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Small-Molecule PERK Inhibitors as a Promising, Anticancer Treatment Approach

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The newest data has reported that activation of the pro-adaptive Protein kinase RNA-like Endoplasmic Reticulum kinase (PERK)-dependent Unfolded Protein Response (UPR) signaling pathway is directly implicated in the cancer development and progression. Hypoxia evokes Endoplasmic Reticulum (ER) stress conditions, that activate PERK and Eukaryotic Initiation Factor 2α(eIF2α) phosphorylation leading to enhanced translation of pro-adaptive Activating Transcription Factor 4 (ATF4). However, upon severe, long-termed ER stress conditions the pro-adaptive UPR is switched into the pro-apoptotic resulting in apoptotic death of cancer cells. The objective of the presented study was to examine the inhibitory activity of the small-molecule PERK inhibitor NCI-A146 selected from the 150 000 compounds by utilizing docking software. Evaluation of its inhibitory activity was conducted on human colon cancer cell line (HT-29), that was pretreated with NCI-A146 at a concentrations range of 3μM to 50μM for 1h, and then treated with thapsigargin (Th) for 2h to evoke ER stress conditions. Cells treated only with Th constitute a positive control; cells without any treatment a negative control. The NCI-A146 inhibitory activity was measured by the evaluation of the level of eIF2α phosphorylation using the Western blot technique. Aa a result significant inhibition of eIF2α phosphorylation was observed after treatment of HT-29 cell line via NCI-A146 ata concentration of 25μM (58%) and 50μM (70%). Thus, our results suggest small-molecule PERK inhibitors may provide a novel, targeted anti-cancer therapy.

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Biography:

Wioletta Rozpędek studied biology at the University of Lodz, Poland. She specialized in the field of neurophysiology and cell biology. Currently she is a PhD student at the Department of Clinical Chemistry and Biochemistry of Medical University of Lodz, Poland. She is working on molecular basis of cancer and neurodegenerative diseases associated with Endoplasmic Reticulum stress and activation of PERK-dependent signaling pathways. Her area of focus includes use of small-molecule inhibitors as a novel therapy against neurodegenerative diseases and cancer.