Mechanistic insights on the anticancer effects of metformin in primary breast cancer cells.

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Metabolic disorders, like obesity, type 2 diabetes (T2D) and metabolic syndrome, have been implicated in breast cancer (BC) progression. In this regard, insulin has been shown to promote mitogenic and metastatic responses in BC through diverse signaling pathways. Moreover, high levels of insulin and elevated expression of its cognate receptor, namely insulin receptor (IR), have been associated with increased BC incidence, resistance to treatments and poor outcome. Metformin (1,1-dimethylbiguanide hydrochloride) is the most commonly prescribed drug for T2D treatment worldwide. Worthy, metformin has been shown to interfere with BC cell growth. In order to provide novel insights through which metformin can elicit anti-cancer responses in BC, we performed bioinformatics analysis as well as TaqMan Gene Expression Assay, flow cytometry, immunofluorescence, immunoblots, 2D and 3D proliferation assays and motility experiments. A naturally immortalized BC cell line (namely BCAHC-1) and important components of the tumor microenvironment, like cancer-associated fibroblasts (CAFs) derived from BC patients, were used as model systems. We found that metformin inhibits the activation of main transduction pathways, the gene expression changes and the proliferative effects induced by insulin in BCAHC-1 cells. Moreover, metformin prevented the insulin-stimulated induction of CXC chemokine receptor 4 (CXCR4), which has been involved in BC metastatic dissemination. Next, metformin suppressed the invasion of CAFs triggered through CXCR4 by insulin stimulated BCAHC-1 cells. Our findings may suggest novel transduction mechanisms involved in the inhibitory effects elicited by metformin in both BC cells and CAFs.