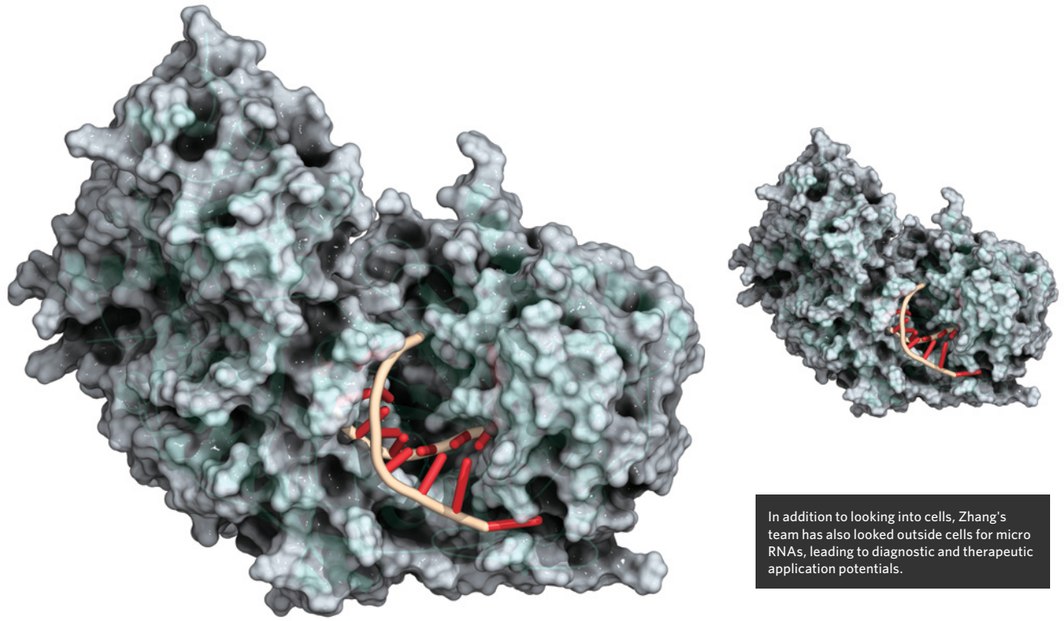

In addition to looking into cells, Zhang's team has also looked outside cells for micro RNAs, leading to diagnostic and therapeutic application potentials.

LOOKING OUTSIDE THE CELL FOR POTENTIAL

Since finding that microRNA is also present outside cells, a team from NANJING UNIVERSITY IN CHINA has made key contributions to the field of extracellular RNA, and has opened a path to new diagnostic and therapeutic potential.

Since microRNA (miRNA) was first discovered, most researchers have believed it to be an intracellular molecule like other forms of RNA.But Chenyu Zhang, dean of the Nanjing University's School of Life Sciences, thought otherwise. He leads a group that has been studying miRNA for more than 10 years, and has found a variety of extracellular functions for this nucleic acid (exRNA). The work could unlock persistent mysteries in intercellular and interspecies communication and could lead to new diagnostics and therapeutics. Here, Zhang discusses their exploration of exRNAs, and the importance of their key findings.

What led you to study extracellular miRNA?
I've been working in medical biology for years, and my research serves to translate fundamental life science discoveries into biomedical applications. I've been studying miRNA, which is a small non-coding form of RNA, since the early 2000s, and I run a lab researching miRNA expression profiles and their relevant functions in cancer tissues.

In a lab meeting in 2007, on a whim I thought we should try testing miRNA in blood. We performed RT-PCR analysis, and detected the expression of miRNA in both serum and plasma. This was an exciting discovery. We repeated the experiment in animal serum, and found miRNA presence as well. Since then, exRNA has been a focus of my research, as I'm eager to explore its biological functions and possible applications.

Why is the discovery of serum miRNA important?
Traditionally, RNA was thought to be unstable in extracellular environment, where ribonucleases will degrade RNA. So when I had the idea to test the presence of exRNA, many thought it was crazy. But we challenged the conventional thought, showing that RNAs are not just confined intracellularly. Later, other studies also provided evidence for miRNA circulation in bodily fluids like saliva, urine, and breast milk, in a stable, cell-free form. This is a paradigm shift and promoted our study on trans-kingdom exchange of these biomolecules.

