Секция «Биоинформатика»

Virulence inhibition through quorum sensing of Pseudomonas aeruginosa: Multiple binding modes of quercetin with transcriptional regulator LasR.

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Pseudomonas aeruginosa is one of the most dangerous superbugs and is considered as a big threat by World Health Organization and Centers for Disease Control and Prevention. So new antimicrobials are urgently needed. It affects patients with AIDS, cystic fibrosis, cancer, burn victims. This bacterium also forms biofilms, which increase antibiotic and multidrug resistance. Biofilm formation is regulated through a system called quorum sensing as well as this system controls CRISPR-Cas adaptive immune system of *P. aeruginosa*. Thus disrupting this system is considered a promising strategy.

Flavonoids are widely distributed in the plant kingdom and known for their numerous roles in plant physiology. They exhibit a large spectrum of biological activities, such as antiatherogenic, antioxidant, anticancer, anti-inflammatory and antimicrobial activity. One such flavonoid is quercetin and it has been shown quercetin inhibits biofilm formation and virulence through transcriptional regulator LasR, but structural details are unknown [2]. Quercetin is a flavonoid and Generally Recognized as Safe (GRAS) compound.

In the present study, we tried to analyze the mode of interactions of LasR with quercetin. Because of the lack of full structural information about LasR protein, the structure was reconstructed [1]. We used a combination of molecular docking with various programs, molecular dynamics (MD) simulations and machine learning techniques for the study [1]. We show that quercetin has two binding modes, and they are not competitive (Fig. 1). One binding mode is the interaction with Ligand binding domain (LBD) (Fig. 2a). The second binding mode includes conservative amino acids from Ligand binding domain and DNA binding domain (Fig. 2b). Biochemical studies show that hydroxyl group of ring A in quercetin is necessary for inhibitory activity [2]. In our model, it interacts with Leu177 in the second binding mode. This could explain the molecular mechanism of how quercetin inhibits pathogenicity and quorum sensing circuitry through the LasR protein. Two binding modes may explain why quercetin is effective at inhibiting biofilm formation and virulence gene expression. Thus the anti-infective strategy based on natural products represents a new therapeutic approach in the biomedical field and ecologic alternatives to antibiotics with the advantage that bioactive compounds are not growth inhibitors and selection factors.

References

1) Grabski H, Hunanyan L, Tiratsuyan S, Vardapetyan H. Interaction of N-3-oxododecanoyl homoserine lactone with transcriptional regulator LasR of Pseudomonas aeruginosa: Insights from molecular docking and dynamics simulations //bioRxiv. – 2017. – С. 121681.
2) Paczkowski J, Mukherjee S, McCready A, Cong J, Aquino C, Kim H, Henke B, Smith C, Bassler B. Flavonoids suppress Pseudomonas aeruginosa virulence through allosteric inhibition of quorum-sensing receptors //Journal of Biological Chemistry. – 2017. – Т. 292. – №. 10. – С. 4064-4076.

