รูปแบบ Abstract (บทคัดย่อ)

Project Code : TRG5880230
(รหัสโครงการ)

Project Title : Exploring the mechanism of carbapenem permeation through the outer membrane channel from Pseudomonas aeruginosa for future drug development: Molecular dynamics studies
(ชื่อโครงการ)

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Project Period : 2 years
(ระยะเวลาโครงการ)

Abstract

Pseudomonas aeruginosa is a leading nosocomial human pathogen. The major bottleneck to fight against these bacterial is their impermeable outer membrane (OM). Only specific substrates can penetrate through OM of *P. aeruginosa* via substrate-specific porins, so they become one of the most problematic drug-resistant pathogens. Carbapenems are the most effective drugs against infection with *P. aeruginosa*. One of active carbapenems used for *P. aeruginosa* is imipenem (IMI), employing the Outer membrane carboxylate channels D1 (OccD1) as an entry way. Unlike IMI, ertapenem (ERTA) was found to show weak activity due to its permeability problem. To date, no microscopic evidence can explain why IMI is preferred over ERTA. Therefore, we primarily conducted Molecular Dynamics (MD) Simulations to discover the behaviours of these drugs inside OccD1 comparing to the ligand-free state. We reported here another possible binding site in the constriction region close to the side pore opening. Overall, both drugs employ the core lactam part to tether themselves in the binding site,

whereas the tail guides a permeation direction. L132 and F133 seem to be key interactions for the core attachment. Approximately, at least 4 hydrogen bonds are required for drug binding. The direction of L2 motion also plays a role. The inward flipping traps IMI in the constriction area, while shifting towards a membrane of L2 allows ERTA contacts more water and consequently gets expelled to the protein mouth. The opening of L2 seems to facilitate the rejection of ERTA.

เนื้อหางานวิจัยประกอบด้วย วัตถุประสงค์ วิธีทดลอง ผลการทดลอง สรุปและวิจารณ์ผลการทดลอง และข้อเสนอแนะสำหรับงานวิจัยในอนาคต

Keywords : Molecular dynamics simulations, OccD1, imipenem, ertapenem
(คำหลัก)

Introduction

The gram-negative bacteria employ water-filled porins with various grades of selectivity to transport nutrients and ions across their outer membrane [1-3]. Especially, porins were found to be an entrance for many antibiotics [4-7]. Based on their degrees of substrate selectivity, 2 groups of porins can be divided. The first group is general porins (e.g. OmpC and OmpF) mediating the passage of a range of solutes based on their size, while the second is substrate-specific porins containing unique binding site for substrate [8]. For notorious human pathogens such as *Pseudomonas aeruginosa*, they have impermeable membrane due to the absence of general porins [1]. Consequently, the uptake of nutrients and ions in *P.aerugonosa* can be occurred through substrate-specific porins (e.g. the uptake of phosphate is employed by phosphate-specific OprP channel [9]). The substrate-specific channels have a narrow pore with high affinities for substrate binding and recognition [10]. In *P.aeruginosa*, the uptake of most small and water-soluble metabolites are conducted by the Occ (Outer membrane carboxylate channel) protein family. To date, 19 proteins are in this family and divided into 2 subfamilies (OccD and OccK). Both subfamilies facilitate the transport of carboxylate-containing solutes. The OccD family prefers basic amino acids, whereas the cyclic compounds are specific for the OccK family [10]. Especially, OccD1 (or OprD), the first member of the OccD family, was found to facilitate the uptake of positively charged amino acids, small peptides, and importantly some carbapenems [11,12].