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Metformin-Cisplatin Combination Treatment Alters mRNA Expression of Hexokinase II Gene in LNCaP and PC3 Prostate Cancer Cell Lines

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Aim of the study: Metformin is an antidiabetic drug with anticancer properties. Cisplatin is known as one of the most potent chemotherapeutics for treatment of various types of cancer. In order to overcome cisplatin resistance and toxicity, the drug can be combined with other chemotherapeutics that sensitize tumour cells to cisplatin. The ability of metformin to potentiate cisplatin-mediated killing of cancer cells in vitro, makes it a plausible candidate for combination with cisplatin-based therapy. The aim of this study is to examine the combined effect of these drugs on mRNA expression of Hexokinase II gene participating in glycolysis as well as cancer promotion.

Material and Methods: The effects of drugs on prostate cancer cell lines were analysed using androgen dependent LNCaP and androgen independent PC3. LNCaP and PC3 cell lines were cultured in RPMI-1640 medium and Ham's F12 medium with containing 10% fetal bovine serum (FBS), 1% L-glutamine and 1% penicillin-streptomycin solution, respectively. Cells were treated with either metformin alone in the range of 1–10 mM, cisplatin alone or a combination of these two drugs. Cytotoxicity of drugs were determined with Alamar Blue Assay and IC50 was calculated. The effects of drugs on mRNA expressions were determined by q-RT PCR technique and results were normalized with GAPDH as an internal reference. Statistical analyses were performed by using GraphPad Prism version 6 statistical software package for Windows. All results were expressed as means with their Standard Deviation (SD). Unpaired, two-tailed ANOVA test and $p<0.05$ were chosen as the level for significance.

Results: IC50 values of cisplatin were calculated for each cell line and found to be 17μM for LNCaP and 30μM for PC3 cell line. Both alone or combination of drugs were inhibited the proliferation of LNCaP and PC3 cells in a concentration dependent manner. Hexokinase II mRNA expressions were significantly downregulated ($p=0.05$) in metformin/cisplatin treated cells compared to control groups. This study suggest that metformin and/or cisplatin combination may decrease the tumour promotion as well as glucose utilization of LNCaP and PC3 cells by downregulating Hexokinase II gene expression. In addition to its anticarcinogenic properties, adjuvant role of metformin may be investigated in combination therapy for different cancer types.

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