World Academy of Science, Engineering and Technology
International Journal of Bioengineering and Life Sciences
Vol:17, No:10, 2023

Exploring the Role of Phosphorylation on the β-lactamase Activity of OXA24/40

Authors : Dharshika Rajalingam, Jeffery W. Peng

Abstract : Acinetobacter baumannii is a challenging threat to global health, recognized as a multidrug-resistant pathogen. -lactamase is one of the principal resistant mechanisms developed by A. baumannii to survive against -lactam antibiotics. OXA24/40 is one of the types of -lactamases, a well-documented carbapenem hydrolyzing class D -lactamases (CHDL). It was revealed that OXA24/40 showed resistivity against doripenem, one of the carbapenems, by two different mechanisms as hydrolysis and -lactonization. Furthermore, it undergoes genetic mutations to broaden the -lactamase activity to survive against antibiotic environments. One of the crucial characterizations of prokaryotes to develop adaptation is post-translational modification (PTM), mainly phosphorylation. However, the PTM of OXA24/40 is an unknown feature, and the impact of PTM on antibiotic resistivity is yet to be explored. We approached these hypotheses using NMR and MS techniques and found that the OXA24/40 could be phosphorylated in vitro. The Ser81 at the active STFK motif of OXA24/40 of catalytic pocket was identified as the site of phosphorylation using 1D 31P NMR experiment, whereas S81 is required to form an acyl-enzyme complex between enzyme and -lactam antibiotics. The activity of completely phosphorylated OXA24/40 wild type against doripenem revealed that the phosphorylation of active Ser inactivates the -lactamases activity of OXA24/40. The 1D 1H CPMG NMR-based activity assay of phosphorylated OXA24/40 against doripenem confirmed that both deactivating mechanisms are inhibited by phosphorylation. Carbamylated Lysine at the active STFK motif is one of the critical features of CHDL required for the acylation and deacylation reactions of the enzyme. The 1D 13C NMR experiment confirmed that the K84 of phosphorylated OXA24/40 is de-carbamylated. Phosphorylation of OXA24/40 affects both active S81 and carbamylated K84 of OXA24 that are required for the resistivity of -lactamase. So, phosphorylation could be one of the reasons for the genetic mutation of OXA24/40 for the development of antibiotic resistivity. Further research can lead to an understanding of the effect of phosphorylation on the clinical mutants of the OXA24-like -lactamase family on the broadening of -lactamase activity.

Keywords : OXA24/40, phosphorylation, clinical mutants, resistivity
Conference Title : ICPCSB 2023 : International Conference on Protein Chemistry and Structural Biology
Conference Location : New York, United States
Conference Dates : October 09-10, 2023