TITLE

Cancer Stem Cells and the drug recalcitrance paradigm

ABSTRACT

The primary characteristics of adult stem cells of prolonged quiescence, self-renewal and plasticity to differentiate into multiple cell types are evolutionarily conserved from fruit fly to humans. The first proof-of-concept for similar capabilities in cancer was provided from Prof. John Dick's group through the isolation of leukemic stem cells in 1994. Almost a decade later subsequent studies led to identification of cancer stem cells and tumor-initiating cells (TICs) in solid malignancies capabile of quiescence, self-renewal, differentiation and tissue regeneration. A surge of interest in these populations has recently identified their contribution to tumor heterogeneity. Our efforts in elucidating the basic biology and regulatory mechanisms has revealed tumors as being dynamically evolving biological systems through acquisition of phenotypic, cellular, molecular and functional heterogeneity driven by such TICs. This identification opens up possibilities of precision monitoring of regeneration in residual tumor cell fractions after drug treatment. We thus put forth and tested a set of marker- independent principles using flow cytometry that can be applied to resolve different cell groups that are integral tumors and which include host cells, components of tumor regenerative hierarchies, evolving tumor cell populations with intrinsic genetic instability, and differential cycling tumor populations cells within a tumor. The regenerative potential of each of these populations provides a real-time definition of recalcitrant malignant disease, and can be applied in basic and applied research. We have thus developed an analytical tool for predicting drug efficacies by profiling perturbations within discrete tumor cell subsets in response to different drugs and candidates. The same possibility can be a 'paradigm shift' in the current drug design, screening and development pipeline and personalized medicine.