ISSN 2618-1584 Vol. 8, Issue 3: 72-77, DOI: 10.25236/FMSR.2026.080310

Research Progress on the Resistance Mechanisms of Klebsiella Pneumoniae

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Abstract: *Carbapenem-resistant Klebsiella pneumoniae (CRKP) has become a major global public health threat. The situation of its multiple drug resistance, rapid transmission, and difficulty in treatment has brought about severe challenges to clinical anti-infection treatment. This article reviews the research progress regarding the drug resistance mechanism of CRKP since 2020, concentrating on the mutation and spread of carbapenemases, the driving function of mobile genetic elements, the hidden state of heterogeneous drug resistance, and also the synergistic effect of outer membrane porins, efflux pumps and biofilms. The results indicate that KPC enzyme variants (e.g., KPC-2, KPC-227, KPC-204) in clinically prevalent CRKP strains can affect the efficacy of novel enzyme inhibitors such as ceftazidime/avibactam, and also influence mobile genetic elements such as plasmids. This article is meant to provide references for the mechanism research, clinical detection, and the development of new treatment strategies related to CRKP.*

Keywords: *Carbapenem-resistant Klebsiella pneumoniae, resistance mechanisms, carbapenemases, mobile genetic elements, heterogeneous resistance, efflux pumps, biofilms*

1. Introduction

Klebsiella pneumoniae (KP) that was first isolated from the lung tissue of a deceased pneumonia patient by Karl Friedländer in 1882 belongs to the genus Klebsiella of the Enterobacteriaceae family and is one of the most important pathogens in that genus [1]. The Klebsiella pneumoniae has no flagella or spores, and most strains possess capsules and pili. In terms of the type of infection, it can be categorized into the common type (cKP) and the hypervirulent type (hvKP). In recent years, carbapenem-resistant Klebsiella pneumoniae (CRKP) has become one of the core issues in the global anti-infection research because of its multiple drug resistances, rapid evolution ability and clinical treatment difficulties. According to a systematic review (covering 1284 CRKP isolates from 19 provinces in China), the combined isolation rate of CRKP within Klebsiella pneumoniae in China is 20% (95% CI: 0.10–0.31) [2]. Among them, the respiratory tract infection actually accounts for as much as 77%. Incorporating the research progress in the past five years both at home and abroad, the resistance mechanisms of CRKP mainly include the mutation and dissemination of carbapenemases, the promoting role of mobile genetic elements, the clinical concealment of heterogeneous resistance, and the synergistic effects of outer membrane porins, etc. This article is going to summarize the key mechanisms and the representative studies as mentioned above.

2. The Mutation of Carbapenemases and the Emergence of New Resistance Genes

The mutation of carbapenemases is currently the core mechanism of CRKP's resistance. Common types include the KPC type (*Klebsiella pneumoniae* carbapenemase), the NDM type (New Delhi metallo-β-lactamase) and the OXA-48 type. In the Chinese bacterial resistance monitoring study from 2017 to 2018, a total of 129 clinical isolates of CRKP were identified. It was found that KPC-2 was dominant among carbapenem-resistant Enterobacteriaceae (CRE) with a detection rate of 77.52% (the main gene among 112 isolates) [3]. As of January 2025, all over the world, 242 clinical variants of KPC have been discovered. Mutation hotspots are concentrated in three loop regions that are close to the active site [4]. Accurately identifying KPC variants is extremely important for guiding medication. For example, for strains with the D179Y mutation, ceftazidime/avibactam (CZA/AVI) should be avoided,

