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Effects of Starvation, Glucose Treatment and Metformin on Resistance in Chronic Myeloid Leukemia Cells

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Abstract : Chemotherapy is widely used for the treatment of cancer. Doxorubicin is an anti-cancer chemotherapy drug that is classified as an anthracycline antibiotic. Antitumor antibiotics consist of natural products produced by species of the soil fungus Streptomyces. These drugs act in multiple phases of the cell cycle and are known cell-cycle specific. Although DOX is a precious clinical antineoplastic agent, resistance is also a problem that limits its utility besides cardiotoxicity problem. The drug resistance of cancer cells results from multiple factors including individual variation, genetic heterogeneity within a tumor, and cellular evolution. The mechanism of resistance is thought to involve, in particular, ABCB1 (MDR1, Pgp) and ABCC1 (MRP1) as well as other transporters. Several studies on DOX-resistant cell lines have shown that resistance can be overcome by an inhibition of ABCB1, ABCC1, and ABCC2. This study attempts to understand the effects of different concentration levels of glucose treatment and starvation on the proliferation of Doxorubicin resistant cancer cells lines. To understand the effect of starvation, K562/Dox and K562 cell lines were treated with 0, 5 nM, 50 nM, 500 nM, 5 uM and 50 uM Dox concentrations in both starvation and normal medium conditions. In addition to this, to interpret the effect of glucose treatment, different concentrations (0, 1 mM, 5 mM, 25 mM) of glucose were applied to Dox-treated (with 0, 5 nM, 50 nM, 500 nM, 5 uM and 50 uM) K562/Dox and K652 cell lines. All results show significant decreasing in the cell count of K562/Dox, when cells were starved. However, while proliferation of K562/Dox lines decrease is associated with the increasingly applied Dox concentration, K562/Dox starved ones remain at the same proliferation level. Thus, the results imply that an amount of K562/Dox lines gain starvation resistance and remain resistant. Furthermore, for K562/Dox, there is no clear effect of glucose treatment in terms of cell proliferation. In the presence of a moderate level of glucose (5 mM), proliferation increases compared to other concentration of glucose for each different Dox application. On the other hand, a significant increase in cell proliferation in moderate level of glucose is only observed in 5 uM Dox concentration. The moderate concentration level of Dox can be examined in further studies. For the high amount of glucose (25 mM), cell proliferation levels are lower than moderate glucose application. The reason could be high amount of glucose may not be absorbable by cells. Also, in the presence of low amount of glucose, proliferation is decreasing in an orderly manner of increase in Dox concentration. This situation can be explained by the glucose depletion -Warburg effect- in the literature.

Keywords : drug resistance, cancer cells, chemotherapy, doxorubicin
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