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D Chaitanya Dixit
Department of Pharmaceutical Analysis, KV Subba Reddy Institute of Pharmacy, Dupadu, Kurnool, Andhra Pradesh, India

M Aparna
Final Year B.Pharm Student, KV Subba Reddy Institute of Pharmacy, Dupadu, Kurnool, Andhra Pradesh, India

BV Ramana
Department of Pharmaceutics, Dr. KV SubbaReddy Institute of Pharmacy, Dupadu, Kurnool, Andhra Pradesh, India

M Sri Ramachandra
Department of Pharmacology, Dr. KV Subba Reddy Institute of Pharmacy, Dupadu, Kurnool, Andhra Pradesh, India

Corresponding Author:
D Chaitanya Dixit
Department of Pharmaceutical Analysis, KV Subba Reddy Institute of Pharmacy, Dupadu, Kurnool, Andhra Pradesh, India

Circular RNAS: Emerging roles in gene regulation, biomarkers, and therapeutic targets

D Chaitanya Dixit, M Aparna, BV Ramana and M Sri Ramachandra

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Abstract
Circular RNAs (circRNAs) are stable, non-coding RNAs formed by back-splicing with key roles in gene regulation, disease diagnosis, and therapy. They act through microRNA sponging, protein interactions, transcriptional regulation, and translation. Abnormal circRNA activity is linked to cancer, neurodegenerative, and cardiovascular diseases. Their unique structure, stability, and low immunogenicity make them valuable biomarkers and promising tools for RNA-based therapeutics, with the first circRNA drug (RXRG001) already in clinical trials.

Keywords: IRES, Circular RNA, gene regulation, biomarkers, therapeutics, back-splicing

1. Introduction
Circular RNAs (circRNAs) are a distinct class of endogenous non-coding RNAs that form a covalently closed loop via a process called back-splicing. Once considered splicing artifacts, circRNAs are now recognized as important regulatory molecules. Their circular structure confers exceptional stability by resisting exonuclease-mediated degradation, giving them longer half-lives than linear RNAs.

Key features include:-
- High tissue-specific expression (notably in the nervous system and heart).
- Evolutionary conservation across species.
- Regulatory roles in physiology and disease (cancer, neurodegeneration, cardiovascular, and autoimmune disorders).

With advances in RNA-seq and computational biology, circRNAs are now studied as biomarkers and therapeutic agents, making them central to modern RNA biology and medicine.

2. Literature Review
Research on circRNAs has grown rapidly
- Recent studies (2025, Zhang & Chen) emphasize circRNAs' unique closed-loop structure, highlighting their use in precision medicine, vaccines, and gene therapy. Synthetic circRNAs, being more stable than linear mRNA, are attractive for drug delivery.
- Cancer research (2024, Zhang *et al.*) focuses on engineered circRNAs in cancer vaccines, addressing design, delivery, and antigen selection.
- Earlier works (2017-2019) demonstrated circRNAs' abundance, stability, and regulatory potential, especially in breast cancer.
- Foundational research (2013-2015) identified circRNAs across eukaryotes, revealed challenges in detection, and confirmed their evolutionary conservation.

Together, these studies established circRNAs as a ubiquitous, stable, and functional RNA class, paving the way for clinical applications.

3. CircRNA Biogenesis and Structure

3.1 Formation Mechanisms

CircRNAs form by back-splicing, where a downstream splice donor joins an upstream acceptor.

- **Lariat-driven circularization:** Involves exon skipping and lariat intermediates.
- **Direct back-splicing:** Simultaneous formation of circRNAs and linear RNAs.

3.2 Regulatory Factors

- **Promoting factors:** Quaking (QKI) and Muscleblind-like (MBNL) proteins.
- **Inhibitors:** ADAR1 editing disrupts complementary sequences needed for circularization.

3.3 Classification

- **ExoniccircRNAs (ecircRNAs):** Cytoplasmic, coding potential.
- **Intronic circRNAs (ciRNAs):** Nuclear, regulate transcription.
- **Exon-intron circRNAs (EIciRNAs):** Hybrid, transcriptional roles.
- **Fusion circRNAs (f-circRNAs):** Generated from chromosomal translocations, often linked to cancer.