ISSN 2618-1584 Vol. 8, Issue 3: 72-77, DOI: 10.25236/FMSR.2026.080310

but may be sensitive to carbapenems [4, 5]. An assessment of 45 KPC variants shows that single detection methods (like the modified carbapenem inactivation test and molecular PCR) may have differences in sensitivity. At present, it is proposed to combine phenotyping screening and gene sequencing so as to enhance the detection rate [4]. (Detailed comparisons of commonly used assays for carbapenemase and its variant detection in CRKP are listed in *Table 1*.) The resistance profiles of major KPC variants are summarized in Table 2. The IncFIIK34 plasmid, which harbors the KPC-2 gene and has a high degree of combination efficiency, is spread among the global carbapenem-resistant hypervirulent Klebsiella pneumoniae (CR-hvKp), thereby making the treatment more challenging [6]. In the actual clinical treatment, the efficacy of aminoglycoside drugs on KPC strains that carry aminoglycoside-modifying enzyme (AME) genes is indeed rather limited. Even if they are quite sensitive in terms of phenotype, treatment failure may still take place due to hidden drug resistance [7]. In contrast, polymyxin B and tigecycline keep a relatively high sensitivity (95%) to most CRE strains [6, 8]. Although CZA shows excellent in vitro activity (100% susceptible) against KPC-2 and OXA-48-like enzyme-positive strains [9, 10], the problem of variant drug resistance is becoming increasingly prominent. At present, some variant strains (such as KPC-19 and KPC-232) that are quite prevalent in the Chinese hospital environment are mainly associated with the ST11 clone [4, 11]. ST11-KL64 is the dominant clone of KPC-variant strains that are resistant to CZA/AVI, and short-term CZA/AVI therapy will lead to drug-resistant mutations [11]. Similarly, Shi et al. reported multiple novel CZA-resistant KPC-2 variants in two patients, further highlighting the rapid evolution of resistance under clinical selective pressure [12]. In a study, an isolated ST11-K64 *Klebsiella pneumoniae* strain carried both KPC-204 (with a DDK insertion at position 270) and the novel variant KPC-227 (harboring the D179Y mutation). Although KPC-227 restores susceptibility to carbapenems, it retains resistance against ceftazidime/avibactam (CZA). The D179Y mutation reduces the enzyme's hydrolytic capacity by lowering its binding affinity toward meropenem. By contrast, Sun et al. documented that KPC-204 confers cross-resistance to both carbapenems and CZA [5]. Clinical evidence supporting the efficacy of novel combinatorial agents such as meropenem/vaborbactam remains insufficient. Accordingly, developing rapid identification assays for KPC variants, exploring phage therapy, and discovering novel β-lactamase inhibitors have become core research priorities against CRKP. (Comparative performances of diverse detection approaches for carbapenemases and their variants in CRKP are summarized in *Table 1*.) Consistent with this viewpoint, a recent in vitro investigation involving 40 clinical KPC-producing CRKP isolates demonstrated that CZA pressure not only enriched well-characterized variants such as KPC-33 (which harbors D179Y) but also induced a previously unreported 15-amino-acid insertion mutant, KPC-136; notably, CZA exposure simultaneously promoted biofilm maturation via the *lsrR*-mediated quorum-sensing pathway [13].

Table 1. Comparison of detection methods for carbapenemases and variants in CRKP

Method	Target	Advantages	Limitations	Best for
Modified carbapenem inactivation test (mCIM)	Carbapenemase activity	Simple, no special equipment	Cannot distinguish enzyme types or variants	Initial screening
Conventional PCR	Known genotypes (e.g. blaKPC)	Rapid, specific	Cannot detect novel or unknown mutations	Known resistance genes
Whole-genome sequencing (WGS)	All gene mutations + plasmid typing	Precise, can identify new variants	Costly, longer turnaround, complex analysis	Research, molecular epidemiology
Phenotypic + CZA susceptibility testing	Resistance to CZA	Direct clinical relevance	Does not identify specific variant	Routine clinical testing

Table 2. KPC variants and their resistance profiles

KPC variant	Key mutation(s)	Susceptibility to carbapenems	Susceptibility to CZA	Prevalent clone	References
KPC-2	None (wild-type)	Resistant	Susceptible	ST11	[3]
KPC-204	DDK insertion at position 270	Resistant	Resistant	ST11-K64	[5]
KPC-227	D179Y	Susceptible (restored)	Resistant	ST11-K64	[5]
KPC-19	Multiple mutations	Resistant	Resistant	ST11	[4,11]
KPC-232	Multiple mutations	Resistant	Resistant	ST11	[4]

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3. The driving role of mobile genetic elements (MGEs) in the spread of antibiotic resistance genes

