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Citation	The 2015 Global Breast Cancer Conference (GBCC 2015) and 4th International Breast Cancer Symposium (IBCS), Jeju Island, South Korea, 23-25 April 2015. In abstracts Book, 2015, p. 395-396
Issued Date	2015
URL	http://hdl.handle.net/10722/215354
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Prostaglandin E2 Receptor Regulates Metastasis and Stem-Cell Like Properties in Triple-Negative Breast Cancer Through SCL19A3

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Background/Purpose: Majority of *BRCA1* mutation-associated tumors share phenotypic similarity to triple-negative breast cancer (TNBC), understanding the biology of TNBC may improve management of these patients. TNBC is associated with increased risk of metastatic disease and poor prognosis. Prostaglandin E (EP) receptors have been associated with tumor metastasis, however, the contribution on cancer stem cell compartment remains unstudied.

Methods: EP2 was predominantly expressed in human primary tumor tissues. A stable EP2-expression cell line was used to study tumorigenesis and distant metastasis in metastatic breast cancer mice model. Larger tumors and more distant metastasis were seen in MD-231-EP2 bearing mice when compared with control. Characterization of EP2 receptor on cell proliferation, flow cytometry and invasion were performed in transfected cells. Profiles of drug transporters and epithelial–mesenchymal transition (EMT) genes were compared. Tumorsphere assay was used to examine the stem-cell like properties.

Results: EP2 siRNA or antagonist (AH6809) retarded cell proliferation and invasion. Upregulation of SLC19A3 and downregulation of ZEB1 and Twist were observed by blocking EP2. There was an inverse correlation between EP2 and SLC19A3 in primary tumors. Overexpression of SLC19A3 retarded breast cancer growth and EMT phenotype. Enhanced expression of Aldehyde dehydrogenase (ALDH) (cancer stem cell marker) was seen in xenograft tumors. Twist and ALDH expression were increased in tumorspheres and the ALDH activity was reduced by blocking EP2. Twist expression was higher in breast cancer patients and was associated with ALDH expression.

Conclusion: Taken together, EP2/SLC19A3 signaling axis regulates metastasis and



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stem-like cell properties in TNBC. These findings suggest that targeting EP2 receptor offers a therapeutic strategy for TNBC.

**Poster
Exhibition**