etc. Li-Sheng has published 30 academic articles in high-impact journals, including 10 first- or co-first-authored papers in *Nature Biotechnology*, *Nature Cell Biology*, *Nature Protocols*, *Cell Research*, *Molecular Cell*, *PNAS*, *Angewandte Chemie*, *ACS Chemical Biology*, *Organic Letters*, etc. In April 2023, Li-Sheng joined HKUST and started his independent research in chemical biology, epigenetics, immunology, cancer biology, and computational biology.