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Metastasis and chemoresistance in CD133 expressing pancreatic cancer cells are dependent on their lipid raft integrity

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Abstract

Metabolic rewiring is an integral part of tumor growth. Among metabolic pathways, the Mevalonic-Acid-Pathway (MVAP) plays a key role in maintaining membrane architecture through cholesterol synthesis, thereby affecting invasiveness. In the current study, we show for the first time that $CD133^{Hi}$ pancreatic tumor initiating cells (TIC) have increased expression of MVAP enzymes, cholesterol-content and Caveolin expression. Further, we show that CD133 in these cells is localized in the lipid-rafts (characterized by Cav-1-cholesterol association). Disruption of lipid-rafts by either depleting Cav-1 or by inhibiting MVAP by lovastatin decreased metastatic-potential and chemoresistance in $CD133^{Hi}$ cells while not affecting the $CD133^{lo}$ cells. Additionally, disruption of lipid-raft results in deregulation of FAK-signaling, decreasing invasiveness in pancreatic-TICs. Furthermore, this also inhibits ABC-transporter activity resulting in sensitizing TICs to standard chemotherapeutic agents.

Repurposing existing drugs for new clinical applications is one of the safest and least resource intensive approaches to improve therapeutic options. In this context, our study is extremely timely as it shows that targeting lipid-rafts with statins can sensitize the normally resistant pancreatic TIC^{Hi}-cells to standard chemotherapy and decrease metastasis, thereby defining a novel strategy for targeting the TIC^{Hi}-PDAC.