

Pentose phosphate pathway inhibition induce Endoplasmic Reticulum stress and autophagy

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Pentose phosphate pathway (PPP) is a major glucose catabolism pathway that supplies the cell with a reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) and ribose-5-phosphate. NADPH is necessary for the detoxification of reactive oxygen species (ROS) and reductive biosynthesis. A key player in this pathway is the enzyme glucose-6-phosphate dehydrogenase (G6PD) that reduces NADP⁺ to NADPH, oxidizes glucose-6-phosphate and prevents ROS accumulation. Here, we show that the natural molecule 3,4',5-trihydroxystilbene-3- β -d-glucoside (Polydatin) inhibits glucose-6-phosphate dehydrogenase (G6PD). As expected, G6PD inhibition causes an imbalance in NADP⁺/NADPH ratio, leading to a redox imbalance, followed by Endoplasmic Reticulum (ER) stress, autophagy, cell cycle block and apoptosis. We have demonstrated a link between G6PD inhibition and ER stress, showing that Unfolded Protein Response mediator such as PERK and IRE-1 have a key role in inducing autophagy and apoptosis after PPP block. Moreover, combination of PPP inhibition with autophagy inhibitors, such as chloroquine, strongly potentiate cytotoxicity on cancer cells, evidencing the role of autophagy as an escaping mechanism. This results shows that double inhibition of PPP and autophagy may be an affective therapeutic strategy against cancer.

Keywords

Pentose Phosphate Pathway, PERK, IRE-1, Autophagy, Everolimus, Chloroquine