Endoplasmic reticulum stress dependent control of hypoxic regulation of gene expressions

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The endoplasmic reticulum stress and hypoxia are obligate component of tumor growth and are responsible for intensification of cell proliferation and down-regulation of apoptotic processes through genome reprogramming. We have studied effect of hypoxia on the expression of nuclear genes encoding mitochondrial proteins in wild type and ERN1 knockdown U87glioma cells. It was shown that hypoxia significantly increased the level of HIF1A protein in both wild type and ERN1 knockdown glioma cells. Furthermore, exposure of wild type U87 glioma cells under hypoxic condition led to up-regulation only smaller part of studied genes. These changes are correlated with strong up-regulation of HIF1A protein in glioma cells treated by hypoxia. At the same time, the expression of larger part of studied genes was down-regulated in wild type glioma cells. These results clearly demonstrated that there are other mechanisms of hypoxic regulation of gene expressions, in addition to HIF-mediated mechanism. We have also shown that ERN1 inhibition modified the hypoxic regulation of most studied gene expressions in gene-specific manner: removed or decreased the effect of hypoxia on the expression of most studied genes. At the same time, the hypoxic regulation of some gene expressions was similar in both wild type and ERN1 knockdown glioma cells or significantly increased. Moreover, we identified several genes which expression was resistant to hypoxia treatment in wild type glioma cells and shown that ERN1 knockdown introduced sensitivity of these gene expressions to hypoxic regulation. It is possible that endoplasmic reticulum stress reprograms genome function preferentially through ERN1 signaling pathway and modifies hypoxic regulation for elimination the toxic effects of hypoxia. The results of this study clearly demonstrated that hypoxic regulation of gene expressions in glioma cells is possibly realized through different mechanisms and preferentially modified by ERN1 signaling pathways.