Metastasis of pancreatic cancer: An uninflamed liver micromilieu controls cell growth and cancer stem cell properties by oxidative phosphorylation in pancreatic ductal epithelial cells.

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) is commonly diagnosed when liver metastases already emerged. We recently demonstrated that hepatic stromal cells determine the dormancy status along with cancer stem cell (CSC) properties of pancreatic ductal epithelial cells (PDECs) during metastasis. This study investigated the influence of the hepatic microenvironment - and its inflammatory status - on metabolic alterations and how these impact cell growth and CSC-characteristics of PDECs. Coculture with hepatic stellate cells (HSCs), simulating a physiological liver stroma, but not with hepatic myofibroblasts (HMFs) representing liver inflammation promoted expression of Succinate Dehydrogenase subunit B (SDHB) and an oxidative metabolism along with a quiescent phenotype in PDECs. SiRNA-mediated SDHB knockdown increased cell growth and CSC-properties. Moreover, liver micrometastases of tumor bearing KPC mice strongly expressed SDHB while expression of the CSC-marker Nestin was exclusively found in macrometastases. Consistently, RNA-sequencing and in silico modeling revealed significantly altered metabolic fluxes and enhanced SDH activity predominantly in premalignant PDECs in the presence of HSC compared to HMF. Overall, these data emphasize that the hepatic microenvironment determines the metabolism of disseminated PDECs thereby controlling cell growth and CSC-properties during liver metastasis.

Involved Units and Groups

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