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The role of two-component regulatory system in β-lactam antibiotics resistance

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ABSTRACT

The irrational use of antibiotics in agriculture and in the medical field has led to a variety of pathogenic microorganisms that produce drug resistance and even multidrug resistance. B-lactam is one of the most widely used antibiotics to treat infectious diseases. Resistance to β-lactam resistance can be primarily due to the presence β-lactamase, mutation of β-lactam targets and overexpression of efflux pumps. Two-component regulatory systems are composed of histidine kinase and response regulator that regulate gene expression under different environmental conditions. In this review, we summarized the mechanisms by which β-lactam resistance is developed and the role of the two-component regulatory system in β-lactam resistance.

1. Introduction

In recent decades, due to the continuous discovery of antibiotics, all kinds of infectious diseases can be effectively treated. However, the frequent and improper use of antibiotics leads to the emergence of new drug-resistant bacteria and even super resistant bacteria. If antibiotic resistance is not controlled, we are likely to face the situation without medicine to treat infectious diseases in the near future. Therefore, the pathogenic microorganism antibiotic resistance has been extensively studied in recent years. Resistance to β-lactam (a most widely used antibiotic) resistance can be primarily due to the presence β-lactamase, mutation of β-lactam targets and overexpression of efflux pumps. Two-component regulatory systems are composed of histidine kinase and response regulator that regulate gene expression under different environmental conditions. In this review, we summarized the mechanisms by which β-lactam resistance is developed and the role of the two-component regulatory system in β-lactam resistance.

2. β-lactam antibiotic

Antibiotics are secondary metabolites or semi-synthetic or synthetic derivatives that can inhibit and kill pathogenic microorganisms. Some antibiotics also have anti-tumor, antiviral, immune suppression, and insecticide effects. According to chemical structure antibiotics can be divided into β-lactam antibiotics, macrolides, aminoglycoside and tetracycline antibiotics. β -lactam antibiotics have a wide range of antibacterial activity with small side effects. It is the most widely used commercial antibiotics to treat infectious diseases. Common β-lactam antibiotics include carbapenem, penicillin, monobactams, and cephalosporins. As shown in Fig. 1, β-lactam antibiotics have a common ring structure. This ring has an astonishing structural similarity to D-alanine-D-alanine, the substrate of transpeptidase or penicillin binding protein (PBPs) (Zeng and Lin, 2013). PBPs are necessary enzymes the synthesis of peptidoglycan (PG), key component of cell wall. B-lactam antibiotics can bind to the active sites of PBP and inhibit their activity, thus destroying the integrity of the cell walls and cell death (Fisher et al., 2005). Antibiotics have saved countless lives since antibiotics were put into use, but these indispensable antibiotics are rapidly losing their potency due to overuse or wrong use in human and animal health, a phenomenon known as antibiotic resistance. There are many complex mechanisms in bacteria that make themselves resistant to antibiotics. Like most antimicrobial agents, bacteria produce resistance to β-lactam antibiotics through three major mechanisms. The most common mechanism of β-lactam resistance is the production of β-lactamase, which

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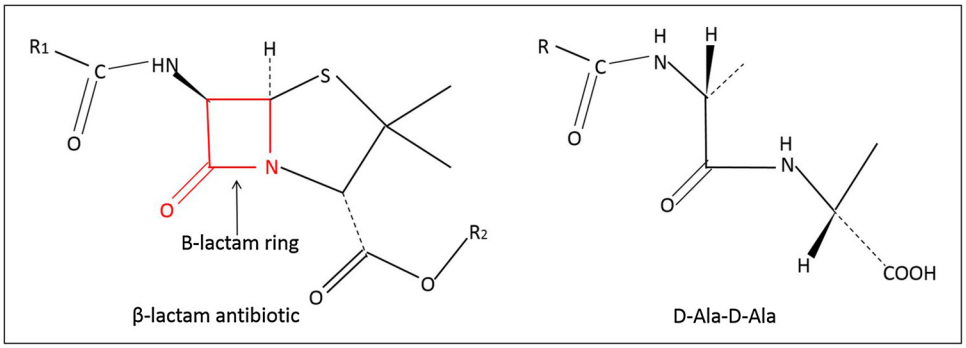

Fig. 1. Molecular structure of β-lactam antibiotic and D-alanine-D-alanine(D-Ala-D-Ala).The four-member lactam ring in β-lactam antibiotic was high lighted in red. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

