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Response of glioblastoma cells to activation of the G-protein coupled estrogen receptor, GPER1/GPR30, and possible crosstalk with the aryl hydrocarbon receptor.

Glioblastomas are almost invariably fatal brain tumors. Glioblastoma incidence in men is 1.5 times that of pre-menopausal women and this difference decreases post-menopause. Therefore estrogen is thought to play a protective role, although the mechanism is not well understood. Glioblastomas produce and respond to a tryptophan derivative, kynurenine, that binds and activates the aryl hydrocarbon receptor (AHR). Promiscuity of ligand binding can result in cross talk between AHR and nuclear estrogen receptors and both receptor types are known to use the p300 acetyltransferase as a cofactor. We demonstrated that inhibition of p300 resulted in a reduction of proliferation of CH157-MN meningioma cells. Treatment with β-estradiol or kynurenine partially abrogated this effect, suggesting both ligands may act through another receptor that we hypothesize to be the G-protein linked estrogen receptor, GPER1/GPR30. We verified the expression of GPER1, estrogen receptor β; some estrogen receptor β isoforms and AHR by CH157-MN cells and U-87 and A-172 glioblastoma cells. Inhibition of p300 with C646 reduced proliferation of both U87 and A172 cells. In U87 cells, this effect was abrogated by co-treatment with β-estradiol, the xenobiotic AHR agonist 2',3',7,8'-tetrachlorodibenzo-p-dioxin, and the GPER1 agonist G-1. Exogenous kynurenine did not abrogate the effect of p300 inhibition. However, in A172 cells, none of the agonists abrogated the effect of p300 inhibition, possibly due to the higher kynurenine production in A172 cells. Treatment of A172 and U87 cells with G-1 resulted in decreased cell proliferation which was abrogated by co-treatment with the GPER1 antagonist G-36.