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Crosstalk of Myotubularin-related protein 7 with RAS/WNT Driver Pathways in Colorectal Cancer

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WNT/β-catenin and RAS pathways are extensively accepted as two essential contributors to colorectal cancer (CRC) tumorigenesis. *APC* and *KRAS* mutations occur in CRC commonly and jointly. However, the intricate crosstalk between *APC* and *KRAS* remains poorly understood.
In this study, we investigated the interaction between myotubularin-related protein 7 (MTMR7) and the RAS/WNT driver pathways in CRC. Our previous research has shown that MTMR7 inhibits RAS/ERK 1/2 signaling and activates the tumor suppressor PPARγ. Building on these findings, we now reveal that MTMR7 enzyme, along with a peptide derived from its coiled-coil (CC) domain, acts as an inhibitor in the WNT signaling pathway, confirmed through both *in vitro* and *in vivo* studies. We also discovered that β-catenin stability is contingent on its interaction with RAS, and disruption of this interaction leads to the independent degradation of both β-catenin and RAS. Transfection of the MTMR7-full length (FL) plasmid into HEK293T, SW480, and HCT116 cell lines, followed by co-immunoprecipitation (Co-IP) assays, demonstrated that MTMR7 interferes with β-catenin and RAS interaction. In summary, our findings emphasize the complex mechanism of MTMR7 inhibition of the WNT signaling cascade, underscoring its therapeutic potential in treatment-resistant CRC.