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Perspective

Non-coding RNAs in Cancer: Biomarkers and Therapeutic Targets

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DESCRIPTION

For decades, the central dogma of molecular biology emphasized the role of protein-coding genes in disease, including cancer. However, with the rise of genome-wide sequencing technologies, researchers have discovered that less than 2% of the human genome encodes proteins the rest, once dismissed as "junk DNA," is now known to produce a vast array of non-coding RNAs. These RNA molecules don't translate into proteins, but they exert powerful regulatory functions over gene expression, chromatin architecture, and cellular signaling. Increasing evidence reveals that non-coding RNAs are not only deeply involved in cancer development and progression, but also represent a new generation of diagnostic biomarkers and therapeutic targets.

Non-Coding RNAs (ncRNAs) encompass various types, but in cancer biology, the most studied classes are microRNAs, long non-coding RNAs, and circular RNAs.

MicroRNAs are short, 22 nucleotide-long RNAs that post-transcriptionally regulate gene expression by binding to the 3' untranslated region of target mRNAs, leading to degradation or translational repression. In cancer, miRNAs can act as tumor suppressors or oncogenes depending on their targets.

For instance, miR-21, one of the most frequently upregulated miRNAs in cancers such as breast, lung, and colorectal cancer, targets tumor suppressor genes like *PTEN* and *PDCD4*, thereby promoting cell proliferation and inhibiting apoptosis. Conversely, let-7 family miRNAs, which suppress oncogenes, are often downregulated in aggressive tumors.

LncRNAs are transcripts longer than 200 nucleotides that regulate gene expression at multiple levels epigenetically, transcriptionally, and post-transcriptionally. They act as scaffolds, guides, decoys, or enhancers in regulatory complexes.

One notable example is *HOTAIR*, which reprograms chromatin state by recruiting polycomb repressive complexes to specific genomic loci.

Circular RNAs are covalently closed-loop RNAs are more stable than linear RNAs and can act as miRNA sponges, sequestering miRNAs to regulate the availability of their mRNA targets. For instance, ciRS-7 acts as a sponge for miR-7, a known tumor suppressor miRNA. Deregulation of this axis has been implicated in brain, lung, and colon cancers. These ncRNAs collectively participate in hallmarks of cancer such as sustained proliferative signaling, evasion of apoptosis, angiogenesis, immune evasion, and metastasis. Biomarkers of the Future: Non-coding RNAs in cancer detection and prognosis. Non-coding RNAs offer several advantages as cancer biomarkers: they are often expressed in a tissue- and cancer-specific manner, can be detected in bodily fluids, and show early changes during tumorigenesis. This makes them valuable for early detection, diagnosis, prognosis, and monitoring response to therapy.

MiRNAs are stable in blood, urine, saliva, and other fluids, making them attractive for liquid biopsy. For instance, elevated miR-141 levels in serum are associated with prostate cancer, while reduced miR-34a is observed in various cancers with poor prognosis. Some miRNAs have been incorporated into commercial diagnostic panels.

LncRNAs such as PCA3 (prostate cancer antigen 3) have already made their way into clinical practice. The PCA3 urine test is FDA-approved for aiding prostate cancer diagnosis. Similarly, the expression of lncRNAs like *H19* and *UCA1* is being explored in bladder and ovarian cancers. CircRNAs, owing to their high stability, are emerging as robust biomarkers. Studies have linked specific circRNA expression profiles to cancer stage, metastasis, and treatment response.

Therapeutic targeting turning non-coding RNA into weapons against cancer

The reversibility and specificity of ncRNA-mediated gene regulation make them attractive drug targets. Unlike gene mutations, which are irreversible and difficult to fix, the dysregulation of non-coding RNAs can be modulated using synthetic molecules. Efforts are underway to restore tumor-suppressor miRNAs or inhibit oncomiRs. AntagomiRs, chemically modified antisense oligonucleotides, are used to inhibit oncomiRs like miR-21 or miR-155 in preclinical models. Although MRX34 trials were halted due to immune-related adverse events, they paved the way for safer delivery platforms and combination strategies. Therapeutically targeting lncRNAs

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remains more complex, but antisense oligonucleotides (ASOs), small interfering RNAs (siRNAs), and CRISPR-based technologies are being explored.

Challenges and opportunities

Stability and immunogenicity: Some ncRNA drugs trigger immune responses or degrade rapidly in circulation. Nonetheless, advances in nanoparticle delivery systems, chemical modifications, and target validation techniques are steadily addressing these issues. Combined therapies pairing ncRNA targeting with chemotherapy, immunotherapy, or radiotherapy offer a promising future.

COCLUSION

Non-coding RNAs have shifted the paradigm of cancer biology. Once ignored as non-functional noise, they are now recognized as master regulators in tumorigenesis, metastasis, and drug resistance. As diagnostic biomarkers, they offer precision and early detection. As therapeutic targets, they hold the promise of disrupting cancer at its regulatory core. The challenge now lies in translating this knowledge into routine clinical practice. With further research, improved technologies, and interdisciplinary collaboration, non-coding RNAs could become central pillars in the fight against cancer, reshaping how we diagnose, monitor, and treat this complex disease.