Mobile Genetic Elements (MGEs), which are a kind of DNA fragment that is able to move within a genome or among different genomes, are basically "movable genetic material units". According to their structure and the way they move, they can be classified into plasmids, transposons, insertion sequences, integrons, phage elements, integrative conjugative elements, and gene transfer agents (GTAs) [14]. Within CRKP, the mobile genetic elements (MGEs) are the core driving forces for the rapid evolution and the spread of drug-resistant genes (such as blaKPC and blaNDM) [15,16]. Integrons, through specific recombination at the attI-attC sites, integrate independent drug-resistant gene cassettes (such as the aminoglycoside-resistant gene rmtB) onto their own platforms resulting in the creation of multiple drug-resistant units. For example, among CRKP strains in Ningbo, 91.7% carry the IS26 insertion sequence, which accelerates mutation of the blaKPC gene through recombination [16]. As a circular DNA molecule that can replicate autonomously, the plasmid is the main vector for the horizontal transfer of carbapenemase genes (like blaKPC and blaNDM) among different strains and even different bacterial species. Plasmids and integrative conjugative elements (ICEs) can directly connect the donor and recipient bacteria through conjugative pili, promoting the horizontal transfer of antibiotic resistance genes among different strains [17]. It is found that insertion sequences (IS5, ISKox3) will frequently insert into the capsule synthesis genes, thus resulting in "capsule phase variation", enhancing the biofilm formation ability and environmental adaptability of carbapenemase-producing Klebsiella pneumoniae (CRKP). This indicates that the mobility of mobile genetic elements can regulate the expression of the host genes. Indeed, a study led by Huashan Hospital of Fudan University has for the first time systematically reported on the isolation of Klebsiella pneumoniae that carries blaKPC-2 from clinical patient samples. After ceftazidime-avibactam is used, multiple new blaKPC variants appear. For example, the team led by Feng Jie discovered that the IS26 insertion sequence is a crucial element that causes the multidrug-resistant gene regions such as blaKPC-2 to expand in a dynamic and unstable way according to [18]. This IS26-associated genomic alteration is a crucial way in which bacteria have evolved to achieve high resistance to avoid antibiotic attacks. Integrons are genetic entities that have site-specific recombination systems. They are capable of seizing, inserting and displaying foreign resistance gene cassettes. In CRKP there are widely existing class I integrons and the gene cassettes they carry can make bacteria develop resistance to many antibiotics like aminoglycosides and trimethoprim-sulfamethoxazole, coupled with the resistance to carbapenems a difficult-to-treat multi-drug resistance phenotype is thus produced [19]. A recent clinical report from a Chinese hospital further highlights the role of IS26 in generating novel resistance determinants. Within a high-risk ST11-KL64 clone, an IS26-flanked element gave rise to a plasmid-borne KPC-157 (KPC-2 with N132S) and a CTX-M-249 variant, which together conferred co-resistance to imipenem/relebactam and ceftazidime-avibactam, demonstrating that mobile elements can rapidly adapt to new combination therapies [20].

4. The concealment and clinical risk of heteroresistance

Heteroresistance means that there are only a small number of drug-resistant subpopulations in the bacterial population, and conventional drug susceptibility testing may underestimate its drug resistance situation [21]. A longitudinal study carried out by Ruijin Hospital discovered that ST15-type CRKP exhibited heterogeneous resistance to polymyxins from the initial stage, and after polymyxin treatment, these subpopulations gradually developed into complete resistance (*mgrB* mutant strains were detected on day 14). As reported by *Tang et al. (2025)*, heteroresistance can serve as a precursor for full antimicrobial resistance development, necessitating regular molecular monitoring with subclonal isolation and molecular typing for high-risk patients [22]. In the same patient cohort of ST15 CRKP, a follow-up study revealed that under combined pressure from polymyxins, ceftazidime-avibactam and meropenem, three distinct KPC variants emerged within a short period, including a novel blaKPC-151 with a Y241-T243 deletion plus a serine substitution. All variants conferred CZA resistance while restoring carbapenem susceptibility, and they originated from an IS26-flanked mobile element, suggesting that IS26 itself may act as a risk factor for rapid CZA-resistance evolution [22].

5. The synergistic effect of other auxiliary resistance mechanisms

In addition to the core mechanisms mentioned above, the drug resistance of CRKP also depends on auxiliary mechanisms like the loss of outer membrane porins, the activation of efflux pumps and the

