https://doi.org/10.1038/s41557-025-02029-x

Sensing RNA

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Analysing the sequence, concentration and sub-cellular location of RNA can provide insight into physiological processes and enable disease diagnosis. This issue draws together several articles describing chemical advances that can be applied to detect RNA.

RNA is ubiquitous in life — and studying the function and behaviour of RNA are fundamental aspects of modern biochemical research. Cells hold their genetic information in DNA, transcribe it into RNA and then translate it into protein, thus making RNA molecules useful analytes for diagnosing diseases that involve increased production of specific proteins. The increased concentration of the corresponding RNA can be used as a diagnostic biomarker. Methods to analyse the localization of RNA to specific organelles also provide insight into the normal functioning of the cell and its dysregulation in diseases. In this issue, we highlight several articles that showcase the detection of RNA sequence, concentration and localization — including two examples using RNA itself as a tool to sense RNA analytes.

In an Article in this issue, a team led by William Greenleaf and Rhiju Das describe the design of single-molecule RNA logic gates, as well as RNA sensors capable of detecting the concentration of input RNAs. Upon binding the input RNA(s), the RNA sensor is stabilized in a conformation that enables it to bind to an output molecule (either a fluorescent protein or an RNA conjugated to a fluorescent dye) that generates a fluorescent signal. The applications they showcase culminate in an impressive proof-of-concept demonstration of a sensor that calculates the ratio of three RNA sequences that are indicative of active tuberculosis infection.

The way in which these sensors were designed was somewhat out of the ordinary: sequences suggested by participants of Eterna — an online game that challenges players to solve puzzles based on RNA folding — were experimentally tested, and results were fed back to the Eterna community to inform their future designs. The researchers also developed an algorithm, named Nucleologic, that incorporates strategies developed by Eterna players to automate the design of RNA sensors. This Article is complemented by a News & Views piece written by Angela Yu, Gabriel Fonseca and Jazmine Cardenas, who discuss the strengths and limitations of crowdsourcing and computational automation in sensor design.

The challenge faced by Greenleaf, Das and co-workers was in the complexity of designing a sensor capable of calculating the ratio of three inputs. But another issue faced by those in the field is how to detect small changes in RNA, which are important because small mutations in a cell's genetic material — even variations of a single nucleotide — can have substantial effects on its function. In another Article in this issue, a team led by Fan Hong and Alexander Green describe the development of an RNA switch for identifying single nucleotide mutations that they name FARSIGHT. Their elegant system, based on strand exchange reactions between the input and sensor RNAs, leads to folding of the RNA sensor into a conformation that can bind a fluorogenic molecule (resulting in a fluorescence signal) only in the presence of the correct target sequence. The specificity of this system means that if there is a single-base mutation in the target sequence, the process leading to fluorescence isn't activated.

The News & Views piece from Xianglin Zhu and Ruijie Deng that accompanies this Article nicely sets out how this strategy could be further developed to widen potential applications. For example, they note that multiple experiments are currently required to optimize probe–target hybridization and aptamer formation, and suggest that probe design could be facilitated using AI-assisted prediction models. Zhu and Deng also set out how FARSIGHT could be adapted to enable real-time tracking of RNA within living cells.

The third highlighted Article — from a team led by Peng Chen, Jun Liu and Xinyuan Fan — does indeed report the development of a strategy for profiling mitochondrial RNA in cells. The use of a small-molecule chemical probe for RNA detection, rather than an RNA-based system, distinguishes this paper from the other two in this issue. The photocatalytic proximity labelling probe described by Chen, Liu, Fan and co-workers is developed from a strategy they previously reported for labelling mitochondrial proteins (*Nat. Commun.* **15**, 2712; 2024). While other methods already exist for subcellular-resolved RNA analysis, the strategy set out by Chen, Liu, Fan and colleagues avoids limitations such as low resolution, contamination, and dependence on genetic manipulation inherent to existing techniques. Moreover, this strategy excitingly enables simultaneous profiling of mitochondrial RNA and mitochondrial proteins.

Providing an expert opinion in an accompanying Research Briefing, Ivan Corrêa highlights the applicability of this method to immune cells (which are usually challenging to probe), resulting in new insight into the role of mitochondrial RNA regulation in T-cell maturation. Yunpeng Bi (the first author of the Article) and Xinyuan Fan also use this piece to set out some areas for future development of this technology, including modulating photocatalytic kinetics to improve temporal resolution; expanding this strategy to target subcellular locations other than the mitochondria; and modifying the design of the probe to enable activation by near-infrared light, which can better penetrate living tissues, potentially leading to applications in organisms.

The research collected and highlighted in this issue illustrates the possibilities that RNA provides — both as a sensing target and as a sensor — as well as the variety of design strategies and approaches that it can be combined with. The Articles all represent fantastic examples of how molecular designs and chemical strategies can be the key to fully unleashing RNA's diagnostic and functional potential.

Published online: 2 December 2025