Supplementary Information

Beta-Lactamase DataBase (BLDB) – Structure and Function

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BLDB Presentation

Multidrug-resistant (MDR) gram-negative pathogens, especially Enterobacteriaceae, are emerging worldwide. The MDR pattern is relatively common with resistance appearing to all major classes of anti-gam-negative agents (e.g., β-lactams, fluoroquinolones, and amino-penicillins), and in some cases, resistance to all available drugs. This is particularly worrisome in view of the current dearth of new compounds against MDR gram-negative bacteria.

β-Lactams, due to their safety, reliable killing properties and clinical efficacy, are among the most frequently prescribed antibiotics used to treat bacterial infections. However, their use is being threatened by the worldwide proliferation of β-lactamases (BLs) with broad hydrolytic capabilities, especially in MDR gram-negative bacteria. These BLs are divided into 4 classes based on their sequence identity. Classes A, C and D domain active site serine enzymes whose reaction pathways involve acyl-enzyme adducts while class D represents metallo-β-lactamases (MBLs) which do not form such intermediates (require zinc ion (Zn) for their function). Currently, BL-mediated resistance does not span over the newest and most powerful β-lactams (i.e. cephamycins), whose activity is challenged by the MBLs (IMP, VIM, NDM, ...). In classes A and D serine-carbapenemases (KPC, IMI, KPM, CARA-48, CARA-53, CARA-41, ...).

While a handful of β-lactamases were known in the early 1970s, the number of β-lactamases has ever since been growing rapidly, especially with novel enzymes described, and the current dissemination of some enzymes in clinical isolates that undergo changes in their amino-acid sequence, yielding novel hydrolytic properties. The substrate specificity may be relatively narrow or broad including the extended-spectrum cephalosporins and the carbapenems. The class A enzymes (known primarily as penicillinases) tend to hydrolyze penicillins over cephalosporins as substrates although many variants may hydrolyze significantly broad-spectrum cephalosporins and carbapenems. The class B enzymes (metallo-β-lactamases) typically have an extremely broad-spectrum substrate specificity including all β-lactams except monobactams (aztreonam). The class C enzymes (cephalosporinases) tend to hydrolyze cephalosporins as substrates whereas class D enzymes (carbapenemases) have an unusually high substrate preference for oxacillin and related penicillins. None of the marketed β-lactam molecules may resist to the hydrolysis by β-lactamases.

The aim of the Beta-Lactamase Database (BLDB) is to compile sequence information as well as biochemical and structural informations on all the currently known β-lactamases. BLDB offers in addition tools to analyse β-lactamases and provides important tools to the related web resources (NCBI, PDB, etc.). The comprehensive web-based database may provide at a glance useful insights in the structure-function relationships of β-lactamases, and thus allowing a better understanding of substrate specificities, determine key residues involved in substrate recognition and hydrolysis, and to foresee the impact of mutations in the hydrolysese profile.

**Statistics**

**Enzymes**

Overall (6266); class A (1111); subclass B1 (202); subclass B2 (169); subclass B3 (90); class C (626); class D (984).

**Structures**

Overall (171); class A (34); subclass B1 (16); subclass B2 (14); subclass B3 (45); class C (14); class D (36).

**Mutants**

Overall (167); class A (91); subclass B1 (56); subclass B2 (3); subclass B3 (6); class C (19); class D (13).

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Fig. S1. Global overview of the Home page.

Fig. S2. Global overview of the Enzymes section.
Fig. S3. Global overview of the β-lactamase families that are present in the BLDB.
Fig. S4. Sequence alignment.

Fig. S5. Rooted phylogenetic tree corresponding to the sequence alignment.
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**Fig. S6. Global overview of the Structures section.**

[Structure overview diagram]

**Legend for ligands:**
- #: Ligand covalently bound to active site residues; 
- #: Non-covalent ligand (Michaelis complex); 
- #: Ligand coordinated to active site metal ions.

**Fig. S7. Global overview of the Mutants section.**

[Mutant overview diagram]
**Fig. S8.** Global overview of the Kinetics section, showing the hydrolytic profiles.
Fig. S9. Radar chart showing the superposition of hydrolytic profiles for OXA-40 (blue), OXA-48 (orange) and OXA-163 (green).
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Fig. S10. SequenceServer graphical interface for the nucleotide- and protein-based BLAST queries.
**Fig. S11. SequenceServer formatted results of a protein BLAST query.**

| Number | Sequences producing significant alignments | Total score | E value | Identities |
|--------|---------------------------------------------|-------------|---------|------------|
| 1.     | gi|595266892|gb|AHM26723.1| NDM-1 beta-lactamase NDM-1 [Achromobacter sp. NFS18] | 555.83 | 0.00 | 270/270 (100.00) |
| 2.     | gi|378405411|gb|AF882585.1| NDM-4 metallo-beta-lactamase NDM-4 [Escherichia coli] | 555.06 | 0.00 | 269/270 (99.63) |
| 3.     | gi|537849610|gb|AGU91756.1| NDM-9 New Delhi metallo-beta-lactamase [Klebsiella pneumoniae subs. pneumoniae] | 554.29 | 0.00 | 269/270 (99.63) |
| 4.     | gi|366085573|gb|AE008599.1| NDM-6 NDM carbapenemase [Escherichia coli] | 554.29 | 0.00 | 269/270 (99.63) |
| 5.     | gi|388890593|gb|AFK0349.1| NDM-3 metallo-beta-lactamase [Escherichia coli] | 554.29 | 0.00 | 269/270 (99.63) |
| 6.     | gi|748762923|gb|AJ61443.1| NDM-11 metallo-beta-lactamase NDM-11 [Escherichia coli] | 554.29 | 0.00 | 269/270 (99.63) |
| 7.     | gi|916370098|gb|AK220823.1| NDM-16 class B beta-lactamase [Klebsiella pneumoniae] | 553.52 | 0.00 | 269/270 (99.63) |
| 8.     | gi|848612134|gb|AKN35289.1| NDM-7 (plasmid) [Enterobacter cloacae] | 553.13 | 0.00 | 268/270 (99.26) |
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**Fig. S12.** Sequence alignment of protein BLAST results with the initial query.