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Characterisation of tumorspheres cultured from circulating epithelial tumor cells (CETCs) in pancreatic cancer patients.

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Background: Metastatic disease is a serious threat and the most common cause of *cancer*-associated death in patients with pancreatic cancer. Over 90% of pancreatic cancers progress to become metastatic. The poor prognosis is due to the early dissemination via blood vessels and late detection of the tumor. The presence of CETCs is closely related to tumor metastasis, but it is still unclear whether all CETCs are capable to proliferate and generate metastasis. Therefore, we established an effective method, tumorsphere growth, for identification of cancer stem cells circulating in the blood of patients with pancreatic cancer with subsequent phenotypic and genotypic characterization and testing for resistance to anti-cancer drugs.

Methods: CETCs were enumerated with the maintrac approach and subsequently cultured under conditions favoring growth of tumorspheres. Stem cell markers and ALDH 1 activity was evaluated by fluorescence and gene expression analyses. To estimate the cytotoxic effect of drugs on tumorspheres we incubated them with conventional anticancer drugs in 48 hour culture in different concentrations and for different periods of time.

Results: Only a small proportion of CETCs in pancreatic cancer patients has the ability to form tumorspheres. They display the typical phenotype of cancer stem cells and express high enzymatic activity for ALDH1. Array qRT-PCR analysis revealed that tumorspheres express genes of pluripotency such as SOX2, OCT4 and NANOG. The spheroids were chemoresistant to standard chemotherapeutics.

Conclusions: These data demonstrate that tumorspheres derived from CETCs have cancer stem cells properties and are chemoresistant to the standard cytotoxic drugs used in pancreatic cancer therapy. Studying pancreatic cancer stem cells shows that the conventionally used drugs are ineffective against these cells explaining the low efficiency of chemotherapy in pancreatic cancer and may help researchers to identify targets for new drugs or therapies.

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