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The desaturase SCD1 as key enzyme in colorectal cancer

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Purpose:

Metabolic reprogramming including activation of lipid synthesis has been established as a hallmark of cancer. Here, we analyzed the clinical implication of key enzymes of fatty acid synthesis and processing, including FASN (fatty acid synthase), fatty acid elongase 6 (ELOVL6), the master transcription factor of lipid biosynthesis, SREBP1 (sterol regulatory element binding protein 1), and the steaoryl-CoA desaturase 1 (SCD1), which is essential for the production of mono-unsaturated fatty acids (MUFAs). To investigate its functional role, we generated SCD1 deficient colon cancer cell lines, and tested whether aberrant lipid synthesis is evolutionarily conserved in genetic mouse models for colon cancer.

Methods: The expression of SCD1, SREBP1, FASN and ELOVL6 was quantified in tissues from 78 patients with stage III colon cancer by qPCR, and their clinical and prognostic significance was assessed by Kaplan-Meier analysis. SCD1 and SREBP1 were analyzed on protein level by immunoblot analysis and SCD1 by immunocytochemistry. SCD1 deficiency was implemented in the colon carcinoma cell lines HCT116 and DLD1 by the CRISPR-Cas9 system. Additionally, we analyzed expression of enzymes for fatty acid biosynthesis in intestinal tumors of a genetic tumor mouse model (Apc^{1638N}).

Results: Compared to normal colon, mRNA expression of SCD1 and FASN was highly significantly increased, whereas SREBF1 and ELOVL6 were significantly reduced. SCD1 and SREBP1 were upregulated in tumor tissue on protein level and their mRNA was significantly co-expressed. SCD1 expression was significantly associated with tumor grading and with worse post-operative survival. SCD1 deficiency was successfully demonstrated on DNA, mRNA, protein and lipidomics level. HCT116 cell clones showed a significantly reduced cell proliferation compared to parental cells, especially under low serum concentrations, as well as reduced collective 2D cell migration. Importantly, these effects could be significantly rescued by addition of a fatty acid mixture of the SCD1 products. The invasion potential of SCD1-deficient clones was reduced, whereas transwell migration of individual SCD1-deficient cells through pores was significantly increased. Analysis of genetic mouse models for colon cancer indicated a significant upregulation of *Fasn and Scd2*, whereas *Scd1* was barely expressed in mouse tumors, with lipidomics analysis further supporting an aberrant intratumoral lipid metabolism.

Conclusion: SCD1 expression is a negative prognostic marker in colon carcinoma, indicating a tumor-promoting role. Functionally, the in vitro data demonstrate that SCD1 is essential for maintenance of proliferation under serum depletion and regulated by hypoxia. Further, de novo lipogenesis in colorectal cancer appears to be evolutionarily conserved in murine cancer models.