Chloroquine targets pancreatic cancer stem cells via inhibition of CXCR4 and hedgehog signaling.

Abstract:
Pancreatic ductal adenocarcinoma is one of the deadliest carcinomas and is characterized by highly tumorigenic and metastatic cancer stem cells (CSC). CSCs evade available therapies, which preferentially target highly proliferative and more differentiated progenies, leaving behind CSCs as a putative source for disease relapse. Thus, to identify potentially more effective treatment regimens, we screened established and new compounds for their ability to eliminate CSCs in primary pancreatic cancer (stem) cells in vitro and corresponding patient-derived pancreatic cancer tissue xenografts in vivo. Intriguingly, we found that in vitro treatment with the antimalarial agent chloroquine significantly decreased CSCs, translating into diminished in vivo tumorigenicity and invasiveness in a large panel of pancreatic cancers. In vivo treatment in combination with gemcitabine was capable of more effectively eliminating established tumors and improved overall survival. The inhibitory effect of chloroquine was not related to inhibition of autophagy, but was due to inhibition of CXCL12/CXCR4 signaling, resulting in reduced phosphorylation of ERK and STAT3. Furthermore, chloroquine showed potent inhibition of hedgehog signaling by decreasing the production of Smoothened, translating into a significant reduction in sonic...
hedgehog-induced chemotaxis and downregulation of downstream targets in CSCs and the surrounding stroma. Our study demonstrates that via to date unreported effects, chloroquine is an effective adjuvant therapy to chemotherapy, offering more efficient tumor elimination and improved cure rates. Chloroquine should be further explored in the clinical setting as its success may help to more rapidly improve the poor prognosis of patients with pancreatic cancer.