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Targeting KEAP1 in Colorectal Cancer: Integrative Genomic and Pharmacological Analysis Identifies Dimethylfumarate as a Promising Therapeutic Molecule

Abstract:

Introduction: Kelch-like ECH-associated protein 1 (KEAP1) is a key regulator of cellular redox homeostasis through its interaction with NRF2, and its aberrant expression has been implicated in various cancers. This study investigates the expression profile, regulatory mechanisms, and mutational landscape of KEAP1 in COAD, and evaluates the efficacy of a KEAP1-targeting compound, dimethylfumarate (DMF), an FDA approved treatment for multiple sclerosis, as a potential antitumor compound.

Methods: KEAP1 expression in COAD was analyzed using The Cancer Genome Atlas (TCGA) database. Regulatory mechanisms were assessed by evaluating promoter methylation levels and KEAP1-targeting miRNAs profiling. Candidate therapeutic molecules were extracted from the ChEMBL database, leading to the selection of DMF. TCGA mutational data and maftools package, identified mutations within the BTB domain of KEAP1, which is critical for DMF binding. The structural implications of these mutations were explored by AlphaFold and molecular docking, respectively. The antitumor activity of DMF was evaluated (assessed) ted in vitro on HCT-116 colorectal cancer cells by the MTT assay.

Results: KEAP1 was found to be significantly overexpressed in COAD despite hypermethylation of its promoter, suggesting alternative regulatory mechanisms. The hsa-miR-140, a microRNA predicted to target KEAP1, was downregulated in COAD, potentially contributing to KEAP1 overexpression. On the gene itself, we identified a missense mutation, I125V, within the BTB domain, which may alter KEAP1's interaction with DMF. Treatment with 50 µM DMF reduced HCT-116 cell viability ($P < 0.001$), supporting its antitumor potential.

Conclusion: These findings highlight the multifaceted regulation of KEAP1 in COAD and propose DMF as a promising therapeutic agent, warranting further preclinical and clinical investigations.

Keywords: Colon adenocarcinoma, Dimethylfumarate, KEAP1, miRNA, AlphaFold