Reviewer's report

Title: Differential modulation of nicotine-induced gemcitabine resistance by GABA receptor agonists in pancreatic cancer xenografts and in vitro

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Reviewer: Davide Melisi

Reviewer's report:

I read with great interest the manuscript by Jheelam Banerjee and colleagues entitled: “Differential modulation of nicotine-induced gemcitabine resistance by GABA receptor agonists in pancreatic cancer cell xenografts and in vitro”

The authors showed that in xenografts mice models of pancreatic cancer, GABA significantly reversed gemcitabine resistance, induced by low dose of nicotine, respect to baclofen. The effect of GABA was accompanied by decreases in cAMP, p-CREB, p-AKT, p-Src, p-ERK metalloproteinases-9 and -2 and EGR-1 and increases in cleaved caspase-3 in xenograft. Pancreatic cancer cells exposed in vitro to single doses of nicotine induced the protein expression of MMP-2, MMP-9 and EGR-1 and these responses were blocked by GABA. Moreover baclofen downregulated the protein expression of GABA-B-Rs in both in vitro and in vivo. This response was accompanied by inversed baclofen effects from inhibition of cAMP formation after single dose exposures to stimulation of cAMP formation in cells pretreated for seven days. Therefore, the authors suggest GABA as agent to overcome nicotine-induced gemcitabine resistance in pancreatic cancer.

This present manuscript maintains continuity with other paper already published by the same group in which they reported that high doses of nicotine comparable to the blood nicotine levels in heavy smokers accelerated the progression of pancreatic cancer xenografts by increasing cell proliferation and that treatment of the mice with GABA in the drinking water blocked this effect via GABA-B-receptor (GABA-B-R)-mediated inhibition of cAMP-dependent pathways. Moreover the authors already showed that low dose undergoing NRT failed to increase cell proliferation-mediated pancreatic cancer xenograft progression but instead induced gemcitabine resistance by modulating apoptotic pathways.

Major Compulsory Revisions

I would suggest to add statistical analyses throughout all of the experiments presented. It would be interesting also to see if the reduction in tumor volume translated in increased mice survival in Fig1.

In figure 5, please revise the x-axis legend
Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests