Radiotherapy-induced plasticity of prostate cancer mobilizes stem-like non-adherent, Erk signaling-dependent cells.


Abstract

Fractionated ionizing radiation combined with surgery or hormone therapy represents the first-choice treatment for medium to high-risk localized prostate carcinoma. One of the main reasons for the failure of radiotherapy in prostate cancer is radioresistance and further dissemination of surviving cells. In this study, exposure of four metastasis-derived human prostate cancer cell lines (DU145, PC-3, LNCaP and 22RV1) to clinically relevant daily fractions of ionizing radiation (35 doses of 2 Gy) resulted in generation of two radiation-surviving populations: adherent senescent-like cells expressing common senescence-associated markers and non-adherent anoikis-resistant stem cell-like cells with active Notch signaling and expression of stem cell markers CD133, Oct-4, Sox2 and Nanog. While a subset of the radiation-surviving adherent cells resumed proliferation shortly after completion of the irradiation regimen, the non-adherent cells started to proliferate only on their reattachment several weeks after the radiation-induced loss of adhesion. Like the parental non-irradiated cells, radiation-surviving re-adherent DU145 cells were tumorigenic in immunocompromised mice. The radiation-induced loss of adhesion was dependent on expression of Snail, as siRNA/shRNA-mediated knockdown of Snail prevented cell detachment. On the other hand, survival of the non-adherent cells required active Erk signaling, as chemical inhibition of Erk1/2 by a MEK-selective inhibitor or Erk1/2 knockdown resulted in anoikis-mediated death in the non-adherent cell fraction. Notably, whereas combined inhibition of Erk and PI3K-Akt signaling triggered cell death in the non-adherent cell fraction and blocked proliferation of the adherent population of the prostate cancer cells, such combined treatment had only marginal if any impact on growth of control normal human diploid cells. These results contribute to better understanding of radiation-induced stress response and heterogeneity of human metastatic prostate cancer cells, document treatment-induced plasticity and phenotypically distinct cell subsets, and suggest the way to exploit their differential sensitivity to radiosensitizing drugs in overcoming radioresistance.

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