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Structural studies on Carbapenem-Hydrolyzing Class D serine β-Lactamases from *Acinetobacter baumannii*

The class D serine β-lactamases comprise a superfamily of almost 800 enzymes capable of conferring high-level resistance to β-lactam antibiotics, predominantly the penicillins including oxacillin and cloxacillin. In recent years it has been discovered that some members of the class D superfamily have evolved the ability to deactivate carbapenems, "last resort" β-lactam antibiotics generally held in reserve for highly drug resistant bacterial infections. These enzymes are collectively known as Carbapenem-Hydrolyzing Class D serine β-Lactamases or CHDLs (1). The mechanism of β-lactam deactivation by the class D serine β-lactamases involves the covalent binding of the antibiotic to an active site serine to form an acyl-enzyme intermediate (acylation). This is followed by hydrolysis of the covalent bond (deacylation), catalyzed by a water molecule activated by a carboxylated lysine residue (2). It was initially thought that the carbapenems acted as potent inhibitors of the class D enzymes since the formation of the covalent acyl-enzyme intermediate effectively expelled all water molecules from the active site, thus preventing the deacylation step. Our structural studies on two CHDLs (3,4) have indicated that their carbapenem hydrolyzing ability may be due to two surface hydrophobic residues which allow for the transient opening and closing of a channel through which water molecules from the milieu can enter the binding site to facilitate the deacylation reaction (Figure). Although the hydrophobic residues responsible for the channel formation are present in all class D β-lactamases, sequence and structural differences nearby may be responsible for the evolution of carbapenemase activity in the CHDLs. These mechanisms will be presented, including some insights into the carbapenemase activity of non-*Acinetobacter* CHDLs which show a variation in how deacylation is activated. Future work aimed at improved inhibitor design will also be explored.

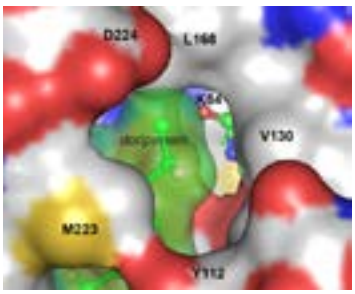

Figure . The surface of OXA-143 calculated with Val130 in an open conformation, showing a hole which opens into the active site

Recent Publications

1. Queenan, A.M., & Bush, K. (2007) Carbapenemases: The versatile β-lactamases. *Clin. Microbiol. Rev.* 20, 440-458.
2. Golemi, D., Maveyraud, L., Vakulenko, S., Samama, J. P., & Mobashery, S. (2001) Critical involvement of a carbamylated lysine in catalytic function of class D β-lactamases. *Proc. Natl. Acad. Sci.* 98, 14280-14285.
3. Smith, C.A., Antunes, N.T., Stewart, N.K., Toth, M., Kumarasiri, M., Chang, M., Mobashery, S., & Vakulenko, S.B. (2013) Structural basis for carbapenemase activity of the OXA-23 β-lactamase from *Acinetobacter baumannii. Chem. Biol.* 20, 1107-1115.
4. Toth, M., Smith, C.A., Antunes, N.T., Stewart, N.K., Maltz, L., & Vakulenko, S.B. (2017) The role of conserved surface hydrophobic residues in the carbapenemase activity of the class D β-lactamases. (2017) *Acta Crystallogr.* D73, 692-701.

Biography

Clyde Smith has over 30 years' experience in the determination of small molecule and protein structures using X-ray crystallography. Dr Smith gained his PhD in Protein Crystallography at Massey University (New Zealand) in 1993, where he studied the structure and metal binding properties of lactoferrin from human milk. He then undertook a two-year NIH-funded postdoctoral fellowship at the University of Wisconsin, working on the structure of the major skeletal muscle protein, myosin. He returned to New Zealand as a FRST postdoctoral fellow studying the structures of thermostable enzymes. In 1997 he was appointed as a Lecturer in Biochemistry in the School of Biological Sciences at the University of Auckland. In late 2003, he moved to the US to take up a Staff Scientist position in the Chemistry Department at Stanford University, working at the Stanford Synchrotron Radiation Lightsource (SSRL). He is currently a Senior Staff Scientist at SSRL. His scientific research in the field of structural biology includes work in antibiotic resistance, folate metabolism and vitamin B12 chemistry.

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