SENSORS AND PROBES

Pinpointing RNA mutations

Riboregulator-based sensors are designed to differentiate single-nucleotide RNA variants in live cells.

Single-nucleotide variations within RNA molecules have critical roles in cell biology and disease progression. Yet, point mutations remain a challenge to identify, particularly in live cells and cell-free systems at physiological temperatures. The Green and Yan groups at Arizona State University have described riboregulator-based sensors, termed single-nucleotide-specific programmable riboregulators (SNIPRs), to detect transcript point variations in live prokaryotic cells and cell-free reactions.

Green comments that that “they [riboregulators] are genetically encoded, and they can be readily programmed to detect different target RNAs.” SNIPRs are engineered to retain a docking site that binds the target RNA and forms a target–SNIPR duplex. When target–SNIPR

hybridization occurs between a pair of perfectly matched sequences, the SNIPR activates the translation of the output protein. In contrast, when a mutant target is present, the free-energy penalty induced by the resulting sequence mismatch prevents SNIPR activation, thus stopping expression of the output protein.

Beyond detection of sequence variants, SNIPRs also allow for detection of chemically modified bases that can induce conformational changes in SNIPRs. Moreover, SNIPRs are compatible with not only live cells but also paper-based colorimetric assays that can be used for the identification of virus strains. To make SNIPRs easy to use, Green and Yan have also developed an algorithm for designing SNIPR sequences.

The researchers hope that SNIPRs will enable detection of drug-resistance mutations for diseases such as malaria, tuberculosis and HIV, and improve understanding of the evolution of drug resistance. Green also remarks that “SNIPRs have been engineered to work with the translational machinery of prokaryotes, so they cannot currently be used in eukaryotic cells or eukaryotic cell-free systems, but we do hope to develop such tools in the future.”

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 Hong, F. et al. Precise and programmable detection of mutations using ultraspecific riboregulators. *Cell* **180**, 1018–1032 (2020).

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