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**Identifying colorectal cancer-specific vulnerabilities in the Wnt-driven long non-coding transcriptome**

**Schwarzmueller L, Adam R, Moreno L, *et al.* Identifying colorectal cancer-specific vulnerabilities in the Wnt-driven long non-coding transcriptome. *Gut* 2025; 74: 571-585. doi: 10.1136/gutjnl-2024-332752.**

The majority of colorectal cancers (CRCs) involve APC (Adenomatous polyposis coli) mutations leading to over-activation of the Wnt (wingless type) signalling pathway. Aberrant activation of the Wnt signalling pathway is a hallmark of CRC, promoting cell proliferation and resistance to death, yet its impact on long non-coding RNAs (lncRNAs) remains underexplored. Using global run-on sequencing, Schwarzmueller *et al.,* identified Wnt-regulated lncRNAs in CRC cell lines and evaluated their functional relevance through CRISPR interference dropout screens.

Key findings include the identification of LINC02418 as an essential lncRNA for CRC cell growth. LINC02418 was found to regulate MYC expression, a critical oncogene in CRC, by interacting with miR-24 in a competing endogenous RNA (ceRNA) network. The suppression of LINC02418 led to MYC downregulation, reduced cancer stem cell functionality, and increased differentiation, thereby impairing tumour growth.

In vivo experiments demonstrated that siRNA-based therapeutics targeting LINC02418 effectively suppressed tumour expansion, offering a novel RNA interference-based strategy to disrupt the Wnt pathway in a cancer-specific manner. Given the challenge of directly targeting Wnt signalling due to its role in normal tissue homeostasis, the study proposes that lncRNA-targeting therapeutics could provide an alternative approach for CRC treatment.

This research highlights the importance of lncRNAs in CRC tumorigenesis and presents LINC02418 as a promising therapeutic target. The findings pave the way for future RNA-based cancer therapies, particularly for cancers driven by Wnt/β-catenin signalling.