4. Mechanisms of Gene Regulation

CircRNAs regulate cellular functions via:

- **miRNA Sponging:** Acting as competitive endogenous RNAs (ceRNAs). Example: CDR1as (ciRS-7) sponges miR-7, regulating neuronal genes.
- **Protein Interactions:** Binding RNA-binding proteins (HuR, hnRNPs, FMRP), affecting localization and function.
- **Transcription/Epigenetic Regulation:** EIciRNAs and ciRNAs enhance/suppress transcription by interacting with RNA Pol II or chromatin modifiers.
- **Protein Translation:** Some circRNAs contain IRES or m6A modifications, allowing translation into proteins, sometimes through rolling-circle translation.

5. CircRNAs as Biomarkers

5.1 Cancer

CircRNAs are dysregulated in cancers, serving as diagnostic and prognostic tools:

- **Colorectal cancer:** circHERC4, circPLCE1.
- **Breast cancer:** circWHSC1, circPRMT5.
- Liquid biopsies (serum, plasma, urine) allow non-invasive diagnostics.

5.2 Neurodegenerative Diseases

- **Alzheimer's:** circ-LPAR1, circ-AXL elevated; circ-PCCA reduced.
- **Parkinson's:** circDNAJC6 linked to prodromal disease stages.

  CircRNAs overcome limitations of conventional biomarkers (blood-brain barrier).

5.3 Cardiovascular & Metabolic Disorders

- **Cardiac injury biomarkers:** circRNAs appear in blood after infarction.
- **Diabetes/obesity:** circRNAs regulate metabolic pathways, detectable in plasma.

6. Therapeutic Applications

6.1 CircRNA Therapeutics

- **Example:** RXRG001 (by RiboX Therapeutics) encodes Aquaporin-1 for radiation-induced dry mouth. Currently in clinical trials.
- **Advantages:** Longer half-life, reduced immune activation, sustained protein expression.

6.2 Vaccines

- circRNA vaccines (e.g., SARS-CoV-2 antigens) outperform linear mRNA vaccines in stability and immune response.
- Potential for cancer vaccines via multi-antigen encoding.

6.3 Targeted Therapy

- Antisense oligonucleotides (ASOs) can silence oncogenic circRNAs (e.g., circPVT1 in breast cancer).
- CircRNAs as drug delivery scaffolds.

6.4 Regenerative Medicine

- CircRNAs aid in tissue repair, reprogramming, and sustained factor expression.
- Applications in stem cell therapy and wound healing.

7. Technical Challenges

- **Detection/Quantification:** Standard RNA tools designed for linear RNAs; need specialized approaches (RNase R digestion, divergent PCR).
- **Functional Validation:** Overlap with linear isoforms complicates knockdown strategies.
- **Therapeutic Development:** Manufacturing, circularization efficiency, delivery (lipid nanoparticles), and regulatory approval remain hurdles.

8. AI and Computational Advances

- **AI in circRNA discovery:** Deep learning models improve circRNA prediction from RNA-seq data.
- **Therapeutic design:** AI assists in vaccine antigen prediction and structure modeling.
- **Multi-omics approaches:** Integrate circRNA data with proteomics and transcriptomics to map regulatory networks.
- **Databases:** circBase, CircInteractome provide centralized resources for researchers.

9. Future Directions

- **Emerging Technologies:** Long-read sequencing (Oxford Nanopore, PacBio), single-cell circRNA profiling, spatial transcriptomics, live imaging.
- **Personalized Medicine:** circRNA signatures for prognosis, therapy selection, and longitudinal monitoring.
- **Combination Therapies:** circRNA-based agents alongside conventional treatments.
- **Regulatory Science:** Need for new frameworks to assess safety, immunogenicity, and off-target effects.

10. Conclusion

CircRNAs have shifted from being seen as splicing errors to central regulators of gene expression with major implications in biology and medicine. Their stability,

specificity, and versatility make them excellent candidates for biomarkers, therapeutics, and vaccines.

Despite challenges in detection, functional validation, and clinical translation, advances in sequencing, AI, and biotechnology are rapidly pushing circRNAs into the mainstream of precision medicine. With ongoing trials like RXRG001, circRNA research is on the cusp of transformative clinical applications.

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