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Cancer stem cells and radiotherapy

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Over the last decades, radiotherapy has been continuously improved by the development of new techniques, by introduction of new combined treatment schedules and by implementation of biologically adapted fractionation schedules. Despite of these achievements, a high number of patients is still developing recurrent tumours after application of curatively intended treatment schedules. It is well known that only a small subpopulation of all tumour cells can cause recurrences. These cells are called cancer stem cells (CSC) and are defined as cells that have the potential to self-renew and to repopulate all subpopulations of tumour cells within a tumour. This definition implies that all CSC need to be killed to permanently cure a tumour. With new experimental techniques, CSC can today be enriched and their biology can trhereby be investigated. Using these sorting techniques„ there is an increasing body of evidence for a higher radioresistance of cell populations enriched by surface markers as compared to their marker-negative counterparts. Also, CSC may express a higher tolerance to hypoxia and seem to be accumulated in specific microenvironmental niches. If such biological differences between CSCs and non-CSCs are confirmed by large-scale studies, this would have the important implications that, novel treatment strategies need to be tested specifically for their effect on CSCs and that biomarkers for prediction of local tumour control after radiotherapy or combined treatments need to be specific to CSCs and not to the bulk of all cancer cells. CSC-based endpoints and biomarkers are eventually expected to allow individualised tailoring of treatment, thereby considerably improving tumour cure rates in the clinics.
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Drug sensitivity of cancer stem cells

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Cancer stem cells (CSCs) are the rare population of undifferentiated tumorigenic cells that are thought to be responsible for tumor initiation, maintenance and spreading. Their existence might also explain why tumours are resistant to many conventional therapies, which typically target the rapidly proliferating tumor cells but spare the slow dividing tumor stem cell population.
The concept of CSCs has profound implications for the development of more effective cancer therapeutics since the selective targeting of these cells offers a potential revolutionary advance in the treatment of cancer, by attacking the roots of the disease.
We developed a technology that allowed us to isolate and expand *in vitro* CSCs from several solid tumors, including glioblastoma, melanoma, breast, lung, colon, thyroid and ovary cancer. We are currently characterizing these tumorigenic cell populations at different levels, including proteome profiling. Such extensive characterization may provide key information on the relevant pathways to be targeted for successful therapies.
A pathway-centered approach may lead to unexplored opportunities for the design of more effective anticancer treatment options. To this end, we are using two complementary strategies based both on high-throughput CSC analysis: a compound library screening on the one hand, and a reverse phase protein microarray-based profiling of active signaling pathways, on the other. The mindful integration of the drug screening and the proteomic analysis results allowed us to identify specific pathway inhibitors which we are currently testing for efficacy in CSC-based mouse xenografts.
Thus, although the identification of CSCs is relatively recent, this research area appears extremely promising since the pharmacological blockade of aberrantly activated signaling pathways in the tumorigenic cell population may represent an effective anticancer strategy.

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Challenges in clinical development of stem-cell therapy

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