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Inducing differentiation of premalignant cells as a novel therapeutic strategy in hepatocarcinoma

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Hepatocellular carcinoma (HCC) represents the second leading cause of cancer-related deaths and is reported to be resistant to chemotherapy caused by tumor-initiating cells. These tumor-initiating cells express stem cell markers. An accumulation of tumor-initiating cells are found in 28-50% of all HCC and is correlated with a poor prognosis. Mechanisms that mediate chemoresistance include drug export, increased metabolism and quiescence. Importantly, the mechanisms that regulate quiescence in tumor-initiating cells have not been analyzed in detail so far. In the present research we have developed a single cell tracking method to follow up the fate of tumor-initiating cells during chemotherapy. Thereby, we were able to demonstrate that mCXCL1 exerts cellular state specific effects regulating the resistance to chemotherapeutics; mCXCL1 is the mouse homolog of the human Interleukin 8, a chemokine which correlates with poor prognosis in HCC patients. We found that mCXCL1 blocks differentiation of premalignant cells and activates quiescence in tumor-initiating cells. This process depends on the activation of the mTORC1 kinase. Blocking of the mTORC1 kinase induces differentiation of tumor-initiating cells and allows their subsequent depletion using the chemotherapeutic drug doxorubicin. Our work deciphers the mCXCL1-mTORC1 pathway as crucial in liver cancer stem cell maintenance and highlights it as a novel target in combination with conventional chemotherapy

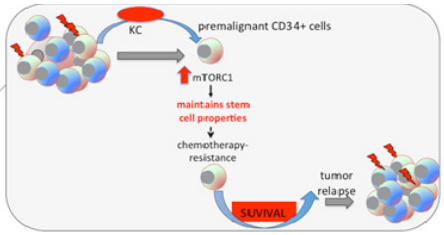

Fig.1: Maintenance of stem cell characteristics by mCXCL1 (KC) via the activation of mTORC1 drives resistance of premalignant tumor-initiating cells. The mechanism induces a G1 arrest of tumor-initiating cells. mTORC1 blockade induces differentiation and sensitivity to doxorubicin.

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