UDC 577.112.7:616

THE EXPRESSION OF COX AND NDUF GENES IN U87 GLIOMA CELLS WITH IRE1 KNOCKDOWN

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Introduction. Tumor growth is tightly associated with the endoplasmic reticulum stress response-signaling pathway and hypoxia. Multiple studies were shown that inhibition of IRE1, a central mediator of the unfolded protein response, results in a significant anti-proliferative effect in glioma growth through down-regulation of angiogenesis and proliferation processes. Mitochondrial enzymes and factors play a vital role in the regulation of cell metabolism and bioenergetics, and most of these proteins take part in the functional reprogramming of mitochondria in cancer as well as in other diseases. The aim of our study was to examine the effect of inhibition of IRE1 and hypoxia on the expression of nuclear genes encoding mitochondrial enzymes of respiratory chain in glioma cells for evaluation of their possible significance in the IRE1-mediated inhibition of glioma growth.

Methods. We used U87 glioma cells and their subline without IRE1 signaling enzyme function, transfected by dnIRE1. The expression level of COX6B1 (cytochrome *c* oxidase subunit 6b1), COX7A2 (cytochrome *c* oxidase subunit VIIa polypeptide 2), COX8A (cytochrome *c* oxidase subunit 8A) and NDUFB5 (NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5) mRNAs as well as ACTB mRNA were measured in U87 glioma cells by quantitative polymerase chain reaction.

Results and Discussion. Inhibition of IRE1 signaling enzyme function down-regulates the expression of *COX6B1*, *COX7A2*, *COX8A* and *NDUFB5* genes in U87 glioma cells in comparison with the control cells. It was also shown that hypoxia slightly suppresses the expression of NDUFB5 gene, but IRE1 knockdown eliminates hypoxic regulation of this gene. At the same time, the expression of *COX6B1*, *COX7A2*, and *COX8A* genes is resistant to hypoxia condition in both types of glioma cells.

Conclusions. Results of our investigation demonstrate that expression of all studied genes is responsible to IRE1-mediated endoplasmic reticulum stress signaling, because inhibition of IRE1 leads to significant changes in their expression in U87 glioma cells in a gene specific manner. In addition, hypoxia does not affect the expression of most of these genes. Therefore, changes in the expression level of nuclear genes encoding COX6B1, COX7A2, COX8A and NDUFB5 proteins may reflect IRE1-mediated metabolic reprogramming of mitochondria and correlate with suppression of glioma cell proliferation upon inhibition of the IRE1 enzyme function.

Acknowledgement. I would like to express my gratitude to my research supervisor Prof. Oleksandr Minchenko and also to all colleagues from Molecular Biology Department of Palladin Institute of Biochemistry for their help in experiments.