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Beyond fantasy, the cryptic dark transcriptome represents an unexplored source of TUMOR SPECIFIC ANTIGENS

Long non-coding RNAs (lncRNAs) are involved in regulating various cellular processes. While initially thought to lack coding potential, recent studies have shown that some lncRNAs can be translated into lncRNA-derived peptides. Despite the growing interest in these peptides, their potential functions and the mechanisms governing their synthesis remain largely unexplored. Here, we investigated the functional impact of non-canonical translation events on cytoplasmic lncRNAs in human cells.

We have recently shown that Xrn1-sensitive cytoplasmic lncRNAs (XUTs) in yeast are translated even in NMD-competent cells, suggesting that despite the cryptic nature of the transcripts, their translation result in detectable products. In human cells, we identified DIS3, and not Xrn1, as the main exonuclease restricting accumulation of lncRNAs in the cytoplasm and revealed thousands of DIS3-sensitive lncRNAs (DISTs). We show that DISTs also display active translation, producing peptides predicted to be high-affinity antigens in multiple myeloma patients carrying DIS3 mutations. Finally, immunogenic tests revealed that the resulting neoAntigens can be recognized by T cell collected from blood, opening new strategies for the next generation of immunotherapies. Overall, our work highlights the central role of translation in the metabolism of cytoplasmic lncRNAs, with different potential outcomes. While the resulting peptides could constitute raw material exposed to the natural selection in yeast, we propose that some could be part of the cell-to-cell communication through tumor-specific antigen presentation in human cells.

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