Illustrations

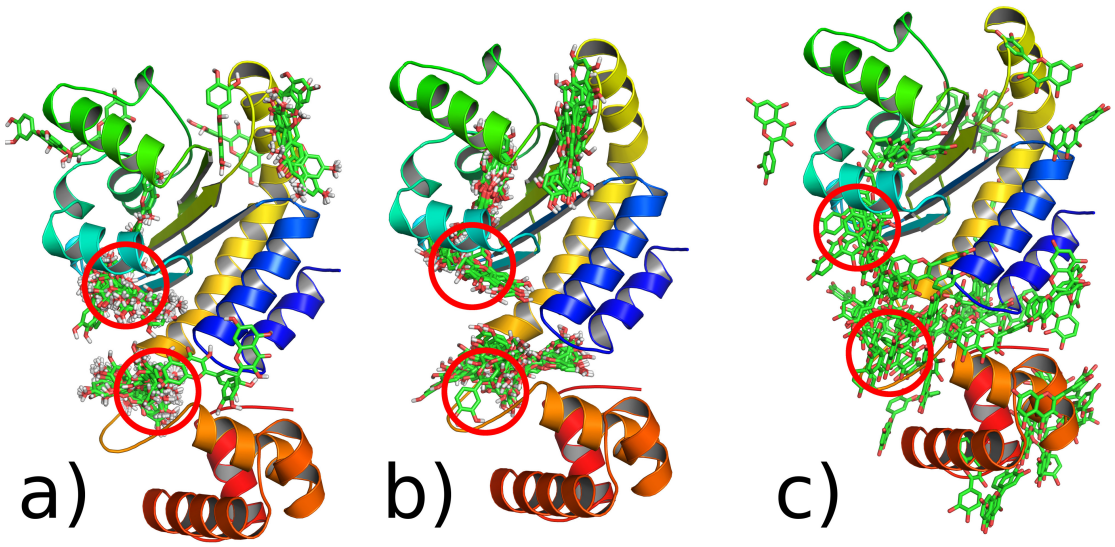

Рис. 1. Blind docking with various molecular docking programs. Red circles - binding interactions that are characteristic to all programs a) Autodock Vina b) rDock c) FlexAid.

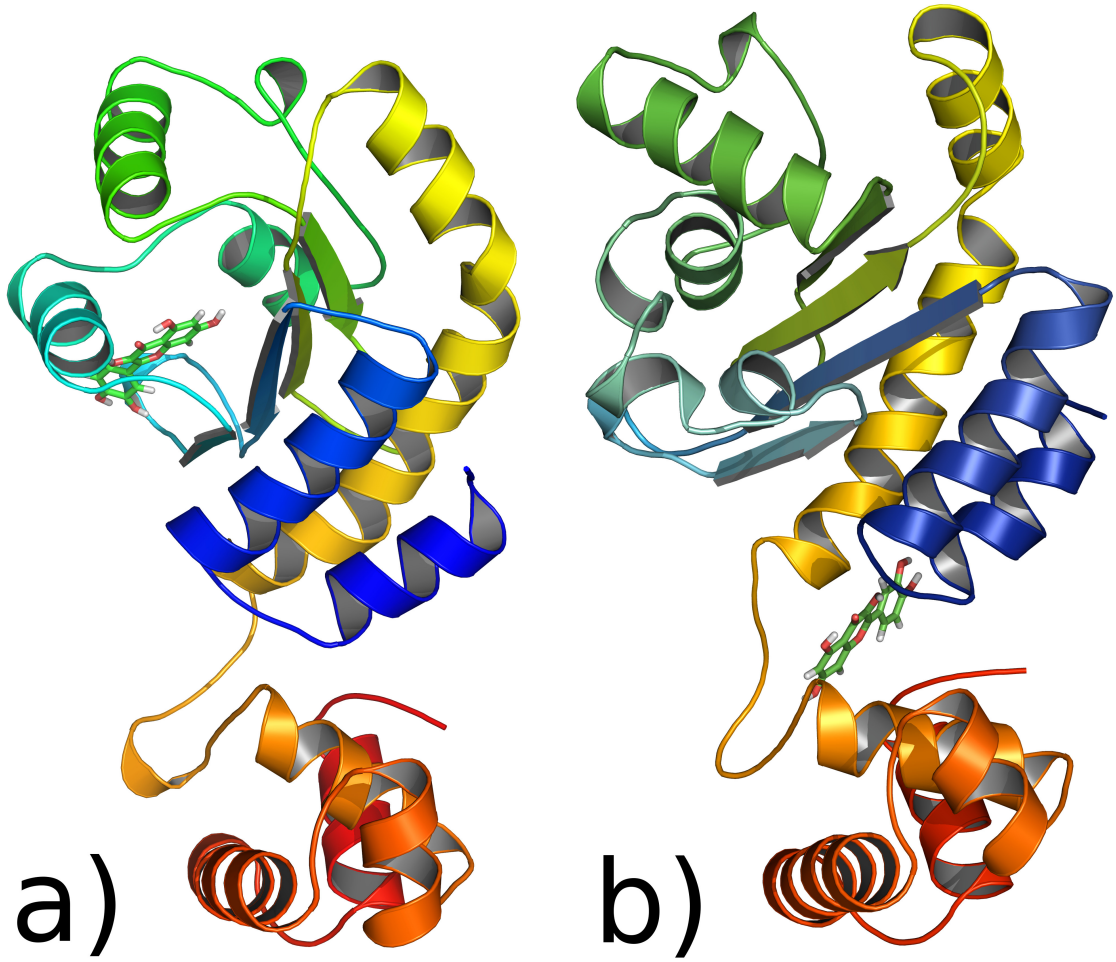

Рис. 2. Binding modes of quercetin. a) with LBD of LasR b) with the bridge of LasR.