Секция «Биоинформатика»

Tyrosine phosphatase-inspired redesign of A17 catalytic antibody

Научный руководитель – Головин Андрей Викторович

Маслова Валентина Дмитриевна
Postgraduate
Московский государственный университет имени М.В.Ломоносова, Факультет биоинженерии и биоинформатики, Москва, Россия
E-mail: val_ma@mail.ru

Valentina Maslova[1,2], Alexander Zlobin[1,2,3], Andrey Golovin[1,2,3]

1) Faculty of Bioengineering and Bioinformatics, Lomonosov Moscow State University, Moscow, Russia
2) Sirius University of Science and Technology, Sochi, Russia
3) Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry of the Russian Academy of Sciences, Moscow, Russia

The development of organophosphate hydrolyzing abzymes may lead to a new generation of bioscavengers against organophosphate poisoning. Antibody A17 is able to perform the first stage of paraoxon hydrolysis, which makes it a promising target for further design. [1]

We studied the possibility of catalytic tyrosine reactivation in A17. Structural analysis of tyrosine-phosphatase enzymes showed the necessity to introduce an acidic residue in the vicinity of the catalytic tyrosine. H-Ala107 being mutated to glutamate was found to be an optimal substitution for this task. We tested conformational stability of structures with additional mutations using molecular dynamics (MD) simulations. Modelling of the H-Ala107Glu abzyme inactivation with hybrid quantum mechanics/molecular mechanics (QM/MM) simulations demonstrat lower reaction barriers. However we observed proton transfer between H-Ala107Glu and phosphoryl oxygen of paraoxone, which may complicate catalytic tyrosine reactivation.

In order to facilitate the second stage of paraoxon hydrolysis we introduced a catalytic dyad into the A17 structure (His-Glu). The resulting abzyme demonstrated possible effectiveness during QM/MM reaction simulations, having the activation barrier at 21.4 kcal/mol. In order to improve the conformational stability of new catalytic residues we searched for additional mutations using Rosetta Enzdes protocol followed by MD simulations of the resulting structures.

The reported study was funded by RFBR, project number 19-34-51043. The research is carried out using the equipment of the shared research facilities of HPC computing resources at Lomonosov Moscow State University. [2]

References

1) Smirnov I., Carletti E., Kurkova I., Nachon F., Nicolet Y., Mitkevich V.A., Débat H., Avalle B., Belogurov A.A., Kuznetsov N., Reshetnyak A., Masson P., Tonevitsky A.G., Ponomarenko N., Makarov A.A., Friboulet A., Tramontano A., Gabibov A. Reactibodies generated by kinetic selection couple chemical reactivity with favorable protein dynamics // Proc. Natl. Acad. Sci. U. S. A.– National Academy of Sciences, 2011.– Vol. 108, № 38.– P. 15954–15959.

2) Supercomputer lomonosov-2: Large scale, deep monitoring and fine analytics for the user community // Supercomput. Front. Innov.– FSAEIHE South Ural State University (National Research University), 2019.– Vol. 6, № 2.