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ER+-derived breast cancer stem cells reveal a high expression of the serpin protease inhibitor PI-9.

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Introduction: Breast cancers (BC) are the major cause of death in women. More than 70% of BCs express high levels of estrogen receptor-α (ERα) and are sustained for their growth by the hormone. Estrogens seem to protect BC cells from apoptosis mediated by immunosurveillance associated with cytotoxic T lymphocytes and NK cells granzyme B release. However, the production of granzyme B inhibitor PI-9 by tumor cells causes a short-circuit in immunosurveillance's signalling. Although it has been shown the role of PI-9 in BC cells, its presence has not been investigated in tumor stem cells so far.
Methods: Cell viability was evaluated by MTT, cell cycle by propidium iodide staining; mRNA and protein levels by qPCR and western blotting. Tumorspheres from ERα+BC MCF7 cells were isolated in ultra-low attachment conditions. The higher expression of stemness markers (Nanog, Oct3/4 and Sox2) was found in tertiary tumorspheres which were used in our study.
Results: Low doses (10 nM-10 μM) of 17-β estradiol consistently increased the number of MCF7 cells more than tumorspheres, while higher doses (50-100 μM) reduced cell number as a consequence of G2/M cell cycle arrest. The analysis of ERα disclosed the presence of three different isoforms (66, 46 and 36 kDa) in MCF7 cells. In contrast, tumorspheres exhibited an increase in ERα36, which lacks transcriptional activity, while the level of ERα66 was undetectable. Then, we analyzed the level of PI-9, which is transcriptionally regulated by ERα66. Surprisingly, we found that tertiary tumorspheres, express higher levels of both PI-9 protein and mRNA than MCF7 cells.
Conclusions: Our data provided evidence that the high level of PI-9 in ER+ tertiary tumorspheres could supply a selective advantage to BC stem cells by interfering with immune-surveillance systems. Ongoing studies aim to elucidate the relationship between the levels of different ERα isoforms and PI-9 high expression in BC-stem cells.