223rd WPI-IIIS Seminar

Metabolic regulation of modified RNA in physiology and pathology

More than 150 types of RNA modifications have been identified in RNA species from all kingdoms of life. During RNA catabolism, most modified nucleosides are resistant to degradation and are released into the extracellular space. Previously, we discovered that N6-methyladenosine (m6A), one of the most abundant modifications in mRNA, selectively activates G protein-coupled receptors as an endogenous ligand and triggers pathophysiological immune responses. However, m6A signaling is not fully understood. Recently, we found a complex and evolutionarily conserved mechanism to downregulate m6A signaling. This signaling consists of sequential metabolic processing of m6A by two enzymes, resulting in the conversion of m6A to an unmodified nucleoside. Using biochemical, structural, cell biological and *in vivo* approaches, we show that dysregulation of either component leads to massive accumulation of m6A, which impairs cellular energy metabolism. Importantly, we found a direct link between the defective metabolic processing of m6A and human disease. Taken together, our study demonstrates that m6A derived from RNA catabolism must be tightly regulated to alleviate its intrinsic toxicity.

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Date: **Tuesday, March 25, 2025**
Time: **11:30 – 12:30**
Venue: **1F Auditorium, IIIS Building**

✻On-site participation only

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