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Targeting the epigenome with BET inhibitors modifies stemness landscape in triple negative breast cancer

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Background: Triple negative breast cancer (TNBC), whose therapeutics options are limited to standard chemotherapy, are enriched in cells with stem-like features (CSC). For this reason, targeting stemness could be an interesting approach to treat this breast cancer subtype. Epigenetic machinery is crucial for the maintenance of the stemness phenotype. As the family of epigenetic readers BET are emerging as novel targets for cancer and have shown preclinical effect in breast cancer, in this work we intend to evaluate the effect of the BET inhibitor (BETi) JQ1 on stemness in TNBC.

Methods: To identify stemness-related genes targeted by JQ1, MDA-MB-231 were treated with JQ1 and transcriptomic analyses were performed using Affymetrix Transcriptome Array. Results were confirmed by qPCR in MDA-MB-231, MDA-MB-231-derived spheroids and spheroid-derived tumours (preclinical *in vivo* model). To investigate the effect of BET inhibition on TNBC stemness properties, limiting dilution assays, matrigel invasion experiments, immunofluorescence staining and flow cytometry studies were performed using MDA-MB-231 spheroids. For the outcome analysis, we took advantage of the online tools Kaplan-Meier Plotter and an integrated response database to study the relationship between the identified stemness genes and patient's prognosis and patient's response to chemotherapy, respectively.

Results: In this work, we demonstrate that the BETi JQ1 can modify the expression of stemness-related genes in TNBC. Among others, *CD44/CD24* ratio and *ALDH1A1* expression, both classical stemness markers, were diminished by JQ1. Also, using a validated spheroid model, which better mimicked the intrinsic characteristics of CSC, we show that JQ1 decreased surface expression of CD44, self-renewal and invasion capabilities, and induced cell cycle arrest in G0/G1, therefore altering stemness phenotype in TNBC. Our results also associate four of the identified stemness genes, *GJA1, CD24, EPCAM,* and *SOX9*, with worst patients' outcome in TNBC. Last, *in silico* analysis uncovered that another two of the stemness-related genes decreased by JQ1, *ABCG2* and *RUNX2*, predicted low response to chemotherapy in TNBC patients.

Conclusions: In this article, we propose a novel role for the BETi JQ1 as a stemness-targeting drug. Accordingly, BET inhibition modifies stemness landscape in TNBC by impacting its associated features.

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