Abstract 510: Targeting metabolic vulnerabilities to reduce triple negative breast cancer health disparities

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Abstract

Triple negative breast cancer (TNBC) occurs in 10-15% of all breast cancer (BC) patients, yet it accounts for almost half of all BC deaths. Women of African ancestry (WAA) are twice as likely as women of European Ancestry (WEA) to be diagnosed with advanced TNBC with worse prognosis. Emerging data shows that insulin resistance and high circulating levels of insulin are more prevalent in WAA with invasive BCs than in WEA, and activation of the AKT/mTOR pathway by insulin may occur in aggressive TNBC. Reports show diabetic patients treated with metformin, a biguanide drug used to treat diabetes type 2, have reduced incidence of BC and improved survival. However, anticancer actions of metformin require use of high drug doses with limiting side effects in vivo. To address this challenge, we used a structure-activity strategy to develop biguanide analogues with more potent anticancer action and safety at lower doses in vivo. Using TNBC cell proliferation in vitro to screen analogues, promising candidates were identified that exerted dose-dependent inhibition of cell proliferation at significantly lower doses than that of parental metformin ($P<0.01$). As antitumor effects of metformin are attributed in part to activation of LKB1-AMPK pathways, we find that biguanide analogues also strongly induce AMPK phosphorylation on Western immunoblots and significantly reduce phosphorylation of downstream mTOR signaling pathway components including p70S6K, S6 ribosomal protein and 4E-BP1. Further, analogues induce TNBC cell apoptosis in vitro at lower doses than metformin. In vivo, analogues were more effective than metformin in stopping human TNBC xenograft progression in nude mouse models ($P<0.001$). Notably, analogues were also more effective than metformin at blocking lung metastases in syngeneic murine 4T1 TNBC models ($P<0.05$). Transcriptome analyses comparing mammary tumors and lung metastases revealed that analogue JD006 down-regulated genes related to oxidative phosphorylation in lung metastases treated with JD006 and increased expression of genes related to T-cell activation. Further, gene expression in tumors treated with JD006 showed significant down-regulation of long non-coding RNAs that associate with the up-regulation of malignant transformation and activation of M1 macrophages. Importantly, our data indicate that analogue JD006 modulates the activity/trafficking of myeloid-derived suppressor cells (MDSC) and tumor infiltrating lymphocytes (TIL) that may significantly impact TNBC responses to immune checkpoint inhibitors. Further understating of potential biologic differences between TNBC of WAA and WEA is needed to design more effective therapeutic strategies to reduce TNBC health disparities. New targeted treatments could be beneficial for patients afflicted with this deadly disease. (Funding: CBCRP B27IB3869, 4IB-0058; NCI U54 CA143930; JCCC BC Award, Team Research Grant; UCLA TDG).

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