Therapeutic targeting of distinct subsets of cancer stem cells within triple negative breast cancers

Diana J Azzam
Miller School of Medicine, USA

Breast cancer is a leading cause of death in women, due primarily to metastatic disease rather than the primary tumor. Triple-negative breast cancers (TNBC) do not express estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER2) and this aggressive histological subtype has limited treatment options and very poor prognosis following progression to disease recurrence after standard adjuvant chemotherapy regimens. Thus, there is an urgent clinical need to identify new therapeutic targets in order to improve the outcome for these patients. Increasing evidence suggest that cancer stem cells (CSCs) mediate therapy resistance and metastasis and may thus be responsible for cancer relapse and deaths in breast cancer patients. We have recently identified distinct subsets of CSCs in the most deadly form of TNBC cell lines and patient derived cultures. Within CD44+ populations, CD24 expression defines two subsets of CSC subpopulations: CD24neg and CD24+. CD24+ is more aggressive than CD24neg cells. CD24+ cells are highly enriched in self-renewing and tumor-initiating potential compared to their CD24neg counterparts. Most strikingly, CD24+ cells have an exclusive potential to form spontaneous metastasis from orthotopic xenografts. CD24+ showed greater motility and invasion than CD24neg, and preferential expression of gene profiles observed in breast cancers metastatic to lung, brain and bone. Here, we test the differential response of these subsets to chemotherapy and Gamma-Secretase Inhibitors (GSI). Surviving CD24+ cells were enriched by paclitaxel treatment: >80% of cells surviving at day 8 were CD24+ and survival of CD24neg progeny from CD24+ was dramatically attenuated. In contrast, the two TNBC subsets differed notably in their responses to RO4929097, a GSI in clinical trials for cancer. RO4929097 reduced the self-renewal of CD24+cells, but had no effect on proliferation or survival of CD24neg. Only CD24+-generated tumors responded to RO4929097 while the drug had no effect on tumors derived from CD24neg cells, which comprise a majority of the population in TNBC lines. This data provides rationale for further testing of combined chemotherapy and Notch-targeting drugs in the treatment of this deadly cancer. It also supports the use of CD24 as a marker in TNBCs to screen and identify new therapeutic drugs that selectively target the most aggressive CSCs.