Biomarker discovery

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Scouring for essential non-coding RNAs

RNA-targeting CRISPR screens reveal hundreds of functional long non-coding RNAs that are crucial for cell survival and implicated in cancer progression.

The human genome encodes thousands of long RNAs that are not translated into protein. Some of these long non-coding RNAs (lncRNAs) are known to regulate gene expression or to form intracellular structures, but functional roles have been identified for less than 1% of lncRNAs. By using CRISPR screens, Neville Sanjana and colleagues have now generated maps of the landscape of essential lncRNAs across multiple human cell types.

As they report in *Cell*, the researchers deployed RNA-targeting CRISPR–Cas13 screens to systematically disrupt more than 6,000 lncRNAs across 5 different human cell lines. This strategy overcomes central limitations of previous DNA-targeting methods, in particular the inadvertent modification of nearby genes or regulatory elements. Through these screens, Sanjana and colleagues identified 778 lncRNAs that are essential for cell survival, with 61% of them being essential in only one cell line and 39% being broadly essential across multiple cell types. Notably, most essential lncRNAs functioned independently of their nearest protein-coding genes.

Single-cell analyses revealed that the disruption of essential lncRNAs impaired cell-cycle progression and triggered cell death. The researchers also found that the essential lncRNAs showed dynamic expression patterns during development, with many being highly expressed in early developmental stages. Moreover, by analysing approximately 9,000 tumour samples across 29 cancer types, they discovered that the expression of essential lncRNAs was frequently dysregulated in the cancer tissues; essential lncRNAs could therefore serve as tumour biomarkers.

A comprehensive map of functional lncRNAs opens new therapeutic possibilities, particularly in the treatment of cancer, where essential lncRNAs could be targeted using antisense oligonucleotides. However, in their study, the researchers focused only on cell-survival phenotypes and on lncRNAs expressed in the chosen cell lines. Future screens across more cell types and phenotypes are likely to reveal additional functional lncRNAs and thus further expand our understanding of the non-coding genome.

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