Microbiome-derived hydrogen sulfide as a trigger for CIMP colorectal cancer

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Abstract: Hydrogen sulfide (H_2S) is a microbiome-derived gas and endogenous product of cysteine metabolism that mediates sulfhydration of protein Cys residues, contributing to cell signaling and oncogenesis. Notably, a 3-enzyme sulfide oxidation unit (SOU) resides in mitochondria that serves to metabolize H_2S to innocuous thiosulfate and thereby limit protein sulfhydration and preserve "normal" physiology. At physiological levels, H_2S promotes anti-inflammatory signaling, ATP production and cell growth. At supra-physiological levels that can arise from the gut microbiome, H_2S can overwhelm the SOU's capacity for detoxification, and serve as an oncogenic driver. Although prior studies showed that H_2S can drive oncogenesis, the molecular mechanisms remain obscure. Our preliminary studies reveal that exposure of colonocytes in culture to H_2S at levels that exceed the mitochondrial capacity for oxidative detoxification (i.e. that upregulate protein-sulfhydration) evokes abundant intracellular accumulation of the oncometabolite L-2- hydroxyglutarate (L-2HG). Further, preliminary studies identify lactic dehydrogenase A (LDHA) as the enzymatic source of H_2S-triggered L-2HG accumulation, and α-ketoglutarate (α-KG) synthesis by phosphoserine amino transferase (PSAT1) as the immediate precursor of L-2HG. We also found that the bacterial fermentation product butyrate, shown to trigger endogenous H_2S production in colonocytes, also synergizes with H_2S to trigger robust L-2HG accumulation. We hypothesize that sulfide-producing bacteria of the microbiome (e.g. *Fusobacter* sp.), synergistically-complemented by microbiome-derived butyrate, create oncogenic levels of H_2S and provide a molecular basis for the CpG island methylator phenotype (CIMP) of colorectal cancer (CRC). We hypothesize that L-2HG accumulation in colonocytes inhibits α-KG-dependent histone and DNA demethylases, resulting in hypermethylation of genes that promote CIMP CRC. The proposed research seeks to assess H_2S as a fundamental driver of CIMP in patient-derived PDX cells, and establish underlying molecular mechanisms.