ARYL HYDROCARBON RECEPTOR EXPRESSION CHANGES IN GEMCITABINE-RESISTANT PANCREATIC CANCER CELLS

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Pancreatic ductal adenocarcinoma (PDAC) is a devastating disease and the sixth leading cause of cancer related deaths globally. The poor disease prognosis is a result of late diagnosis and limited therapeutic options. Due to late diagnosis systemic treatment with chemotherapy is usually the only option [1]. Gemcitabine (GEM) is the gold standard first-line single chemotherapy agent for pancreatic cancer [2]. Aryl-carbon receptor (AhR), a ligand-activated transcription factor. AhR is expressed in several tumor cells and regulates the expression of genes in the signal transduction pathways [3]. Elevated AhR levels in PDAC patients correlate with worse outcomes [4]. There are speculations that AhR can be linked the gemcitabine resistance, however, the role of AhR in modulating gemcitabine sensitivity and the development of gemcitabine resistance is not fully understood.

This research aims to assess alterations in AHR expression and gemcitabine IC_{50} values in gemcitabine-resistant pancreatic cancer cells.

This study used commercial pancreatic cancer cell lines Su.86.86 and BxPC-3. Cells planted in 96-well plates were treated with increasing doses of gemcitabine to measure gemcitabine resistance both before and after resistance development. IC_{50} values were computed by linear regression analysis, and cell metabolic activity was assessed using the resazurin reduction test. The expression of AHR mRNA was assessed before and after resistance acquisition. TaqMan probes were used in real-time PCR analysis after RNA was extracted using column-based kits and reverse-transcribed to cDNA. Using the $2^{-}\Delta\Delta Ct$ technique, relative gene expression changes were computed.RT-qPCR $2^{-}\Delta\Delta Ct$ analysis showed reduced basal AHR expression in gemcitabine-resistant pancreatic cancer cells compared with non-resistant cells.

Relative AHR expression was 0.578 in resistant BxPC-3 cells and 0.459 in resistant SU.86.86 cells. Treatment with IC_{50} doses of gemcitabine increased AHR expression in both resistant and non-resistant cells in both cell lines. Despite this induction, gemcitabine-resistant cells demonstrated considerably higher IC_{50} values than non-resistant cells. IC_{50} values increased from 27 nM to 1856 nM in BxPC-3 cells and from 37 nM to 24 268.9 nM in SU.86.86 cells.

Pancreatic cancer cells with acquired gemcitabine resistance exhibit decreased basal AHR mRNA expression, even though IC_{50} doses of gemcitabine induce AHR similarly, indicating a link between low AHR levels and resistance to gemcitabine in resistant cells

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