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Cancer stem-like cells (CSC) induce aggressive tumor phenotypes such as metastasis formation, which is associated with poor prognosis in triple-negative breast cancer (TNBC). Repurposing of FDA-approved drugs that can eradicate the CSC subcompartment in primary tumors may prevent metastatic disease, thus representing an effective strategy to improve the prognosis of TNBC. We have investigated spheroid-forming cells in a metastatic TNBC model. This strategy enabled us to specifically study a population of long-lived tumor cells enriched in CSCs, which show stem-like characteristics and induce metastases. To repurpose FDA-approved drugs potentially toxic for CSCs, we focused on pyrvinium pamoate (PP), an anthelmintic drug with documented anticancer activity in preclinical models. PP induced cytotoxic effects in CSCs and prevented metastasis formation. Mechanistically, the cell killing effects of PP were a result of inhibition of lipid anabolism and, more specifically, the impairment of anabolic flux from glucose to cholesterol and fatty acids. CSCs were strongly dependent upon activation of lipid biosynthetic pathways; activation of these pathways exhibited an unfavorable prognostic value in a cohort of breast cancer patients, where it predicted high probability of metastatic dissemination and tumor relapse. Overall, our studies describe a new approach to target aggressive CSCs that may substantially improve clinical outcomes for patients with TNBC, who currently lack effective targeted therapeutic options.

References:
Keywords: breast cancer, cancer progression, metastasis, stem cell biology, molecular markers of metastasis and progression, cancer metabolism, lipid anabolism, mitochondria, OxPHOS, computational methods, gene expression profiling, molecular modeling.

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