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Tumorspheres cultured from circulating epithelial tumor cells (CETCs) overexpress stem cell markers in patients with solid cancers.

Background: Solid malignancies continuously shed tumor cells which may enter the circulation, spread to other tissues and initiate metastases, but it is assumed that only a small subpopulation among CETCs is capable of metastasis formation, the subpopulation of CETCs capable of forming tumorspheres *in vitro* and carrying stem cells properties. The aim of this study was to characterize the pattern of expression of the tumorspheres as compared to CETCs.

Methods: Blood samples were obtained from patients diagnosed with solid tumors. CETCs were enumerated with the maintrac method and subsequently cultivated in epithelial stem cell-selective medium. Immunofluorescence and qRT-PCR were performed to examine the metastatic ability of tumorspheres in vitro.

Results: Analysis of surface markers in non-adherent tumorspheres forming from CETCs under stem cell- selective conditions after a period of 14 days showed typical phenotype for cancer stem cells depending on type of cancer. Furthermore, spheres had high enzymatic activity for ALDH 1. Array qRT-PCR analysis revealed that putative stem cell markers, such as Oct4, Sox2, Nanog, EpCAM, ALDH1 and CD133 are overexpressed in relation to house-keeping genes RPL13a and GAPDH in tumor spheres in contrast to the significantly lower expression level of these stem cell markers in individually isolated CETCs. High expression level of pluripotency genes in tumorspheres was associated with aggressive tumor behaviour in terms of tumor progression and type of cancer.

Conclusion: Here we show that stem cell markers are overexpressed in tumorspheres as compared to CETCs. Obviously only a small population of CETCs can be grown into spheres which possess stem cell properties and most probably are responsible for recurrence and treatment failure. Precise characterization of CETCs and tumorspheres on the single cell and sphere level will contribute to a better understanding of metastasis formation and lead to development of cancer stem cell based cancer therapy.

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