Секция «Биоинформатика»

De novo design of protein switches

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Biomolecules govern life on Earth. To cope with any organism disorders, I as a scientist must know how they work at the molecular level and be able to manage their work. Since proteins are the main functional mechanisms of living systems, my attention is focused on them.

Almost all protein engineering so far has involved the naturally occurring proteins' modification. Once the fundamentals of protein organization and work are understood, it should be possible to design from scratch (de novo) a customized proteins' world, leading to advances in therapy and these molecular machines' deeper understanding [1].

Despite allosteric regulation of proteins is widespread in nature, its de novo design remains challenging since it requires explicit modeling of multiple states with comparable free energies. However, recent advances in this field, such as protein logic gates [2] and LOCKR systems [3-5], unleashes the potential of this method. Therefore, this work aims to design a protein switcher which depending on pH changes its shape in a controlled manner. The protein could be applied as a regulator of such vital mechanisms as transcription, apoptosis, and many signaling pathways, including cancer ones.

The protein switcher consists of two major parts: an unchanging rigid core and a flexible switcher directly participating in conformational changes. The core contains a proteolysis site, comprising amino acids that vary their protonation and charge in response to pH changes. Changes in these amino acids are perceived by the switcher through the emergence of electrostatic repulsion and steric clashes, and it acquires a new predetermined conformation to take a more favorable position for a new (protonated or deprotonated) state of the whole protein. After the moving, the proteolysis site on the core has become available for cleavage by proteases, followed by the switcher's falling away. In this regard, almost anything can be encoded in the switcher (from toxic peptides to labeled amino acids) depending on the application.

De novo design of the protein switcher is carried by the well-known Rosetta software package. Rosetta is intended for macromolecular modeling. It is a large collection of methods, written mainly in C++, allowing to measure and evaluate various physical characteristics (energy, conformational, structural, etc.) of biological macromolecules. To check the pH-dependent change in the protein switcher shape the hybrid quantum mechanics molecular mechanics (QM/MM) modeling method is used. The quantum part of the system includes the pH-susceptible core's amino acids and the rest part of the protein is considered mechanically.

The de novo designed protein switcher possesses the above-described characteristics and, in simulations, has shown a high potential for a controlled change in shape in response to pH variation leading to the proteolysis site opening in the core. In the future, it is planned to test these results experimentally, as well as the possibility of proteases' cleavage of the site.

Источники и литература

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