The antipsychotic drug penfluridol displays cytotoxicity in breast cancer cells by inducing mitochondrial damage and activating the endoplasmic reticulum stress response

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Breast cancer (BC) is the most diagnosed cancer and the 2nd leading cause of cancer mortality. Brain metastasis is detrimental since most of the available treatments fail to reach the central nervous system (CNS). Drug repurposing by reducing the time and costs required for de novo drug discovery, represents a promising approach in cancer therapy. Psychotropic drugs have been widely exploited owing to their safety and long clinical use. Herein, based on our previous screening, we investigated in BC cells the cytotoxic activity of the commercially available psychotropic drug penfluridol (PF). Notably, PF displayed a 24 h IC_{50} of 5 μM in human estrogen receptor-positive MCF7 cells and estrogen receptor-negative MDA-MB-321 cells. Also, 0.5 μM PF treatment significantly inhibited the clonogenicity of stem-like BC cells. Besides, 16 h pretreatment with PF 5 μM sensitized by 50% BC cells to doxorubicin.
Because of the cationic amphiphilic nature of PF, we investigated the mitochondrial activity of BC cells in response to PF treatment. We observed a significant decrease in the mitochondrial membrane potential, while oxygen consumption rate results revealed a compromised mitochondrial activity and the inhibition of nearly all mitochondrial complexes. Investigation of the integrated stress response—as a response to mitochondrial dysfunction— disclosed the phosphorylation of IRE1α and eIF2α already after 3 h of treatment with PF 5 μM along with an increase in ATF4 protein levels. mRNA analysis unveiled increased DDIT3/CHOP expression while immunofluorescence displayed nuclear localization. Proteomic data showed cell cycle block, DNA damage, and altered cell metabolism. Ongoing metabolomic analysis aims for a comprehensive understanding of PF activity.
In conclusion, our data support the repurposing of PF for BC treatment, and, considering PF localization in the CNS, our findings are a promising starting point for the management of BC patients undergoing brain metastasis.