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Computational design of molecular probes targeting CD95 signaling pathway

Ivanisenko N.V.[1, 2]*, Ivanisenko V.A.[1, 2], Lavrik I.N.[1, 3]

[1] *Institute of Cytology and Genetics, SB RAS, Novosibirsk, Russia*

[2] *Kurchatov Genomic Center of the Institute of Cytology and Genetics, SB RAS, Novosibirsk, Russia*

[3] *Translational Inflammation Research, Medical Faculty, Otto von Guericke University Magdeburg, Magdeburg, Germany*

** n.ivanisenko@gmail.com*

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Motivation and Aim: There are two types of apoptosis induction: intrinsic-mediated via mitochondria and extrinsic-mediated via death receptor (DR) activation. The induction of apoptosis via CD95 is largely controlled by the Death-Inducing Signaling Complex (DISC), which is formed upon CD95 stimulation. CD95 DISC comprises oligomerized, CD95, the adaptor protein FADD, procaspases-8/10 and cellular FLICE inhibitory proteins (c-FLIP). Deregulation of the CD95 pathway is associated with multiple disease development, including cancer and neurodegenerative diseases. Computational design of molecular probes targeting CD95 platform components is of high interest to study detailed molecular mechanisms of CD95 molecular platform organization and development of new treatment approaches.

Methods and Algorithms: Virtual screening of small molecule compounds was done using GLIDE software. Molecular modeling was carried out using Rosetta and AlphaFold software. Mathematical modeling of CD95 pathway activation was carried out by solving systems of ODE with Scipy module in Python.

Results: Molecular models of the CD95 platforms for cell death initiation were reconstructed *in silico*. Small molecule compounds targeting major components of CD95 platform were predicted using virtual screening approach of large databases of chemical compounds and validated experimentally. Kinetic mathematical model was further developed to analyze the observed effects of small molecule compounds on DISC activation.

Conclusion: The developed models suggest the significant role of c-FLIP in regulating the cell death activation, molecular platform stoichiometry and activity of developed small molecules compounds.

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