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Cd36 Mediated Metabolic Reprogramming in Cancer Stem Cells Contributes to Drug Resistance to mTOR Inhibition in Pancreatic Neuroendocrine Tumors

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BACKGROUND: Pancreatic neuroendocrine tumors (PNETs) represent a rare group of neoplasms with robust angiogenesis and heterogeneity. Current therapeutic efficacy is limited, accompanied by resistance to targeted chemotherapies, such as everolimus (a derivative molecule from rapamycin, an mTOR inhibitor), in which cancer stem cells (CSCs) play a critical role. CD36 as a fatty acid receptor that drives cancer cell stemness and promotes drug resistance by importing long chain free fatty acid into the cells to generate energy ATP and fuel CSCs. We hypothesize that CD36 in CSCs reprograms metabolic pathways in PNETs to enhance CSC features via regulation of fatty acid metabolism and thus contributes to mTOR inhibition resistance.

METHODS: A drug-resistance model was established in PNET cells with long-term treatment of rapamycin. Tumorsphere formation efficiency was assayed after knocking down CD36 in the drug-resistant cells, along with characterization of stemness features by performing RT-qPCR, Western blot, and immunofluorescence microscopy. Furthermore, tumor invasion and migration assays were performed in the control and drug-resistant cells with treatment of palmitic acids (long-chain fatty acids) and etomoxir (inhibitor of fatty acids oxidation). CSC-related gene signatures were analyzed by RT-qPCR.

RESULTS: The drug-resistant PNET cells showed increased stemness-associated gene expression and demonstrated CSC features, which were attenuated by knocking down CD36. CD36 knockdown also decreased tumor cell migration and invasion in response to fatty acid exposure, along with decreased CSC marker expression. Moreover, the changes in aggressiveness and CSC gene transcription in drug resistant cells may be associated with CD36-mediated fatty

acid oxidation.

CONCLUSION: CD36-mediated fatty acid metabolism is essential for maintaining stemness features, which may contribute to therapeutic resistance and metastatic relapse in PNETs.

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