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MiR-21 in Colorectal Cancer: Biological Promise, Mechanistic Gaps, Clinical Caution

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MicroRNA-21 (miR-21) is frequently upregulated in colorectal cancer (CRC) and has been associated with tumor progression and poor prognosis. However, its clinical and biological roles remain complex and context-dependent. Evidence indicates that miR-21 is dysregulated in multiple diseases, limiting its specificity as a standalone diagnostic biomarker for CRC. Moreover, recent studies suggest that miR-21 participates in diverse processes including modulation of inflammatory signaling, remodeling of the tumor microenvironment, immune regulation, and chemotherapy resistance. Despite promising experimental findings, therapeutic targeting of miR-21 has not yet progressed to clinical trials due to challenges in delivery and specificity. Future studies using advanced models such as CRISPR-based gene editing and patient-derived organoids may clarify the functional significance of miR-21 and determine its potential as a clinically actionable target in CRC.

Dear Editor-in-Chief

A recent study by Kordkatouli *et al.* provides new insights into the multifaceted involvement of microRNA-21 (miR-21) in colorectal cancer (CRC) [1]. The study highlights several important observations, including that miR-21 tends to be upregulated in tumors that progress, spread to lymph nodes, and are associated with a worse patient prognosis. Although these patterns emerge in many studies, it is worth noting that miR-21 is dysregulated in a wide range of malignancies and other disorders. Hence, investigating its presence in colorectal cancer in the current context is imperative.

Colorectal tumor formation is not simply a genetic process. Epigenetic factors, particularly microRNAs such as miR-21, play pivotal roles in modulating tumor development. Although high expression of miR-21 is often reported in advanced cases, this alone should not be taken as proof of its causal role. This microRNA is also associated with heart disease, liver damage, and other cancers, making it a nonspecific marker unless used in a more comprehensive diagnostic framework [2].

This idea is supported by a 2023 meta-analysis [3] that found that approximately 70% of CRC patients have detectable levels of miR-21 in their blood. Therefore, when this microarray is used independently, it misses

a significant number of cases due to its low specificity of about 79%. As a result of this finding, miR-21 should not be used as a screening test alone; instead, it should be used in conjunction with other established diagnostic methods, such as colonoscopy or multi-marker panels.

Contrary to previous thought, the function of miR-21 in cancer appears to be highly dependent on the involvement of stromal or immune cells. There are even studies that directly challenge the presumed role of miR-21 as a tumor progenitor. For example, Jiang *et al.* (2020) found that miR-21 inhibits TGFBI, which in turn induces pyroptosis. Based on these results, it appears that this microRNA may promote tumoral cell death rather than survival in some contexts. These changes suggest that tissue context and disease stage are important factors to consider when studying the functional activities of miR-21 [4]. Findings from other cancers also provide useful analogies. For example, research by Chi *et al.* in breast cancer showed that inhibition of miR-21, likely by reactivating suppressed immune responses, improved T-cell infiltration and suppressed tumor growth. To date, few studies have focused on the immune system in colorectal cancer, which is surprising given the growing role of immunotherapy in the treatment of gastrointestinal malignancies [5].

Overly simplistic conclusions often miss crucial information. For example, the presence of inflammation in colorectal cancer in particular makes the task much more difficult. In an AOM/DSS colitis model, deletion of miR-21 has been shown to reduce tumor formation. This is likely because miR-21 suppresses pro-inflammatory signaling pathways, such as the IL-6/STAT3 pathway. Although this review confirms the inflammatory component, it primarily focuses on the COX-2/PGE_2 axis and neglects to properly address other inflammatory pathways, such as miR-21. A deeper look into the specific mechanisms of inflammation involving miR-21 would be invaluable [6].

Another area of investigation is how miR-21 functions beyond the cell, via exosomes released by cancer-associated fibroblasts. Its role in shaping the tumor microenvironment, influencing stromal remodeling, and possibly even suppressing the immune system, is still not fully understood. Whether miR-21 from nonmalignant sources plays a role in metastasis or immune evasion is a question that requires direct testing [7].

In addition to its immune-related roles, miR-21 directly influences chemotherapy resistance. It inhibits autophagy and reduces PDCD4 expression, reducing drug efficacy. In colorectal cancer (CRC), it contributes to resistance to 5-fluorouracil and oxaliplatin. Here, miR-21 is not simply a passive marker, but a functional mediator of treatment failure [8].

Although miR-21 affects multiple central signaling cascades, such as the PI3K-AKT and MAPK pathways, efforts to target it therapeutically have been limited to in vitro settings. For example, Xu and colleagues used antisense oligonucleotides in xenograft models to restore PTEN expression and suppress tumor progression. However, to date, no miR-21-based therapeutic has reached clinical trials [9].

Significant obstacles remain, most notably the precise delivery of anti-miR-21 therapies to tumor tissue while sparing healthy cells. Therefore, various gene delivery methods, such as ligand-targeted oligonucleotides and nanoparticle formulations, are currently under investigation and development [10, 11].

In conclusion, the lack of comprehensive validation and delivery options for miR-21 has kept its clinical application in limbo, despite its promising status as a marker. However, as a precise functional technique, future research should emphasize the use of CRISPR-based miR-21 deletion in tissue-specific models or organoids generated from patients.

Studies such as these are also crucial to understanding whether targeting miR-21 improves CRC outcomes.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ETHICS APPROVAL

Not applicable.

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