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Non-coding RNAs in Cancer: From Computational Discovery to Functional Validation and Clinical Translation

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To the Editor,

The 5 studies recently published in your journal (1-5) collectively address a critical and rapidly evolving area of cancer research: the identification of non-coding RNAs as diagnostic and prognostic biomarkers. Synthesizing their findings reveals several important themes and future directions that merit attention.

First, the integration of deep learning with high-dimensional transcriptomic data is reshaping biomarker discovery. Kousehlou et al. (1) demonstrated how an autoencoder can reduce 8,900 long non-coding RNAs to 1,000 features, ultimately identifying 4 hub lncRNAs (Lnc-FAM84A-1, LINC01866, Lnc-KCNE4 - 2, and Lnc-NUDT12 - 4) that stratify patients with esophageal squamous cell carcinoma into distinct survival groups. This approach underscores a broader trend: as genomic datasets grow in size and complexity, computational methods that extract meaningful patterns without prior feature selection will become indispensable. Future studies should focus on validating these lncRNA signatures in larger, multicenter cohorts and exploring their functional mechanisms.

Second, the context-dependent nature of ncRNA function presents a recurring challenge. Asadi et al. (2) found that circPVT1 was significantly upregulated in gastric cancer tissues and correlated with higher tumor grades, whereas miR-203a-3p showed no significant difference in expression between tumor and normal tissues. This finding contrasts with the conventional competing endogenous RNA model and suggests that circPVT1 may exert its oncogenic effects through alternative microRNA (miRNA) targets or independent mechanisms. Similarly, Rostamnejad et al. (3) observed that FOXA1, NEAT1, and RMRP were all upregulated in breast cancer, but no promoter mutations were detected, implying that epigenetic or posttranscriptional regulation drives their dysregulation. These findings highlight the need for functional validation, such as CRISPR-Cas9 knockout or overexpression assays, to move beyond correlative observations.

Third, the interplay between ncRNAs and key signaling pathways is emerging as a central theme. Mirzaei-Nasab et al. (4) predicted and partially validated interactions between lnc-LRR1 - 1.2 and MOB1A, as well as between hsa_circ_0001380 and SMARCA2, in hepatocellular carcinoma. These interactions point to a complex regulatory network involving the Hippo pathway, which is critical for cell growth and proliferation. In lung cancer, Yari et al. (5) demonstrated that miR-128, miR-335 - 5p, and miR-1254 were downregulated, whereas VEGF and K-RAS were upregulated, suggesting that these miRNAs may modulate angiogenesis and proliferation through these pathways. Together, these studies support a pathway-focused approach to ncRNA research, shifting the focus from individual molecules to the networks they regulate.

Fourth, the translational potential of ncRNAs as noninvasive biomarkers is increasingly evident. Yari et al. (5) detected differential expression of miRNAs and messenger RNAs (mRNAs) in both peripheral blood and tissue samples from patients with non-small cell lung cancer, supporting the feasibility of liquid biopsy-based diagnostics. Similarly, Asadi et al. (2) highlighted circPVT1 as a promising biomarker, with an area under the curve of 0.84 for distinguishing gastric cancer from normal tissue. However, standardized detection methods, large-scale validation, and integration with existing diagnostic

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workflows are essential for these biomarkers to achieve clinical utility.

Finally, these studies reveal several gaps and future directions. First, most reported findings are based on relatively small sample sizes (eg, 25 - 60 patients), limiting their generalizability. Second, the functional roles of the identified ncRNAs remain largely unexplored; mechanistic studies are needed to determine how they influence cancer progression. Third, the interplay among different classes of ncRNAs, including lncRNAs, circular RNAs, and miRNAs, and their target genes requires systematic investigation using multi-omics approaches. Fourth, the development of ncRNA-based therapeutics, such as antisense oligonucleotides or miRNA mimics, remains in its infancy and warrants dedicated preclinical research.

In conclusion, the 5 studies (1-5) collectively advance our understanding of ncRNAs in cancer biology while revealing important gaps. Future research must prioritize functional validation, larger cohort studies, and the development of standardized clinical assays. Addressing these challenges is essential to fully realize the potential of ncRNAs as diagnostic, prognostic, and therapeutic tools.

Footnotes

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