A COMBINATION OF RAPAMYCIN, Ω3-PUFA DOCOSAHEXAENOIC ACID AND EPIGALLOCATECHIN-3-GALLATE FOR THE SIMULTANEOUS SUPPRESSION OF PI3K/MTOR PATHWAY AND WNT/B-CATENIN SIGNALLING IN COLORECTAL CARCINOGENESIS

Luigi Ricciardiello

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A combination of Rapamycin, DHA, and EGCG (RDE) simultaneously inhibits PI3K/mTOR and Wnt/β-catenin pathways in colorectal cancer models, with effects varying by genetic background.

KEY POINTS

- RDE strongly inhibited PI3K/mTOR by downregulating phospho-P70S6K and phospho-S6R protein expression across all tested genetic backgrounds including APC-mutated cell lines, FAP patient organoids, and sporadic CRC organoids.
- In APC-mutated SW480 and HT-29 cell lines and in HCT116 cells, RDE inactivated the Wnt/β-catenin pathway and inhibited β-catenin nuclear translocation, with HCT116 also showing reduced viability and apoptosis induction.
- RDE significantly suppressed LGR5 (a marker of intestinal stemness) and induced KRT20 (a marker of differentiation) gene expression, and increased c-MYC expression across organoids regardless of genetic background.
- The dual pathway inhibition by RDE was influenced by genetic backgrounds, showing different responses in FAP normal-appearing mucosa organoids compared to CRC cell lines and organoids.
- The findings suggest RDE as a potential approach for CRC prevention and therapy in preclinical models; this work is relevant to researchers investigating combinatorial pathway inhibition strategies in colorectal cancer.

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