DOI 10.18699/SbPCD-2018-11

Rational design of small-molecule compounds targeting CD95 programmed cell death pathway

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Key words: CD95, apoptosis, virtual screening

Motivation and Aim: There are two types of apoptosis induction: intrinsic-mediated via mitochondria and extrinsic-mediated via death receptor (DR) activation. Currently six DRs are characterized: CD95/Fas, TNF-R1, TRAILR1/2, DR3 and DR6, while CD95/Fas is one of the most studied members of the DR family. 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 accompanies a variety of tumors and neurodegenerative diseases. Currently a limited number of small-molecule agents targeting this pathway is available. Development of DISC targeting compounds is of great interest and the goal of the current work.
Methods and Algorithms: Structure-based molecular modeling techniques including molecular docking, virtual screening, homology modeling and molecular dynamics simulations combined with cellular CD95 activation assays were applied.
Results: Computer-aided design of small-molecule compounds targeting DISC proteins allowed to reveal first agents with propensity to target DISC oligomerization. Novel strategies for inhibition and activation of DISC platform by allosteric and protein-protein interaction mechanisms were proposed.
Conclusion: Combination of structure-based *in silico* and cellular experimental approaches allow to reveal lead compounds for targeting CD95 pathway and development of new anticancer and new anti-neurodegenerative drugs.
Acknowledgements: Supported by the Russian Science Foundation grant No. 14-44-00011.