Abstract

Fatty Acid Desaturase-1 (FADS1) or delta 5 desaturase (D5D) is a rate-limiting enzyme involved in the biosynthesis of long-chain polyunsaturated fatty acids (LC-PUFAs), i.e., arachidonic acid (ARA) and eicosapentaenoic (EPA). These LC-PUFAs and their metabolites play essential and broad roles in cancer cell proliferation, metastasis, and tumor microenvironment. However, the role of FADS1 in cancers remains incompletely understood. Utilizing The Cancer Genome Atlas (TCGA) database, we explored the role of FADS1 across different cancer types using multiple bioinformatics and statistical tools. Moreover, we studied the impact of a FADS1 inhibitor (D5D-IN-326) on proliferation of multiple cancer cell lines. We identified that FADS1 gene is a pan-cancer predictor for cancer survival. The mRNA expression of FADS1 is significantly associated with tumorigenesis, metastatic and cancer recurrence. At the molecular level, FADS1 is associated with cholesterol biosynthesis and cell cycle control genes. Interestingly, FADS1 expression is higher when TP53 is mutated. Tumors with increased FADS1 expression also demonstrated an increased fibroblasts and macrophages infiltration among most cancer types. Our in vitro assays showed that D5D-IN-326 significantly inhibited cell proliferation of multiple cancer cell lines in a dose-dependent manner. Mechanistically, FADS1 inhibition exacerbate ER stress in cancer cells, leading to reduced cell proliferation, which is mediated by the ATF4-ATF3 signaling. Lastly, single nucleotide polymorphisms (SNPs) which are well-established expression quantitative trait loci (eQTLs) for FADS1 in normal human tissues are also significantly correlated with FADS1 expression in tumors of multiple tissue types, potentially serving as a marker to stratify cancer patients with high/low FADS1 expression in their tumor tissue. Our study suggests that FADS1 plays multiple roles in cancer biology and is potentially a novel target for precision cancer treatment.