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New opportunities for use of novel, small-molecule PERK inhibitors

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The newest data reported that PERK/eIF2α/ATF4/CHOP signaling pathway, that has a dual pro-adaptive or pro-apoptotic role, has a significant impact on development and progression human diseases e.g. cancer, neurodegenerative diseases, diabetes mellitus type 2. We selected set of potential PERK inhibitors included 150,000 compounds by utilizing docking software. To evaluate their biological activity the time resolved fluorescence test was utilized. We obtained 209 compounds and their specific ability for the inhibition PERK was measured by evaluating PERK phosphorylation at a concentration range of 250 nM to 5000 nM of each inhibitor using the radioactive kinase assay. We selected 9 compounds that inhibited PERK at 1000 nM and higher concentrations and were the most suitable inhibitors for subsequent *in vitro* analysis. We utilized human neuroblastoma cell line SH-SY5Y that was treated with selected inhibitors at a concentrations range of 0.15 μM to 50 μM and with thapsigargin to evoke endoplasmic reticulum stress. Moreover, we had two positive controls: SH-SY5Y without inhibitors and without thapsigargin, and the second one without inhibitors, but treated with thapsigargin. Then, we extracted total cell proteins and measured PERK activity by evaluating the level of PERK substrate eIF2α phosphorylation using the Western blot technique. As a result, inhibitor marked number 8 had the highest biological activity and significant inhibition of eIF2α phosphorylation was noted at 25 μM and higher concentrations. In conclusion, our results suggest that use of small-molecule PERK inhibitors, as a multifunctional drug, may contribute to the development of groundbreaking anti-cancer therapy leading to apoptotic cell death of cancer cells.

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Biography

Wioletta Rozpędek studied Biology at the University of Lodz, Poland. She is specialized in the field of Neurophysiology and Cell Biology. Currently, she is a PhD student in 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 ad activation of PERK-dependent signaling pathways. Her area of focus includes use of small-molecule inhibitors as a novel therapy against Alzheimer's disease and cancer.

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