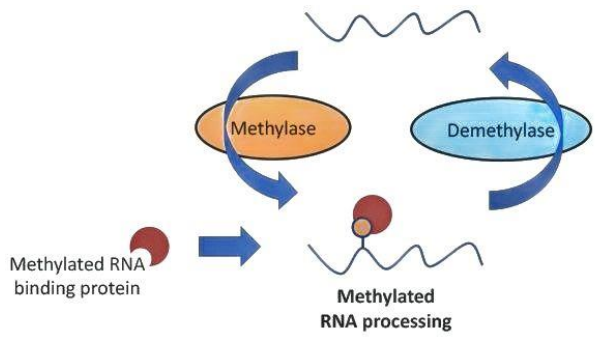
NEW TECHNOLOGY REDEFINES UNDERSTANDING OF HOW RNA IS REGULATED

Synopsis

- *Novel quantitative and precise method to sequence RNA methylation*
- *RNA demethylases do not reverse functional RNA methylation, but instead suppress disruptive RNA methylation*
- *Importance of quantitative precision in deciphering correct functions of epitranscriptomic factors*



Previous model for functional RNA methylation reversal

Focusing on human mRNA modifications N6-methyladenosine (m6A), Dr Sho Goh and his team members, Ms Casslynn Koh and Mr Goh Yeek Teck, developed a quick and user-friendly method to sequence RNA methylation precisely and quantitatively.

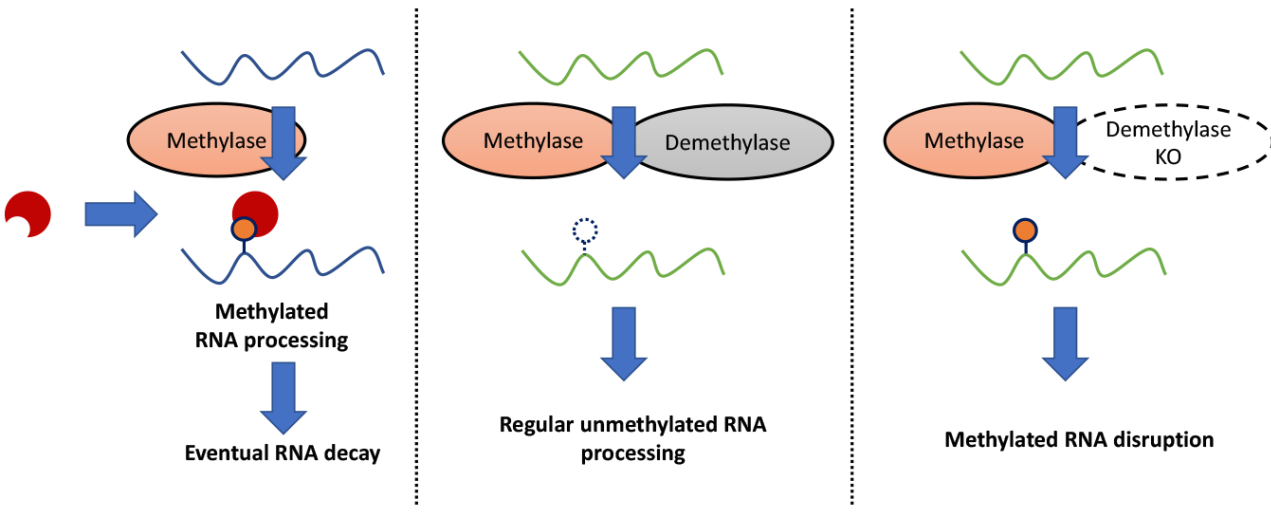
m6A plays a central role in regulating almost all forms of RNA metabolism. It gained prominence after next-generation sequencing mapped it in the human transcriptome.

However, the most common m6A-sequencing method suffers from poor resolution (~150nt). Other single-base-resolution m6A-sequencing techniques developed are also time-consuming, cumbersome, hazardous, and are not quantitative in nature.

To solve this problem, the team developed m6A-crosslinking-exonuclease-sequencing (m6ACE-seq), a quick and user-friendly technique that maps quantitative methylome changes at single-base-resolution. m6ACE-seq enabled them to generate the first human atlas of quantitative single-base-resolution RNA methylome, revealing the importance of individual m6A factors on shaping the human methylome.

For instance, the previous discovery of m6A eraser enzymes suggested that m6A is a reversible RNA modification. Although there are multiple recent reports with conflicting views on this model, no study has yet validated that m6A changes at specific sites in response to eraser depletion.

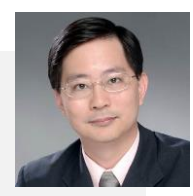
The team's research on epitranscriptomics addresses this ongoing debate. By comparing the various methylomes, in which individual m6A writers and erasers were depleted, they were able to demonstrate that m6A eraser enzymes do not reverse functional RNA methylation. Instead, they are required to suppress disruptive RNA methylation and prevent such methylation from accumulating to damaging levels. Failure to do so subjects certain RNAs to unwanted regulatory pathways, which can have broad implications on cellular processes. For instance, erasers have recently been shown to regulate various human cancers. The findings in this study will allow other scientists to re-examine the actual mechanisms that govern how eraser misregulation contributes to cancer progression.



New model for disruptive RNA methylation suppression. RNAs meant to be methylated (blue) are only acted on by methylases/writers. RNAs meant to remain unmethylated (green) are acted on by both methyltransferases and demethylases/eraser, resulting in no net accumulation of RNA methylation.

"While '*gene*' and '***gene***' both spell the same word, formatting the latter word changes the emphasis we place on it. This is similar to the study of epitranscriptomics, where the underlying gene sequence remains the same, but chemical RNA modifications enforce an entirely new layer of regulation on molecular, cellular, and developmental biology. "

Dr Sho GOH
GIS Fellow (Human Genetics)
Genome Institute of Singapore



"Epitranscriptomics is an exciting new research area, and this study improves our understanding of how RNA biology regulates multiple forms of cellular function. Future research will explore how disrupting such RNA regulation contributes to disease severity."

Prof Patrick TAN
Executive Director
Genome Institute of Singapore