The detection of miRNA in serum also has clinical implications. Using deep sequencing, we characterized miRNA profiles, and identified unique expression patterns of serum miRNAs for several cancers, and diabetes. This demonstrates the potential of serum miRNAs as biomarkers for the detection of cancer and other diseases, opening the door to new strategies for disease diagnosis and treatment.

How do you explain the stable extracellular existence of miRNA?
We believe the key mechanism that protects miRNA from degradation in extracellular environment lies in the tiny lipid particles known as extracellular vesicles (EVs), which carry RNAs. These nanoscale particles, secreted by cells, have a membrane structure, offering a barrier to shield miRNA from ubiquitous RNA-degrading enzymes. It's also possible that EVs drive the formation of protein-miRNA complexes, enabling the stable existence.

What leads to the release of miRNAs outside cells also deserves exploration. We thought that they may be secreted in EVs in a selective process; released from donor cells in RNA-binding proteins; or possibly leaked from broken or damaged cells caused by tissue injury or cell death. So far, we've only explained the existence of some extracellular miRNAs; there may be other mechanisms.

What are the main areas of focus for your group?
What intrigues me now are the biological functions of exRNAs and relevant mechanisms, such as their roles in signal transfer between cells; how pre-miRNA becomes mature; and how it is absorbed. We are particularly interested in examining the transfer of miRNA between remotely related, complex organisms. Using deep sequencing, we have identified plant-derived miRNAs when studying exRNAs in human blood. Some of these exogenous miRNAs have a similar level of serum concentration as the endogenous ones, suggesting that they are intact and unlikely to have been leaked from the digestive system.

Our studies suggest that miRNAs may facilitate the cross-talk between species by regulating target genes and influencing physiological conditions. Studying cross-kingdom regulation and miRNA transfer may improve our understanding of evolution, shedding new light on the interactions and inter-dependence between species.

How do you address the unanswered questions regarding dietary RNAs?
This is a young field, and questions have been raised by colleagues in other groups.When we found the plant miRNAs in human blood, an immediate question was how these exRNAs withstand stomach acid and digestive enzymes. Our recent discovery of a special protein, SIDT1, in mammal stomachs may help answer this question that has been puzzling scientists for almost a decade. Expressed on gastric pit cells, SIDT1 is found to play a key role in the absorption of dietary miRNAs, a process which requires a low-pH environment, making the stomach the primary site for miRNA absorption. This suggests a new function of the stomach. We are also exploring other uptake mechanisms, and why an acidic environment is needed.

Chenyu Zhang, Dean of the School of Life Sciences, Nanjing University.

What are some potential applications of your findings?
Our findings about dietary RNAs and cross-kingdom miRNA transfer have important implications for developing relevant therapeutics and drug delivery approaches. For instance, we found a miRNA in honeysuckle, which can directly target some influenza viruses and could provide a new strategy for treating virus infections. It also suggests that miRNA might be the active ingredient for many herbal medicines. Moreover, we showed that oral administration of the plant miRNA can retard liver fibrosis, and the finding about SIDT1 sheds light on developing miRNA therapeutics by oral delivery.

Based on our earlier findings about serum miRNAs, we've also developed miRNA-based diagnostics, including a test kit for early detection of pancreatic cancer. I hope to see wider applications of our research results.

What is your plan for future research?
I think we've already built up the pillars for exRNA research. Next, I will focus on finding organelles that regulate functional RNAs and studying the various mechanisms underlying exRNA functions. On the application front, we want to discover more miRNAs that can be used in gene therapy, along with methods to deliver the necessary RNA to the target organs, as well as miRNA-based diagnostic biomarkers. We also want to explore use of miRNA in agriculture, including developing bio-based pesticides, and genetically modifying food plants to make them less vulnerable to diseases. After all, I hope my research will make an impact, both on the scientific community, and on society. ■

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