Molecules and Cells

Journal Club

Discovery of a Novel RNA Suggests That Its Cellular Role Is More Complex than Just a Simple Messenger

A new research discovered that RNA could be glycosylated and displayed on the cell surface, suggesting the potential role of RNAs in inter-cellular communication.

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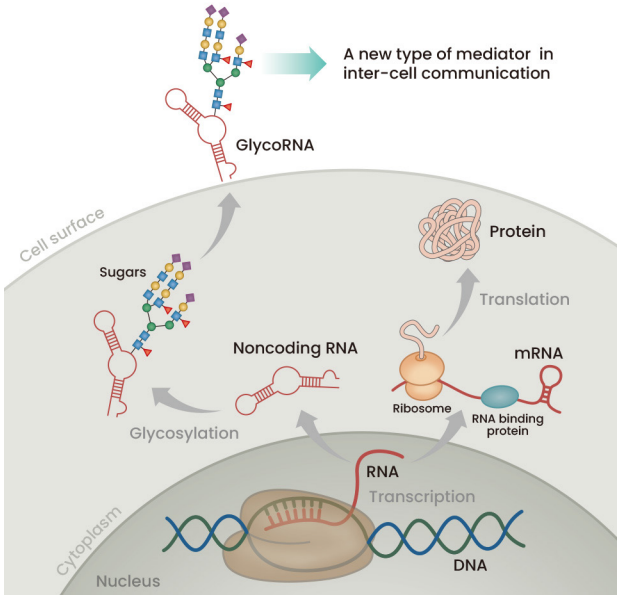

The discovery of glycoRNA, a new type of post-transcriptionally modified RNA, opens up new research avenues for RNA function for cell-to-cell communication.

Ribonucleic acid (RNA) is an important biological macromolecule that is central to all known life. In a cell, RNA is involved in numerous biological pathways, including transferring the messenger instructions from DNA to proteins, the synthesis of proteins, and the catalysis of biological pathways. More than 170 post-transcriptional modifications (PTMs) of RNA have been identified (Boccaletto et al., 2018; Nachtergaele and He, 2017) to date, and these PTMs have been suggested to confer functional complexity to RNA. Accordingly, significant advances have been made over the past few years to understand the complexity of RNA PTMs and their pathophysiological effect.

RNA modified with sialoglycans (glycoRNAs), a new type of modified RNA (Flynn et al., 2021), was identified in a recent research. The investigators showed that these glycoRNAs are conserved RNAs bearing glycans and found in multiple cell types and mammalian species. This finding is surprising because, unlike lipids and proteins, there has been no evidence so far of a direct linkage between RNA and glycans in nature. However, investigators challenged this view by demonstrating glycosylated RNAs in cells using metabolic labeling and biorthogonal chemistry *in vitro* and *in vivo*. In this strategy, they metabolically labeled cells and animals with reporter sugars incorporated into cellular glycans. Using a biotin probe, they further found that glycoRNAs are enriched in sialic acid

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and fucose; such glycosylation was exclusively observed in small noncoding RNAs but not large RNAs such as mRNAs. To identify the potential biological significance of glycoRNA transcripts, the team conducted RNA sequencing of enriched glycoRNAs and revealed that identified glycoRNAs have many well-established and critical cellular roles, including immunogenic antigen formation and cytosolic RNP surveillance. Furthermore, the investigators showed that a cell uses the canonical N-glycan biosynthetic machinery, which is also used for glycosylation of lipids and proteins to glycosylate these RNAs rather than opting for a distinct regulatory mechanism. Finally, using various experimental approaches, including chemical, genetic, mass spectrometry, and proximity-based labeling analysis, the team revealed that the vast majority of glycoRNAs are displayed on the cell surface enabling interactions with extracellular antibodies targeting RNAs and members of the sialic acid binding-immunoglobulin lectin-type receptor family that are well-known glycan-binding receptors. Such discoveries indicate that glycoRNA would have a different cellular distribution than other RNAs found mainly in the nucleus and cytoplasm. These discoveries also highlight the potential significance of glycoRNAs as cellular sensors that could inform a cell of the changes in the extracellular environment by interacting with extracellular cues such as antibodies and receptors expressed in other cells.

The implication of this study is immense, particularly in the research area of RNA biology and glycosylation disorder. While the framework in which glycobiology is understood excludes RNA as a substrate for N-glycosylation, the discovery of glycoRNAs suggests that the current view is incomplete and indicates a new axis for RNA glycobiology. Moreover, glycoRNAs on the cell surface point to the potential roles of RNAs in inter-cellular interactions, which provide new insight into the underlying mechanisms involved in RNA-related pathophysiology. Additionally, it has been well appreciated that dysregulated glycosylation process promotes defects in various cellular functions such as metabolism, inflammatory response, apoptosis, and immune escape. It has been a popular belief for several years that cellular defects caused by aberrant glycosylation are attributable to abnormal glycosylation on proteins or lipids; however, this study provides an important clue that glycoRNAs are alternative players that contribute to the pathology of dysregulated glycosylation in various human diseases.

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CONFLICT OF INTEREST

The author has no potential conflicts of interest to disclose.

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