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### Circular RNAs: Unraveling Their Role in Regulation, Development, and Disease

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#### Introduction to Non-Coding RNAs

The human genome comprises approximately 3 billion base pairs across 23 pairs of chromosomes, yet less than 2% of these sequences encode proteins (Julia di Iulio, 2018). The remaining majority transcribe into non-coding RNAs (ncRNAs), which do not translate into proteins but play pivotal roles in cellular regulation. These ncRNAs fall into two broad categories: small ncRNAs (<30 nucleotides) such as miRNA, siRNA, and piRNA, and long ncRNAs (>200 nucleotides).

Small non-coding RNAs (ncRNAs) regulate gene expression through mechanisms such as gene silencing and chromatin remodeling, playing crucial roles in cellular processes (Rederstorff & Huttenhofer, 2010; Carthew, 2009). Long non-coding RNAs (lncRNAs) are key regulators in development and disease, often acting as molecular decoys or sponges that sequester miRNAs and mRNAs, thereby modulating gene expression (Ma et al., 2015; Paci, 2014). The first bacterial ncRNA, *micF*, was identified in *E. coli* in 1980, marking an important milestone in our understanding of ncRNA function (Delilhas, 2015). More recently, circular RNAs (circRNAs), a novel class of lncRNAs, have garnered increasing attention due to their emerging roles in gene regulation, the cellular response to stress, and the development of various diseases (Memczak, 2013). These circRNAs are unique in that they form covalently closed loops, making them resistant to exonuclease degradation, and they can function as regulators of transcription, splicing, and protein interaction.

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#### Circular RNAs – Features and Functions

CircRNAs are a novel class of lncRNAs formed through a back-splicing mechanism where a downstream splice donor joins an upstream splice acceptor, creating a covalently closed loop (Memczak, 2013). This structure confers resistance to exonucleases, giving them a longer half-life than linear RNAs (~48 hours) (Jeck, 2014).

Initially identified in viroids (Sanger, 1976), circRNAs are now recognized as regulatory elements in eukaryotic gene expression. They function as miRNA sponges, transcriptional regulators, and scaffolds for RNA-binding proteins (Ebbesen, 2016; Li et al., 2017). For instance, CDR1as harbors over 60 binding sites for miR-7, a critical regulator of neuronal development and insulin secretion (Xu et al., 2015).

circRNAs may also serve as delivery agents and play roles in antisense regulation and allosteric modulation of protein complexes (Hentze & Preiss, 2013). Many originate from protein-coding genes and consist entirely of exons (Burd, 2010; Jeck, 2014).

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## Biogenesis of Circular RNAs

CircRNA biogenesis involves canonical and non-canonical splicing pathways. Canonical splicing joins upstream and downstream splice sites linearly, while back-splicing connects downstream donors to upstream acceptors, forming a closed loop (Chen LL, 2015; Wang Y, 2015).

The biogenesis process is driven by intronic complementary sequences and regulated by RNA-binding proteins (Ashwal-Fluss, 2014; Conn, 2015). Models include intron-pairing-driven, lariat-driven, and RBP-driven circularization (Jeck, 2013; Wilusz, 2018).

Expression of circRNAs varies across tissues and developmental stages (Salzman, 2012; Zhang XO, 2016). Their production competes with linear splicing and is influenced by flanking intronic Alu elements, reverse complementary motifs, and RNA polymerase II activity (Zhang et al., 2014; Dong et al., 2016).

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## Classification and Regulatory Roles of circRNAs

Based on their origin, circRNAs are classified as:

1. **Exonic circRNAs (ecircRNAs):** Most abundant and conserved; primarily cytoplasmic.
2. **Intronic circRNAs (ciRNAs):** Derived from lariat introns; nuclear and regulate host gene transcription.
3. **Exon-intron circRNAs (ElciRNAs):** Retain introns and modulate gene expression in cis and trans.

Notable examples include circEIF3J and circPAIP2, which form complexes with U1 snRNA and RNA Pol II to enhance gene transcription (Li Z, 2015; Cech, 2014). icircRNAs like ci-ankrd52 act as transcriptional enhancers by interacting with RNA Pol II (Zhang et al., 2007).

Back-splicing relies on canonical splice signals and may compete with mRNA splicing due to shared splicing factors (Starke, 2014). While ecircRNAs are cytoplasmic and may exit the nucleus during mitosis, icircRNAs remain nuclear and are resistant to debranching enzymes (Panda, 2017; Yang Zhang, 2013).

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## Functional Insights – Proteins and Cellular Stress

Key RNA-binding proteins such as Quaking (QKI), Muscleblind (MBL), and FUS regulate circRNA formation by binding to flanking intronic motifs (Conn, 2015; Ashwal-Fluss, 2014; Errichelli, 2017). These proteins affect epithelial-mesenchymal transitions, cardiac remodeling, and neuronal differentiation.

circRNAs modulate gene expression by competing with mRNAs for RBP binding. For instance, circFOXO3 forms a ternary complex with CDK2 and p21, halting the cell cycle (Du, 2016). circANRIL promotes apoptosis by inhibiting ribosome formation through PES1 interaction (Holdt, 2016).

Exosomal circRNA release and endonuclease degradation are two mechanisms for circRNA clearance (Lasda, 2016; Hansen, 2011). High levels of circRNAs in stressed or cancerous cells point to their regulatory role in homeostasis and tumor resistance (Bachmayr-Heyda, 2015).

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## circRNAs in Disease, Aging, and Translation

circRNAs are increasingly linked to aging and disease. Expression profiles differ significantly in normal versus diseased tissues, such as tumors and lead-exposed neurons (Nan, 2016; Du, 2016b). circCDR1as regulates cell stress by sponging miR-7, which targets apoptosis-related genes like PAK1 (Fischer & Leung, 2017).

In aging, circRNA expression patterns are altered across organisms, often correlating with splicing changes (Westholm, 2014; Cortes-Lopez, 2018).

Translation of circRNAs was first observed in viroids and viruses (Kos, 1986; Perriman, 1998). Proteins like circ-ZNF609 and circMbl demonstrate cap-independent translation via internal ribosome entry sites (IRES) or m6A modifications (Abe, 2015; Legnini, 2017; Yang, 2017).

circRNAs are highly expressed in brain, liver, and heart tissues, with many neuron-specific species suggesting roles in neurodevelopment and synaptic regulation (You X, 2015; Rybak-Wolf, 2015). These findings indicate circRNAs' potential as biomarkers and therapeutic targets in metabolic, cardiac, and neurodegenerative diseases.

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