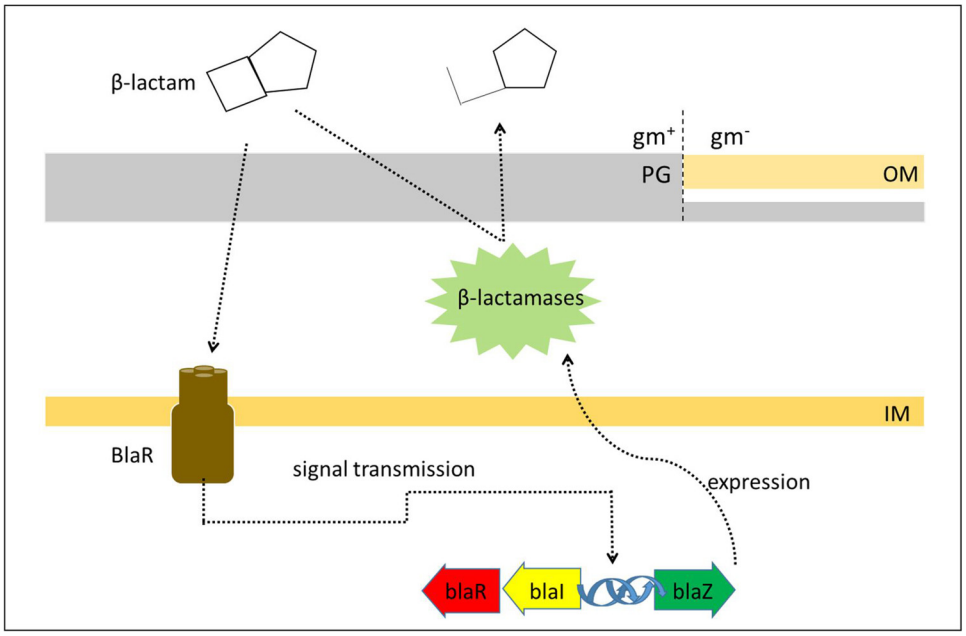

Fig. 2. Mechanism of β-lactamases produced by bacteria. blaR, blaI and blaZ are related genes for the expression of β-lactamases.

degrades β-lactam antibiotics before they reach the targets (Fig. 2) (Bonomo, 2017). Degradation of β-lactam by the enzyme β-lactamase is widely present in Gram-positive and gram-negative bacteria. The second mechanism is to modify the target protein-penicillin binding protein (PBPs), leading to the loss of the affinity between β-lactam antibiotics and its target PBPs (Fig. 3). This is one of the main reasons causing β-lactam resistance in Gram-positive bacteria. For example, a mutation in the PBP5 in Enterococcus faecalis causes the loss of affinity to β-lactam antibiotics, resulting in β-lactam resistance (Sauvage et al., 2002). The third mechanism is to prevent the β-lactam antibiotic from reaching the target by altering the permeability of the outer membrane or increasing the efflux pump activity. For example, overexpression of efflux pump MexA or B-OprM is one of the main causes of antibiotic resistance in *Pseudomonas aeruginosa* and other pathogenic gram-negative bacteria (Fig. 4) (Wilke et al., 2005). In addition, antibiotic resistance genes may be transmitted among different bacterial species through transformation, transduction, and conjugation. What is more frightening is that the spread of the β-lactamase gene is greatly exacerbated by its integration in a movable genetic element, such as plasmids or transposon, which promotes the rapid transfer of genetic material between microorganisms (Weldhagen, 2004).

3. Two-component regulatory system (TCS)

TCS is widely present in bacteria and is one of the main mechanisms for bacteria to respond to environmental signals. In response to specific signals, bacteria can produce acid-resistance, antibiotic resistance and pathogenesis via TCS-mediated gene upregulation or downregulation (Stock et al., 2000). TCS is composed of sensor kinase or histidine kinase (HK) and response regulator (RR). HK is typically localized on the membrane, while RR is usually cytoplasmic. Upon stimulation by the environmental signal, HK is autophosphorylated at the conserved histidine residue and forms dimer. Subsequently, phosphoryl group is transferred from HK to the conserved cysteine residue of RR. Phosphorylated RR regulates gene expression via binding to the specific regions of chromosomal DNA or other indirect mechanisms (Bisicchia et al., 2007).

The first discovered TCS (VicRK or YycFG) is closely related to the survival of Bacillus (Fukushima et al., 2008). Evidence suggested that VicRK can regulate cell wall metabolism, lipid metabolism, biofilm formation, osmotic protection and virulence (Martin et al., 1999; Ng et al., 2004, 2005; Senadheera et al., 2005; Ahn and Burne, 2007; Bisicchia et al., 2007). In *Enterococci*, VanRS responds to the environmental glycopeptide and produces resistance to glycopeptide antibiotic, e.g., vancomycin (Gagnon et al., 2011). CpxAR is commonly present in Gram-negative bacteria and its main function is to sense the osmotic