Antimicrobial Resistance Gallery

Antibiotic inactivation

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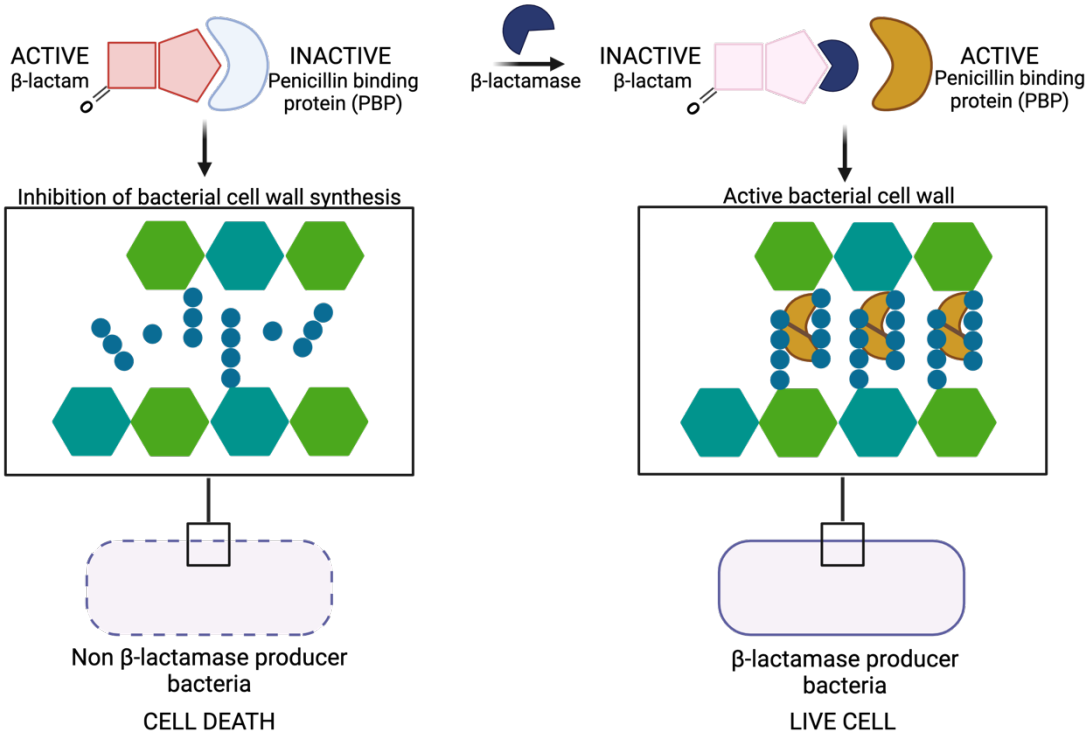

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The Battle Against Beta (β)-Lactamases

In the microscopic battleground of human health, an intimidating enemy has emerged: antimicrobial-resistant bacteria. Among their wide range of survival mechanisms, one particularly concerning strategy is the production of enzymes known as β-lactamases. These are ancient enzymes encoded by genes present in the genome (DNA) of some bacteria but that have also spread across other species by being mobilized on plasmids.

Background

The discovery of β-lactamases cannot be explained without discussing the discovery of β-lactam antibiotics. In 1928, Alexander Fleming was in his lab, throwing out plates from the bench, and found something peculiar on one dish. A mold known by the name of *Penicillium notatum* was inhibiting the growth of bacteria in the immediate zone of the mold. Later, researchers found that this "mold juice" – baptized as Penicillin – could kill a wide range of pathogenic bacteria. Penicillin was first used in a patient in 1942 and widely deployed during war times for treatment of surgeries and wound infections.

How do β-lactams work?

β-lactams are divided into four classes: penicillins, cephalosporins, monobactams and carbapenems. They all share the same activity of inhibiting proteins – the so-called penicillin-binding proteins (PBPs) – involved in bacterial cell wall formation. They do this by covalently binding to PBPs, which determine the strength of the bacterial cell wall, and thereby this type of antibiotic weakens the cell wall structure, subsequently leading to bacterial cell death. Now, almost 100 years later, thousands of penicillin-like antibiotics have been discovered or designed, the most important of which represent 65% of the prescribed antibiotics in the United States market.

The Role of β-lactamases:

β-*lactamases* were found in bacterial species at almost the same time that β-lactams were discovered, but are considered to be ancient enzymes. Their origins can be traced back millions of years and most likely evolved to protect against natural occurring β-lactams, such as the one from the mold that Alexander found in his petri dish. These enzymes share the ability to modify β-lactams by cleaving the β-lactam ring structure that is essential to activity, thereby rendering the antibiotics ineffective.

Extended Spectrum β-lactamases (ESBLs)– an "extended" global health concern:

ESBLs have an expanded spectrum to β-lactams, meaning that instead of having the ability to inactivate ONE drug, they can inhibit MULTIPLE classes of β-lactams, including the most recently introduced in the market. ESBLs are produced specifically by Gram-negative pathogens such as *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. ESBLs were discovered in the ´80s and since then, thousands of them have been reported in America, Europe, Africa and Asia.

A specific case in the clinical setting – the Extended Spectrum Cephalosporinase AmpC:

AmpC is a β-lactamase that is produced by *P. aeruginosa* and other *Enterobacteriaceae*. The overproduction of this enzyme gives the bacteria resistance to 1st and 2nd generation cephalosporins. But bacteria like *P. aeruginosa* have highly plastic genomes that enable them to rapidly evolve by acquiring mutations, including mutations in the gene of β-lactamase that can inhibit the action of many more new cephalosporins.

Take home message

Every year new variants of these enzymes are discovered. The battle against antimicrobial-resistant bacteria, armed with β-lactamases, is a critical challenge for our generation. Understanding the implications of antibiotic resistance and promoting responsible antibiotic use can contribute to the global effort to curb the rise of these resilient microbes. By staying informed and advocating for responsible antibiotic practices, we can help preserve the effectiveness of antibiotics for future generations and ensure a healthier, safer world.