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DOCTORAL THESIS

Novel mechanism of 2DG mediated cancer treatment

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Abstract

2-deoxy-D-glucose (2DG), a non-metabolizable glucose analog, is currently being used in clinical trials to determine its efficacy in augmenting radiotherapy and chemotherapy of various cancers. It is thought to kill cancer cells by inducing glucose deprivation state. However, 2DG only inhibits glycolysis by 15-40%, not sufficient to simulate glucose deprivation. Further, 2-flour-deoxy-D-glucose (2FDG), which is a more potent inhibitor of glycolysis than 2DG, is less effective than 2DG in killing cancer cells. These observations suggest that glucose deprivation is not the mechanism by which 2DG kills cancer cells.

On the other hand, it has been shown that treatment of cancer cells with 2DG leads to increased reactive oxygen species (ROS) production, indicating that cytotoxic effect of 2DG is due to increase ROS. Our lab previously found that inhibition of aldose reductase (AR) activity attenuated 2DG-induced ROS in cardiomyocytes (Tang, et al., 2010). We therefore propose that 2DG-induced ROS increase in cancer cells is a consequence of the depletion of GSH in the process of reduction of 2DG by AR and/or by a related aldose reductase-like enzyme (ARL). These two enzymes are often overexpressed in cancer cells. This proposed project is to test our hypothesis that the cytotoxicity of 2DG is due to the depletion of GSH as a consequence of the reduction of 2DG by AR or ARL.

We found that HepG2, SKOV3, HCT116 and CaCo2 cells were sensitive to 2DG, and these cells over-express AR and/or ARL proteins. However, HT29 cells and SW480 cells, which were not sensitive to 2DG, had low level of AR and ARL proteins,

indicating that there is a close relationship between sensitivity to 2DG toxicity and the level of AR/ARL in these cells. Further, when AR/ARL activity were inhibited in HepG2, SKOV3, HCT116 and CaCo2 cells by AR/ARL inhibitors fidarestat or tolrestat, the cells were protected against 2DG cytotoxicity. Tolrestat or fidarestat significantly restored the drop of GSH levels in 2DG sensitive cancer cells induced by 2DG. On the other hand, MG-132 and bortezomib, which increased the expression of AR/ARL in HT29 and SW480 cells, made HT29 and SW480 cells more sensitive to 2DG. These experiments confirmed our hypothesis that 2DG toxicity in cancer cells was due to oxidative stress induced by AR/ARL.

2DG is not an efficient substrate for AR/ARL enzymes and it is not very efficient in killing cancer cells. Based on our hypothesis, better AR/ARL substrates should be more toxic to cancer cells that overexpress AR/ARL than 2DG. The cytotoxic effects of glyceraldehyde and diacetyl, which were better substrates for AR/ARL than 2DG, were tested. Both glyceraldehyde and diacetyl were more efficient in killing cancer cells that over-express AR and/or ARL (HepG2, SKOV3, HCT116 and CaCo2) than cancer cells with low levels of AR and ARL proteins (HT29 and SW480). Glyceraldehyde and diacetyl were more efficient in lowering the GSH level in cancer cells that over-express AR and/or ARL. In order to further develop glyceraldehyde and diacetyl as anti-cancer drugs, animal studies were carried out to determine their anti-cancer effects. Both glyceraldehyde and diacetyl significantly inhibited the tumor growth in nude mice tumor xenograft model.

In conclusion, this thesis proposed and proved that 2DG kills cancer cells by

lowering intracellular GSH levels as a consequence of its reduction by AR/ARL activities, rather than by inhibition of glycolysis. This novel mechanism predicts that better substrates for AR/ARL than 2DG would be more effective in killing cancer cells than 2DG. This was confirmed by using glyceraldehyde and diacetyl. We believe that this would lead to the development of more efficient anti-cancer drugs.

Key words: 2DG, Polyol pathway, AR, ARL, Oxidative stress, Glyceraldehyde, Diacetyl, Cancer-specific cytotoxicity.

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