Editorial

Journal of Bacteriology and Infectious diseases

2020
Vol. 4, Iss. 2

Mechanistic studies on clinically important beta-lactamases and their rapid detection

Yuan He

Northwest University, China

Mechanistic studies on clinically important beta-lactamases and their rapid detection: Since the discovery of penicillin in 1928, β-lactams have long been used in treating bacterial infections and have dramatically increased the life expectancy of human beings. However, the overuse of antibiotics has also caused rapid emergence of antibiotic-resistant bacteria that are difficult or impossible to defeat. The major mechanism of β-lactam resistance is the acquisition of genes encoding β-lactamases by the bacteria. These enzymes catalyze the hydrolysis of the amide bond in the β-lactam rings, rendering the antibiotics incapable to kill bacterial cells. To date, over one thousand β-lactamases have been identified that can degrade β-lactam antibiotics. Of these bacterial enzymes, carbapenemases are a large class of β-lactamases that can inactivate antibiotics of the “last resort” such as imipenem, peropenem, etc. leaving very limited choices for clinical treatments. In this report, new discoveries of the mechanistic and inhibition studies of representative carbapenemases carried out in laboratory. The design of an innovative methodology for rapid screening of clinical carbapenemase-producing Enterobacteriaceae (CPE) using a new calorimetry approach. These results are believed to provide new insights into current understanding on carbapenemase catalysis and characterization. β-Lactamases, the major resistance determinant for β-lactam antibiotics in Gram-negative bacteria, are ancient enzymes whose origins can be traced back millions of years ago. These well-studied enzymes, currently numbering almost 2,800 unique proteins, initially emerged from environmental sources, most likely to protect a producing bacterium from attack by naturally occurring β-lactams. Their ancestors were presumably penicillin-binding proteins that share sequence homology with β-lactamases possessing an active-site serine. Metallo-β-lactamases also exist, with one or two catalytically functional zinc ions. Although penicillinases in Gram-positive bacteria were reported shortly after penicillin was introduced clinically, transmissible β-lactamases that could hydrolyze recently approved cephalosporins, monobactams, and carbapenems later became important in Gram-negative pathogens. Nomenclature is based on one of two major systems. Originally, functional classifications were used, based on substrate and inhibitor profiles. A later scheme classifies β-lactamases according to amino acid sequences, resulting in class A, B, C, and D enzymes. A more recent nomenclature combines the molecular and biochemical classifications into 17 functional groups that describe most β-lactamases. Some of the most problematic enzymes in the clinical community include extended-spectrum β-lactamases (ESBLs) and the serine and metallo-carbapenemases, all of which are at least partially addressed with new β-lactamase inhibitor combinations. New enzyme variants continue to be described, partly because of the ease of obtaining sequence data from whole-genome sequencing studies. Often, these new enzymes are devoid of any phenotypic descriptions, making it more difficult for clinicians and antibiotic researchers to address new challenges that may be posed by unusual β-lactamases. One of the most studied enzyme families is the group of enzymes known as β-lactamases, with more than 28,900 citations in Medline (https://www.ncbi.nlm.nih.gov/pubmed/). These enzymes, whose most obvious role is to inactivate β-lactam antibiotics, have driven research in academic laboratories since the early 1940s . Perhaps more importantly, they have been responsible for scores of pharmaceutical research programs that have attempted to find ways to protect effective antibiotics from destruction. β-Lactamases provide intellectual challenges for academic investigators with

their deceptively simple mechanisms of action, as enzymes whose hydrolysis activity approaches that of a “fully efficient enzyme” with diffusion-limited reaction rates. Attempts to provide economically viable anti-infective agents that can circumvent the action of these enzymes have yielded substantial economic rewards to successful pharmaceutical companies. As a result, the safe and effective β-lactam antibiotics have become one of the most widely prescribed classes of antibacterial agents . Many review articles have been published about various aspects of these intriguing enzymes , but they have tended to focus on narrowly targeted sets of β-lactamases. In this minireview, a short history of the β-lactamases is presented, emphasizing key points that have driven both academic and pharmaceutical science over the past 75 years. High points in their history will be discussed, based on the. This history is not meant to be a comprehensive review of all the current literature on β-lactamases but is meant to tell a story about where these enzymes came from, how they have driven antibiotic discovery programs, and what challenges they pose for today. β-Lactamases are versatile enzymes with a limited range of molecular structures found in a diversity of bacterial sources. Their commonality is the ability to hydrolyze chemical compounds containing a β-lactam ring. they have been classified biochemically into two broad divisions according to the mechanism by which they perform hydrolysis, either through the formation of an acyl enzyme with an active-site serine or via a hydrolytic reaction facilitated by one or two essential zinc ions in the active sites of metallo-β-lactamases (MBLs) . After sequence analyses became available for key β-lactamases, four molecular classes, A, B, C, and D, were eventually assigned based on molecular size and homology between active-site amino acid motifs . However, biochemical differences between penicillinases and cephalosporinases had been recognized well before sequences were available , and known β-lactamases were distinguished based on functional capabilities related to substrate and inhibitor profile . Early classification schemes relied upon relative hydrolysis rates of penicillins and early cephalosporins, together with the enzymatic response to protein-modifying agents .As additional substrates and inhibitors were introduced into clinical practice and gene sequencing became inexpensive and routine, both molecular and functional characteristics were combined into a more comprehensive classification scheme . Today, at least 17 functional groups associated with the four molecular classes have been distinguished , with the major groups shown in . Enzymes are still differentiated with respect to the relative hydrolysis of the β-lactam substrates, penicillins, cephalosporins, carbapenems, and monobactams. Further differentiation is possible based on reactions with the class A β-lactamase inhibitor clavulanic acid , the broad-spectrum serine β-lactamase inhibitor avibactam , and the metal ion chelator EDTA to identify MBLs.