New Disturbing Trend in Antimicrobial Resistance of Outbreaking and Carbapenemase-Producing Pathogens

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Gram-negative bacteria producing extended-spectrum β-lactamases (ESBLs) are found to be truly multidrug-resistant pathogens causing severe clinical problems. In the present investigations, fifteen class C β-lactamases with extended substrate spectra have been reported in Gram-negative pathogens. Here I wish to draw attention to a new disturbing trend (the recently emerging class C ESBLs [cESBLs]) and the antimicrobial drug development for cESBLs. How do the cESBLs extend the substrate spectrum? The crystallographic structures can answer this question. Until now, there are two only resolved crystallographic structures of cESBLs: (i) GC1 [1]; and (ii) CMY-10 [2-3]. The sequence alignment of natural (clinically-isolated) cESBLs showed that the R2-loop included all regions responsible for the extended substrate spectrum in most (11 of total 15) cESBLs: Ω-loop in three cESBLs; H-2 helix in a 520R cESBL (not natural); H-11 helix in a KL cESBL. These natural mutations in the R2-loop can change the architecture of the active site in cESBLs, thereby affecting their hydrolyzing activity. Owing to a three amino acid deletion (amino acid residues 303-305) in CMY-10 (a cESBL), the R2-loop in the R2 active site displays noticeable structural alterations: the significant widening of the R2 active site. Therefore, the bulky R2 side-chain of oxyimino-cephalosporins could fit snugly into the significant widening of the R2 active site in this way. To decrease the selective pressure of antimicrobial drugs and minimize antimicrobial resistance, it is necessary for health-care professionals to recognize the presence of emerging cESBLs as a new disturbing trend in antimicrobial resistance of Gram-negative pathogens. In view of no drug developments against cESBL-producing Gram-negative pathogens, new β-lactams (or β-lactamase inhibitors) need to be developed by the structure-based drug design (SBDD) method using a similar mechanism (the significant widening of the R2 active site) of the extended substrate spectrum shown in most cESBLs. SBDD against CMY-10 cESBL has been performed and some lead compounds were found.

References

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[This work was supported by the Korea Research Foundation Grant funded by the Korean Government (KRF-2008-313-C00790), the Korea Science and Engineering Foundation (KOSEF) grant funded by the Korea government (MEST) (2009-0077922), and the Driving Force Project for the Next Generation of Gyeonggi Provincial Government in Republic of Korea.]

Keywords: class C extended-spectrum β-lactamases (cESBLs), multidrug-resistant pathogens, CMY-10, R2-loop, drug discovery