CircRNA-mRNA interactions in cancer

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Background: CircRNAs are covalently closed RNA molecules generated through an alternative splicing event known as back-splicing. They are evolutionarily conserved, expressed in a tissue-specific manner, and frequently dysregulated in various pathological contexts, such as cancer. Traditionally associated with a microRNA (miRNA) sponging mechanism, emerging evidence is shifting attention toward circRNA-mRNA interactions as an essential mechanism of gene expression regulation. Method: Using psoralen RNA-RNA crosslinking to stabilise circRNA-mRNA interactions in vivo, we perform selective RNA pulldown and analyse the mRNAs associated with selected circRNAs. We then study these interactions in molecular detail and design LNA antisense oligonucleotides to disrupt them, regulate the targeted gene, and create therapeutic vulnerabilities that can be exploited in a clinical setting. Results: Using the embryonal rhabdomyosarcoma cell model, we discovered and characterised two circRNA-mRNA interactions: circZNF609-CKAP5 (Rossi et al., Mol Cell 2022) and circHIPK3-BRCA1 (Grelloni et al., Mol Cell 2024). We demonstrated how these interactions regulate the binding of RNA-binding proteins that control the translation of their target mRNAs, governing important cellular processes such as microtubule dynamics in the case of circZNF609-CKAP5, or the DNA damage/DNA repair equilibrium in the case of circHIPK3-BRCA1. We also demonstrated that this mechanism operates across a variety of cancer cell models. Finally with the use of modified antisense nucleotides, we can disrupt these interactions in cells, creating therapeutic vulnerabilities that sensitise them to chemotherapeutic drugs. Conclusion: CircRNA-mRNA interactions are a new but widespread mechanism to regulate transcript fate that can be exploited to create increase sensibility to cancer drugs.