Dr. Dzichenka Yaraslau

Target-specific screening of new activity modulators of human steroid hydroxylases

Abstract

Today one of the more often used targets for creation and testing of new drugs are enzymes, which participate in the metabolism of the steroids and, in particular, enzymes of cytochrome P450 system (CYPs). CYPs are heme containing proteins that participate in oxidation of various endogenous and exogenous compounds and playing important role in the metabolism of steroids, bile acids, unsaturated fat acids, phenol metabolites and in neutralization of xenobiotics (drugs, poisons). But until now in the literature systematic investigation of interaction of cytochromes P450 with any class of compounds is not provided. Accessible information is segmentary and incomplete. Having in minds all of these facts, the aim of the research was to establish new types of biological activity of modified steroids expressing pharmacological potential.

Lecture plan

1. Who we are? (short lab presentation).
2. Steroid hydroxylases — key enzymes in human body.
3. *In silico* screening of ligands.
4. Obtaining of human recombinant steroid hydroxylases.
5. Screening of ligands *in vitro* (HTS and titration).
6. Analysis of enzymes activity towards modified steroids.

Biography: PhD in Bioorganic Chemistry; In 2010 finished Belarusian State University, Physical Faculty, Biophysics department, specialty Physics (scientific production activity). From 2010 to 2013 was a PhD student, National Academy of Sciences of Belarus, specialty Bioorganic Chemistry; in 2015 defended a PhD thesis: “Physical-chemical characterization and catalytic properties of human sterol 7α-hydroxylases”. From 2010 works as senior researcher, Laboratory of Protein Engineering, Institute of Bioorganic Chemistry, National Academy of Sciences of Belarus. Delivers lectures on “Bioinformatics and computer-aided drug design“ for students of Biology Faculty of Belarusian State University and MSc students of NAS of Belarus. Scientific interests: Analysis of structure and function of complex membrane multienzyme monooxygenase systems. Computer-aided drug-design. Computer modeling of protein structures. *In silico* and *in vitro* identification of novel ligands of cytochromes P450.

Participation in projects:

1. «Substrate specificity and topological peculiarities of cytochromes P450 7A1, 7B1 and 2E1 active sites» (Belarus-Ukraine bilateral project, 2013-2015, The Belarusian Republican Foundation for Fundamental Research, **participant**)
2. «Identification of modulators of protein-protein interaction processes and transfer of redox equivalents in the system of sterol-hydroxylases» (Belarus-Lithuania bilateral project, 2013-2014, The State Committee on Science and Technology of the Republic of Belarus, **participant**)
3. «Synthesis of novel fluorescent ligands of sterol-7a-hydroxylases and sterol-14ademethylases » (2016-2018, The Belarusian Republican Foundation for Fundamental Research, **coordinator**)
4. «Target-specific screening of new activity modulators of human sterol-hydroxylases» (Belarus-Serbia bilateral project, 2018-2019, The State Committee on Science and Technology of the Republic of Belarus, **participant**)
5. «Novel photoaffine fluorescent ligands of proteins participating in metabolism and transport of steroids» (Belarus-Russia bilateral project, 2019-2021, The Belarusian Republican Foundation for Fundamental Research, **coordinator**)
6. «Complex analysis of posttranslational modifications of human cytochrome P450-dependent monooxygenases taking part in metabolism of xenobiotics» (2019-2021, The Belarusian

Republican Foundation for Fundamental Research, **coordinator**)

Selected publications:

1. Grabovec I.P., Smolskaya S.V., Baranovsky A.V., Zhabinskii V.N., **Dichenko Y.V.**, Shabunya P.S., Usanov S.A., Strushkevich N.V. Ligand-binding properties and catalytic activity of the purified human 24-hydroxycholesterol 7α-hydroxylase, CYP39A1 // J Steroid Biochem Mol Biol. - 2019. - V. 193:105416. doi: 10.1016/j.jsbmb.2019.105416.

2. Komendantova A.S., Scherbakov A.M., Komkov A.V., Chertkova V.V., Gudovanniy A.O., Chernoburova E.I., Sorokin D.V., Dzichenka Y.U., Shirinian V.Z., Volkova Y.A., Zavarzin I.V. Novel steroidal 1,3,4-thiadiazines: Synthesis and biological evaluation in androgen receptorpositive prostate cancer 22Rv1 cells. // Bioorg Chem. - 2019. - V. 91:103142. doi: 10.1016/j.bioorg.2019.103142.

3. **Dzichenka Y.U.**, Gudny E.S., Usanov S.A. Structural features of human cytochrome P450 7B1 with amino acid substitution of Phe470Ile // The Doklady of NAS of Belarus. - 2018. - Vol. 64, No4. - P. 423-431.

4.Yantsevich A.V., **Dzichenka Y.U.**, Ivanchik A.V., Shapiro M.A., Trawkina M., Shkel T.V., Gilep A.A., Sergeev G.V.,Usanov S.A. Proteomic Analysis of Contaminants in Recombinant Membrane Hemeproteins Expressed in E. coli and Isolated by Metal Affinity Chromatography // Applied biochemistry and microbiology. – 2017. – Vol. 53, No2. – P. 1-15.

5.**Dzichenka Y.U.**, Yantsevich A.V., Usanov S.A. Structural and Functional Characteristics of Oxysterol 7α-Hydroxylase with Amino-Acid Substitution R486C and Their Relation to the Appearance of Neurodegenerative Diseases // Journal of Applied Spectroscopy. - 2015. - Vol. 82, No1. - P. 91-97.

6.Tempel W., Grabovec I., MacKenzie F., **Dichenko Y.**, Usanov S., Gilep A., Park H-W., Strushkevich N. Structural characterization of human cholesterol 7α-hydroxylase // Journal of lipid research. - 2014. - jlr. M050765.

7.Yantsevich A.V., **Dzichenka Y.U.**, MacKenzie F., Mukha D.V., Baranovsky A.V., Usanov S., Gilep A., Strushkevich N. Human steroid and oxysterol 7α□hydroxylase CYP 7B1: substrate specificity, azole binding and misfolding of clinically relevant mutants // The FEBS journal. - 2014. - Vol. 281, No6. - P. 1700-1713

Shapira Michail

Comparing the binding activity of enzymes

Abstract

The problem of the scoring function is one of the main problems in computational chemistry and structural biology. Little of existing docking algorithms provide well agreed to lab-chemistry experiment data. Using the library of synthetic steroid compounds and better or less well-known protein models, we compared the binding activity of compounds and designed promising mathematical model to describe these interactions.

Biography: Master of Science in Biology, Ph.D. student (3rd year) and the Junior Researcher in National Academy ofSciences of Belarus, Institute of Bioorganic Chemistry, Laboratory of Protein Engineering. The main field of scientific interest: protein engineering, methods of molecular biology, structural bioinformatics.

Selected publications:

1. "Programmed assembly of long DNA synthons: design, mechanism, and online monitoring." Appl Microbiol Biotechnol. 2019 Sep 12. doi: 10.1007/s00253-019-10099-4.

2. "Proteomic Analysis of Contaminants in Recombinant Membrane Hemeproteins Expressed in E. coli and Isolated by Metal Affinity Chromatography." Applied Biochemistry and Microbiology, 2017, Vol. 53, No. 2