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Endoplasmic reticulum stress plays an important role in tumor growth and chemoresistance

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The endoplasmic reticulum is a dynamic intracellular organelle which is remarkably sensitive to changes in cell homeostasis. Accumulation of unfolded proteins into endoplasmic reticulum leads to stress, the main purpose of which is protection of cells through maintenance of the functional integrity of this intracellular organelle. The unfolded protein response is

understood as an integrated, adaptive biochemical process that is essential for cell homeostasis and absolutely required for maintenance of normal physiological function. Furthermore, the endoplasmic reticulum stress has appeared as a major pathway in renovation of gene expression programs. Numerous data have shown that malignant tumors use the unfolding protein response as well as hypoxia-induced signaling pathways to enhance cancer cell proliferation and suppression of apoptosis under stressful environmental conditions. The rapid growth of solid tumor generates microenvironmental changes in association to hypoxia, nutrient deprivation, and acidosis, which induce cell proliferation and new blood vessels formation mainly through the activation of endoplasmic reticulum stress signalling pathways. Furthermore, the activation of these signalling pathways is important also for cancer progression, particularly the aggressiveness and chemotherapeutic resistance as well as for other types of resistance.

In this regard, the unfolded protein response signaling pathways were selected as promising cancer therapy targets because they are responsible for integrated reprogramming of the cell, including remodeling the gene expression programs, which control cell proliferation, survival, and apoptosis. However, more promising target for cancer therapy is ERN1 signaling pathway of the unfolded-protein response: ERN1 endoribonuclease and ERN1 protein kinase pathways. We have shown that inhibition of ERN1 signaling pathway by dominant-negative construct of ERN1 led to strong suppression of angiogenesis and tumor growth *in vivo* in mouse brain after intracranial implantation of U87 glioma cells expressing either the ERN1 dominant negative construct or the empty vector pcDNA. Similar results were obtained on the chorio-allantoic membrane. Moreover, the ERN1 signaling pathway is responsible for regulation of numerous gene expressions through formation of alternative splice variant of transcription factor XBP1. Therefore, this transcription factor controls the expression of endoplasmic reticulum resident chaperones, growth factors and related proteins, transcription factors, cyclins, proapoptotic factors, and many other proteins, because the inhibition ERN1 signaling pathway affects their expression levels. At the same time, we have shown that the ERN1-mediated expression of epiregulin (EREG) is controlled by ERN1 protein kinase and that silencing of XBP1 by specific siRNA did not affect epiregulin expression in glioma cells. Thus, epiregulin may contribute to glioma progression under the control of ERN1 protein kinase through the autocrine proliferation loop mediated by the growth factor through EGFR in U87 glioma cells. The ERN1-mediated control of gene expression through ERN1 protein kinase represents fundamentally new type of the regulation of gene expressions under endoplasmic reticulum stress condition and possibly in un-

stressed cells also. Therefore, the ERN1 knockdown affects the expression of numerous genes related to the regulation of apoptosis, cell proliferation and survival as well as reprograms the hypoxic regulation of most gene expressions. At the same time, inhibition of ERN1 endoribonuclease only has a stronger suppressive effect on tumor growth and decreases the invasiveness as well as increases the sensitivity of cancer cells to chemotherapy.

Conclusion. ERN1 signaling pathway of endoplasmic reticulum stress plays an important role in tumor growth and chemoresistance because its inhibition has a robust suppressive effect on malignant tumor growth and invasiveness as well as enhances the sensitivity of cancer cells to chemotherapy.