Miranda-Carboni GA et al., Madridge J Cancer Stud Res. 2019
http://dx.doi.org/10.18689/2640-5180.a4.005

madridge CONFERENCES

4th International Cancer Study & Bacteriology Conference

April 3-4, 2019 Philadelphia, USA

Simultaneous Visceral Metastases from Chemoresistant Triple-Negative Breast Cancer is Prevented by Interfering with WNT-Signaling

Miranda-Carboni GA*, Fatima I, El Ayachi I, Seagroves TN and **Krum SA**
UTHSC Center for Cancer Research Memphis, USA

Triple negative breast cancers (TNBCs) evolve to highly chemoresistant subtypes in response to chemotherapy and that frequently metastasize to various organs simultaneously. TNBCs are devoid of a specific-targeted therapy and are active for a WNT10B-network that drives metastasis. Here we demonstrate that WNT inhibition decreased proliferation on multiple TNBC breast cancer cell lines and TNBC PDX tumor-derived cell lines, *in vitro*. The WNT inhibitor ICG-001/PRI-724 led to loss of protein expression of the WNT10B/β-CATENIN direct targets HMGA2, EZH2, AXIN2, MYC, PCNA and CYCLIN D1. In addition, ICG-001 decreased transwell migration assays, correlating with the loss EMT markers VIMENTIN and SNAIL and decreased wound healing capacity. *In vivo,* in chemoresistant patient-derived xenograft (PDX) models of TNBC and MDA-MB-231 cells, we observed similar frequencies of simultaneous visceral metastasis to the lymph node and lungs, but not to the brain, bone, ovaries and liver and WNT-therapy blocked whole body metastasis. Micro-computed tomography (μCT) analysis of bone metastasis from the TNBC PDX model demonstrated differential osteolytic properties than that of the MDA-MB-231 cells, *in vivo*. ICG-001 synergized with doxorubicin, but not with cisplatin-based therapy in the TNBC PDX-derived cells *in vitro*. Mechanistically, loss of protein expression of WNT10B-network genes and EMT-makers was observed in the primary tumors. Moreover, WNT-inhibition sensitized the doxorubicin response, preventing simultaneous visceral metastases to the bone, liver and ovaries in the TNBC PDX tumors. We suggest that WNT-inhibition can sensitize and lower dosages of FDA-approved anthracycline-based therapies to treat simultaneous visceral metastasis of TNBC.