TOWARDS IDENTIFYING KEY DRIVERS OF BREAST CANCER METASTASIS TO THE BONE

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Introduction Metastasis is the cause of death of most cancer patients and approximately 70 percent of metastatic breast cancer patients develop bone lesions. The establishment and growth of metastasis at distant sites is dependent on critical interactions between the tumour cells and the host microenvironment. Our aim is to decipher this process at the molecular level and identify factors that influence migration and invasion of breast cancer cells in the bone.

Material and methods To investigate this mechanism we cultured breast cancer cells with conditioned media derived from bone cells in culture. To best mimic in-vivo conditions, we mechanically stimulated the bone cells to release essential factors that could potentially play significant role in metastasis. As a second approach, we used Chipster software 1 to integrate and analyse publicly available gene expression repositories to identify a set of highly dysregulated genes in breast cancer patients who are highly likely to develop bone metastasis.

Results and discussions Having optimised the mechanical stimulation process and identified the best suitable media for the study, our results show that there is a significant increase in the proliferation and migration of breast cancer cells when they are maintained in media derived from mechanically stimulated bone cells. We are currently using cytokine arrays to specifically elucidate the factors in mechanically stimulated bone media that may be responsible for this. Using our second approach we have been able to identify a set of genes that we believe to be involved in breast cancer metastasis to the bone. We further selected a subset of genes and validated protein and gene expression in cell models. We are planning to investigate the expression of these genes in our patient cohort.

Conclusion Our work suggests that bone cells are releasing specific key factors which are regulating the activity of breast cancer cells and allowing them to metastasize to the bone. We have identified genes that are highly dysregulated in tumours with a higher chance of metastasizing to the bone and have verified the expression of these genes in cancer cell lines. This work will help to identify novel therapeutic targets that can prevent bone metastasis in breast cancer patients.

REFERENCE

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PO-240 TARGETING CANCER STEM CELLS IN MAMMARY TRIPLE NEGATIVE CELL LINE BY RETINOIDS AND LAPATINIB TREATMENTS

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Introduction Cancer stem cells (CSC) are resistant to chemotherapy and radiation and they are also considered as ‘metastasis seed’.

In order to suggest CSCs as a new therapeutic-intervention target, in this work we propose to study the effect of retinoid ATRA (differentiation therapy) and HER2 inhibitor Lapatinib treatment on:

A. Expression profile of pluripotent genes, retinoid receptors system and E-Cadherin levels.

B. In vitro growth, invasive capacity and in vivo metastatic potential.

For this purpose, we use the triple negative murine cell line 4 T1 (tumorigenic and metastatic in BALB/c mice). Previously we corroborate that CSC from 4 T1, MCF7 and T47D (both these last, HER2 negative human breast cell lines), express HER2 only in that cell component.

Material and methods

- Experimental Model: triple negative murine cell line 4 T1 (tumorigenic and metastatic in BALB/c mice).
- Treatments: ATRA (1 μM) and Lapatinib (1 μM)
- RT-qPCR were used to evaluate retinoic acid receptors and pluripotential genes expression- Mammoxpheres culture was used to enrich in CSC component.
- Clonogenic assay was performed by seeding CSC in low density
Invasive capacity was evaluated using Matrigel-coated transwells.

Results and discussions Through RT-qPCR, we could observe that ATRA (1 μM) and Lapatinib (1 μM) treatments, separately or in combination, were able to increase retinoic acid receptors RARα and RARγ and decrease RARβ receptor levels. Moreover, the same treatments induced an increment in E-Cadherin and reduced the expression of main pluripotential genes: NANOG, OCT4 and SOX2. Combination treatment induced growth inhibition in 4 T1 mammospheres and in their clonogenic capacity. Regarding parameters associated with malignant progression using Matrigel-coated transwells, we detect that combined treatment increase CSC invasive capacity, however in experimental metastases assays with pretreated-CSC, treatments separately or in combination significantly decreases lung colonization.

Conclusion Treatments with both ATRA and Lapatinib were able to induce CSC differentiation and reduced their lung nesting ability, leading to a less malignant phenotype.

PO-241 PROGNOSTIC FACTORS FOR OPERABLE BILIARY TRACT CANCER: SERUM LEVELS OF LACTATE DEHYDROGENASE: A STRONG ASSOCIATION WITH SURVIVAL

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Introduction Biliary tract cancers (BTCs) are uncommon but fatal. In the United States in 2017, the estimated numbers of new cancer cases from gallbladder and other biliary tissue was 11 740 (5,320 in males; 6420 in females) and the estimated number of deaths was 3830 (1,630 in males; 2200 in females). Tumours of the biliary tract typically have a poor prognosis, with 5 year survival rates in the range of 5%–15%. BTCs encompass gallbladder carcinoma (GBC), distal bile duct (DBD), intrahepatic (IHC), and hilar cholangiocarcinoma. This study was designed to investigate the prognostic factors for operable BTC.

Material and methods Baseline demographics at diagnosis were retrospectively evaluated in 341 BTC patients undergoing radical surgery from January 2011 to December 2015. The association between prognostic factors and overall survival (OS) was determined by multivariate analysis using the Cox proportional hazards regression model.

Results and discussions Our study showed that 341 patients were included in the analysis, of which 166 (48.7%) were male and 175 (51.3%) were female. Older age, depth of tumour invasion, positive surgical margin, lower haemoglobin, and higher lactic dehydrogenase (LDH) were associated with significantly worse OS using multivariate analysis. In the entire cohort, the estimate of median OS in patients with LDH<271 U/L was 36.291 months (95% confidence interval (CI); 30.899–41.594 months), and 30.736 months (95% CI; 29.154–42.318 months) in patients with LDH≥271 U/L (adjusted hazard ratio (HR)–1.505, 95% CI; 1.009–2.245, p=0.045). Moreover, it was investigated whether serum LDH retained its significance as a prognostic marker in BTC subgroups separately. The results showed that LDH was prognostic in patients with distal bile duct (DBD) carcinoma undergoing radical surgery (HR-2.452, 95% CI; 1.167–5.152, p=0.018). However, there were no statistical differences between LDH and OS in multivariate analysis in the other three individual subgroups except for DBD. This may be due to the limited number of patients in the study, indicating that a greater number of patients may be required for statistical significance.

Conclusion Older age, depth of tumour invasion, positive surgical margin status, lower haemoglobin levels, and elevated serum LDH level are associated with poor survival in operable BTC patients. Serum LDH level is a cost-effective prognostic biomarker in patients with operable BTC and especially DBD carcinoma.