Resource Summary Report

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Helicase-like transcription factor (Hltf) gene-deletion promotes oxidative phosphorylation (OXPHOS) in colorectal tumors of AOM/DSS-treated mice

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Protocol Information

URL: https://dx.doi.org/10.17504/protocols.io.4argsd6

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Summary: The helicase-like transcription factor (HLTF) gene – a tumor suppressor in human colorectal cancer (CRC) - is regulated by alternative splicing and promoter hypermethylation. The detection of hypermethylated HLTF DNA in fecal occult blood tests is an indicator of disease recurrence and poor survival. Hltf-deficiency in the ApcMin/+ mouse strain increased the formation of intestinal adenocarcinoma with a high incidence of gross chromosomal instabilities. To investigate Hltf-deletion effects in CRC without cross-breeding into a tumorigenic strain, Hltf-deletion was studied in mice treated with the carcinogen azoxymethane (AOM) and the proinflammatory agent dextran sodium sulfate (DSS). Hltf-deletion resulted in weight loss beginning at treatment week 6, and poor survival (Kaplan-Meier survival plot). Hltf-deletion increased tumor multiplicity compared to controls, and dramatically shifted the topographic distribution of lesions into the rectum. Differential isoform expression analysis of lesions from control mice revealed both the truncated isoform that lacks a DNA-repair domain and the full length isoform capable of DNA damage repair are present (3:1.8 ratio) during adenocarcinoma formation. iPathwayGuide identified 51 dynamically regulated genes of 10,967 total genes with measured expression. Oxidative Phosphorylation (Kegg: 00190), the top biological pathway perturbed by Hltf-deletion, resulted from increased transcription of Atp5e, Cox7c, Uqcr11, Ndufa4 and Ndufb6 genes, concomitant with increased endogenous levels of ATP (p=0.0176). Upregulation of gene expression, as validated with qRT-PCR, was accompanied by a stable mtDNA/nDNA ratio. This is the first study to show Hltf-deletion in an inflammation-associated CRC model elevates mitochondrial bioenergetics. The distal shift in tumorigenesis indicates the detection of hypermethylated HLTF DNA in stool

samples might be a prognostic biomarker for distal (left-sided) CRC in patients with inflammatory bowel disease.

Associated Publications: Helmer RA, Kaur G, Smith LA, Chilton BS (2019) Helicase-like transcription factor (*Hltf*) gene-deletion promotes oxidative phosphorylation (OXPHOS) in colorectal tumors of AOM/DSS-treated mice. PLoS ONE 14(8): e0221751. doi: 10.1371/journal.pone.0221751

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