Contribution of EMT in radiation resistance of breast cancer
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Abstract: Epithelial-Mesenchymal Transition (EMT) is a key developmental program that is often activated during cancer invasion and metastasis. EMT can be defined as a process that causes complete loss of epithelial traits such as E-cadherin expression and acquisition of mesenchymal properties, such as vimentin expression. EMT cells have stem cells properties and possess the characteristics of cell motility, invasiveness and chemotherapy resistance and these cancer stem cells may be responsible for mediating tumor metastasis and resistance to cancer treatments. However, very little is known about the role of EMT and cancer stem cells in modulating radiation response of human breast cancer cells. We compared expression levels of E-cadherin and other EMT related markers in ER-negative (MDA-MB-231 and Hs578t) and ER-positive (MCF-7) human breast cancer cells. Clonogenic cell survival assays showed that the cell lines expressing estrogen receptor (MCF-7) were more sensitive to increasing doses of radiation and had high expression of E-cadherin. In contrast, ER negative cells (MDA-MB-231 and Hs578t) had no detectable expression of E-cadherin and were more radioresistant. Clonogenic cell survival assays using MCF-M cells generated from the epithelial MCF-7 cells and expressing stable mesenchymal phenotype were more radioresistant compared to the parental MCF-7 cell line. We also transfected MDA-MB-231 and Hs578t cells with a CDH1-expression vector and isolated stable clones. These clones were selected and tested for radiosensitivity. MDA-MB-231 and Hs578t cells transfected with a control vector (pCMV) served as controls. Restoring E-cadherin expression radiosensitized the cells compared to the control vector cell line, suggesting that restoration of E-cadherin expression in mesenchymal-like cells produces a radiosensitizing effect. Our preliminary data demonstrates that EMT, detected as the loss of E-cadherin expression, may regulate tumor cell radiosensitivity, i.e. cells that have undergone EMT are relatively radioresistant compared to the lines that have retained the epithelial phenotype, which are relatively radiosensitive. Thus, there was a general correlation between EMT, based on loss of E-cadherin expression, and radioresistance. Overall, our results suggest that E-cadherin interacts with radiation and enhances the radioreponse of human breast cancer cells. Since it has been demonstrated that the process of EMT contributes to drug resistance and results in cells with CSC-like characteristics, we compared ALDH1 expression in ER positive (MCF-7) and ER negative (MDA-MB-231 and Hs578t) and transfected (MDA-MB231 CDH1 and Hs578t CDH1) cell lines. Our data shows that ALDH1 expression correlates with the ER status of the breast cancer cells, with a higher number of ALDH1+ cells in ER negative compared to ER positive cell lines. Also the transfected cell lines upon restoration of E-cadherin expression show a decrease in the ALDH1+ cell population. Our preliminary investigation leads us to believe that potentially resistant breast cancer stem cell populations appear to be overrepresented in ER negative breast cancer cell lines. Our observation concurs with clinical data that ER negative cancer are resistant to radiation therapy compared to ER positive breast cancers.