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"Developing a CD36 Inhibitor as a Novel Therapeutic Agent for Triple-Negative Breast Cancer"

Triple-negative breast cancer (TNBC) is the most aggressive subtype of breast cancer and is associated with poor prognosis, high rates of recurrence, metastasis, and limited treatment options due to the absence of estrogen receptor, progesterone receptor, and HER2 expression. Although chemotherapy remains the standard treatment for TNBC, therapeutic resistance and relapse remain a major challenge. Evidence suggests that cancer stem cells (CSCs) contribute to tumor progression, metastasis, and therapeutic resistance through enhanced fatty acid metabolism. CD36 is a transmembrane fatty acid transporter that mediates the uptake of long-chain fatty acids and has been implicated in lipid metabolism, tumor progression, metastasis, and CSC maintenance, making it a promising therapeutic target in TNBC.

In this study, we investigated the effects of a newly developed novel CD36 inhibitor, FRCD36-01 using the human TNBC cell lines MDA-MB-231 and MDA-MB-468 as well as the mouse cell line C0321. Kaplan-Meier analysis demonstrated that elevated CD36 expression is associated with poorer relapse free survival in patients with TNBC suggesting its clinical relevance. We also confirmed higher levels of CD36 protein in mammospheres compared to the adherent cells by Western blot analysis. These results suggested the association of CD36 with cancer stemness. We assessed cell viability using MTT assays, cell proliferative capacity through colony formation assays, apoptosis assays to determine the effects of FRCD36-01 on programmed cell death. We also conducted mammosphere formation assays to assess CSC's self-renewal ability, and functional assays, such as fatty acid uptake experiments using the fluorescent fatty acid analog BODIPY FL C16 to confirm inhibition of CD36 mediated fatty acid uptake by TNBC cells. The results demonstrated that FRCD36-01 significantly reduced cell viability, colony formation ability, fatty acid uptake, and mammosphere formation while promoting apoptosis in TNBC cells. The combinational treatment of FRCD36-01 with chemotherapy drug paclitaxel produced greater inhibition compared to either single treatment suggesting that FRCD36-01 enhanced therapeutic efficacy of chemotherapy. These findings demonstrate that inhibition of CD36-mediated fatty acid uptake with our novel FRCD36-01 would be an effective therapeutic approach to treat TNBC. However, further studies are warranted to identify the detail mechanism of this pathway as well as applicability of FRCD36-1 with immunotherapy to treat TNBC.