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STUDY OF CELL REPROGRAMMING IN A MURINE MODEL: FOLLOW-UP OF RADIO-INDUCED CANCEROUS STEM CELLS AND VALIDATION OF THE CYTOKINES INVOLVED

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Many solid cancers are thought to be organized hierarchically with a small number of cancer stem cells (CSCs) able to re-grow a tumor while their progeny lacks this feature. This CSCs are associated with radioresistance. Recent studies have revealed that noncancer stem cells may undergo dedifferentiation subsequently obtaining the phenotype and functions of CSCs. Indeed, ionizing radiation reprogrammed differentiated breast cancer cells into induced cancer stem cells (iCSCs). This mechanism of reprogramming can contribute to relapse. CSCs and iCSCs cannot be distinguished, because they share the same stem cell-like properties. Breast CSCs can be isolated based on their high ALDH1 activity, and iCSC studies require sorting of ALDH1-negative cells. These studies are therefore limited to *in vitro* experiments. *In vivo* reprogramming studies require to design a CSC and iCSC identification system. We compared different promoters for the use of CSC reporters. To do so, we built expression vectors with mNeptune fluorophore expression controlled by different sizes ALDH1A1 and NANOG promoters. We validated the CSC reporter capability using RTPCR expression, flow cytometry and functional assay analyses. Indeed, mNeptunepos cells have an overexpression of stemness-related genes (Oct3/4, Sox2 and Nanog), as well as an increase of mammosphere forming capacity and tumorigenicity, compared to mNeptuneneg cells. We also observed an enrichment for mNeptunepos cells after ionizing radiation and a radiation-induced reprogramming of mNeptuneneg cells into mNeptunepos cells. Our observations on CSC reporters showed that the 900 pb sequence of ALDH1A1 promoter seems to be the best choise for a CSC reporter. Based of this first study, we selected this promotor andgenerated a multigene tracing expression vector to distinguish CSC from iCSC at given time points. This vector contains sequence of CSC reporter, TetON system for inducible CRE expression, CRE recombinase/loxP sites system and mNeptune fluorophore. We are currently validating this vector for it use *in vitro* before to generate transgenic mice model for CSC and iCSC reporter. This vector will be a tool for future studies investigating *in vivo* reprogramming mechanism.

BIOGRAPHY

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