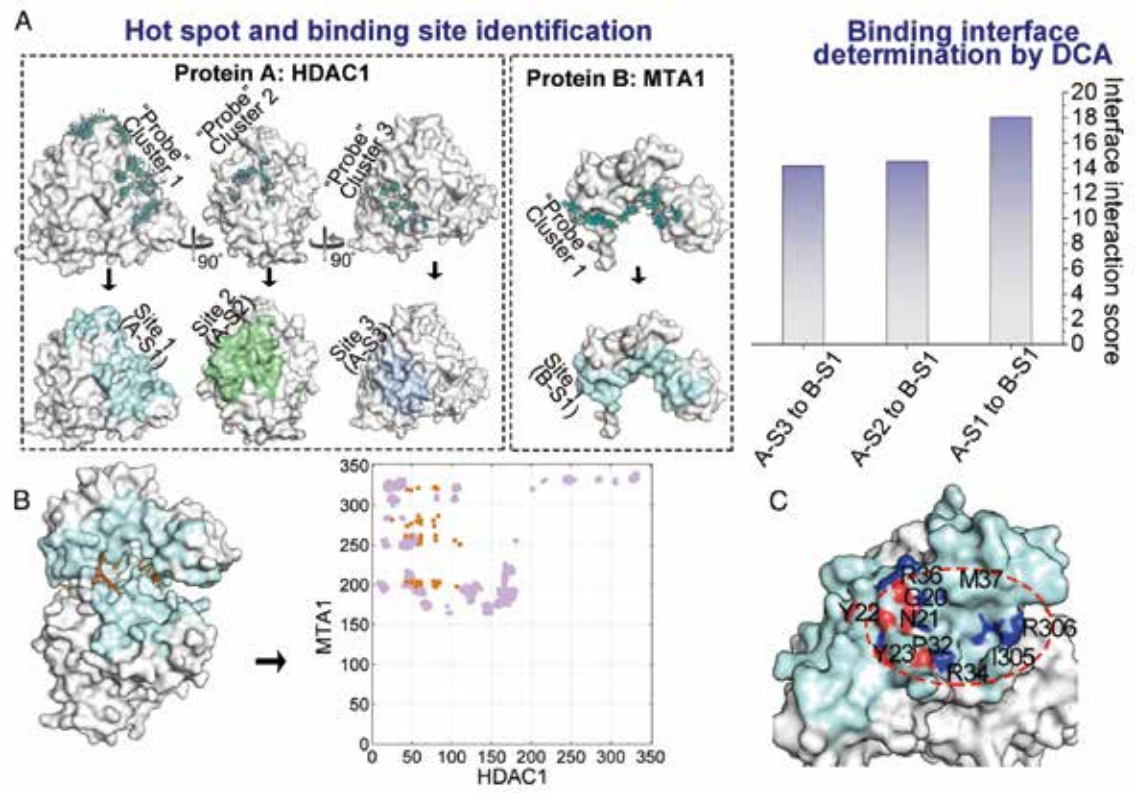
Life Science

New Computational Drug Design Method Integrates Protein-Protein Interaction Prediction and Molecular Docking

Scientists at Rice University and Shanghai Institute of Materia Medica (SIMM), CAS, have developed a computational method with dual function of predicting druggable protein-protein interaction (PPI) interface and designing molecules interfering the PPI interface.

The computational method named Fd-DCA (Fragment-docking and Direct Coupling Analysis combined) uses a series of fragment-sized organic small molecules and aminpo acid residue side chains as probes to identify hot spot regions on the protein surface by employing docking approach. The hot spots are the residue clusters that contribute the majority of the binding affinities of a protein and its partner, and spatially clustered to map out candidate binding sites on the protein surface. Then a coevolution-based interface



Prediction of the druggable heterodimer interface of histone deacetylate 1 (HDAC1)–metastasis-associated protein MTA1 by Fd-DCA. (Image by BAI Fang)

score is used to estimate the potential binding sites. This new computational approach will help researchers predict the druggable PPI interface and perform fragment-based drug design.

PPIs are major components of biological networks and play central roles in regulating cellular functions. Understanding the complex formation of PPIs finds applications in many practical areas, such as rational designing new therapeutic agents and figuring out the mechanisms governing signal transduction networks. The generally large, flat and relatively featureless binding sites of protein complexes pose many challenges for drug design.

Fd-DCA, an integrated approach using molecular fragment docking and coevolutionary analysis, is presented to face these challenges. This computational approach may accurately predict and characterize the binding sites for protein-protein interactions and provide clusters of bound fragment-sized probe molecules on the druggable regions of the predicted binding site. Therefore, Fd-DCA is potentially a useful tool for discovering novel drug candidates.

The study was conducted by members of Rice's Center for Theoretical Biological Physics led by biophysicist Prof. José N. Onuchic and medicinal chemist Prof. JIANG Hualiang at SIMM. The results have been published online in the *Proceedings of the National Academy of Sciences of the United States of America*.

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