MECHANISM BY WHICH MBD2 INHIBITORS SUPPRESS COLORECTAL CANCER PROGRESSION VIA EPIGENETIC REPRESSION OF ONCOGENIC WNT16 ACTIVATION

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Pharmacological inhibition of methyl-CpG-binding domain protein 2 (MBD2) reduces colorectal cancer tumor burden in patient-derived xenograft models by downregulating WNT16 oncogene expression without inducing genomic instability.

KEY POINTS

- MBD2 inhibitor treatment downregulated WNT16 expression at RNA and protein levels and suppressed Wnt/β-catenin signaling in colorectal cancer cells that exhibited hypomethylation at the WNT16 promoter with diminished MBD2 occupancy
- In patient-derived xenograft models, MBD2 inhibition reduced tumor burden without inducing genomic instability, which is a hallmark toxicity of conventional DNA methyltransferase inhibitors
- The study employed clinical specimens, cell lines, patient-derived organoids, and PDX models with whole-genome bisulfite sequencing, RNA-seq, chromatin immunoprecipitation sequencing, and CRISPR interference
- The authors propose that MBD2-targeted therapy achieves precise correction of carcinogenic epigenetic lesions while avoiding genome-wide hypomethylation risks associated with broad-spectrum DNA methyltransferase inhibitors
- This work is relevant to researchers and clinicians investigating targeted epigenetic therapies for colorectal cancer

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