ISSN 2618-1584 Vol. 8, Issue 3: 72-77, DOI: 10.25236/FMSR.2026.080310

formation of biofilms. Porins are channel-forming proteins in the outer membrane of Gram-negative bacteria, and they play a vital role in the drug resistance mechanism of carbapenem-resistant Klebsiella pneumoniae (CRKP) by regulating the transmembrane transport of antibiotics. If the porin genes ompK35 and ompK36 in CRKP are down-regulated or deleted, the number of outer membrane channels will be greatly reduced, which directly blocks the entry of carbapenem antibiotics (such as meropenem and imipenem) into the bacterial cells [23]. Moreover, the permeability of porins is also dynamically regulated by the periplasmic ion concentration and metabolic state. For example, when lipid metabolism is enhanced, it will lead to periplasmic acidification, causing porin conformational changes, and further narrowing the channel diameter. Additionally, molecular dynamics simulations have shown that the amino acid substitution in the porin constriction region can change the electric field or pore size, thus selectively blocking the diffusion of charged antibiotic molecules (like β-lactams) [24]. A large-scale genomic analysis of more than 10,000 blaKPC-positive K. pneumoniae isolates from China has since provided solid clinical evidence for the porin-deficiency mechanism. ST11 accounted for 87.22% of all such strains, and among them 96.13% carried a truncated OmpK35 together with a unique two-amino-acid Gly-Asp insertion in OmpK36 (OmpK36GD). Molecular modelling suggested that the GD insertion blocks the outermost channel of OmpK36. Strains carrying both porin defects showed significantly higher carbapenem MICs, and reintroduction of wild-type porins largely reversed resistance, confirming that OmpK35 loss and OmpK36 structural alteration act synergistically with KPC-2 [25]. In CRKP, the lack of porins often combines with the production of carbapenemases (such as KPC, NDM, etc.) to result in high resistance. Generally speaking, outer membrane porins mainly play an important role in CRKP resistance because of gene deletion and pore diameter change, and they also easily combine with hydrolysis mechanisms (such as the production of β-lactamases, etc.), making the treatment of CRKP more difficult. A recent study has put forward adjuvants that are targeted at the porin regulation pathway (such as the potassium channel Kch) or have been developed to enhance the penetration of antibiotics, which may bring about new strategies for reversing drug resistance [26]. The outer membrane pump (such as the AcrAB-TolC system) belongs to the Resistance-Nodulation-Cell Division (RND) family, and its core structure includes the periplasmic fusion protein AcrA, the outer membrane channel protein TolC, and the drug-proton antiporter AcrB [27]. This system makes use of the energy provided by ATP hydrolysis to actively expel the antibiotics that enter the cell, and if it is overexpressed, it can notably reduce the concentration of antibiotics inside the cell. This is an important mechanism by which carbapenem-resistant Klebsiella pneumoniae (CRKP) develops resistance to various drugs (such as fluoroquinolones, tetracyclines). The biofilm is a three-dimensional structure formed by the extracellular polysaccharide matrix secreted by bacteria, which can physically impede the penetration of antibiotics and enclose the bacteria to form a "dormant" population, further reducing the sensitivity to antibiotics [28]. The activity of the efflux pumps can reduce the accumulation of antibiotics in the bacterial cells, while the biofilm, by restricting the penetration of antibiotics and offering a protective microenvironment, jointly enhances the survival ability of CRKP. The major resistance mechanisms of CRKP discussed above are summarized in Table 3.

Table 3. Summary of major resistance mechanisms in CRKP

Mechanism category	Key molecules/genes	Mode of action	Clinical impact	References
Carbapenemase mutation	KPC-2, KPC-204, KPC-227, NDM, OXA-48	Amino acid substitutions or insertions near the active site; hydrolysis or reduced antibiotic binding	CZA resistance, altered carbapenem susceptibility	[3-5]
Mobile genetic elements	IncFIIK34 plasmid, IS26, integrons	Horizontal transfer of resistance genes; gene amplification and genomic rearrangements	Cross-strain and cross-species spread of resistance	[6,15-16]
Heteroresistance	mgrB mutants, resistant subpopulations	Small subpopulations resistant; missed by routine susceptibility testing	Gradual evolution to full resistance during therapy	[21-22]
Outer membrane porin loss	OmpK35, OmpK36	Downregulation or deletion → reduced antibiotic uptake	Increased MICs for carbapenems	[23-24]
Efflux pump overexpression	AcrAB-TolC (RND family)	ATP-dependent active efflux of multiple antibiotics	Multidrug resistance (fluoroquinolones, tetracyclines)	[27]
Biofilm formation	Extracellular polysaccharide matrix	Physical barrier + induction of dormant subpopulations	Reduced antibiotic penetration, recurrent infections	[28]

ISSN 2618-1584 Vol. 8, Issue 3: 72-77, DOI: 10.25236/FMSR.2026.080310

6. Conclusion

In general, the antimicrobial resistance mechanism of carbapenem-resistant Klebsiella pneumoniae (CRKP) constitutes a sophisticated multi-layered and interconnected regulatory network. Key contributors underlying this resistance foundation include successive mutational evolution of carbapenemases coupled with novel variant generation, rampant dissemination of mobile genetic elements, cryptic progression of heterogeneous resistance phenotypes, and synergistic effects of accessory resistance pathways involving outer membrane porins, efflux pumps, and biofilm formation. In recent years, although the combination therapy of new enzyme inhibitors such as ceftazidime/avibactam has improved treatment options to a certain extent, the continuous evolution of KPC variants and the accumulation of multiple drug resistance mechanisms have increasingly highlighted the decline or even failure of traditional susceptibility testing. Meanwhile, such diverse resistance mechanisms make traditional susceptibility testing difficult to fully reflect the real resistance potential of the strains, thus increasing the risk of treatment failure. Given the current resistance landscape, CRKP prevention and control should prioritize continuous dynamic surveillance of resistance mechanisms, especially molecular epidemiological investigations of key carbapenemase variants such as KPC. In summary, CRKP resistance represents both a basic scientific challenge in microbiology and a practical challenge in clinical anti-infective therapy. Only through integrated, multi-dimensional efforts—including basic research, clinical monitoring, and novel drug development—can the public health threat of CRKP be effectively addressed.

Acknowledgements

This work was supported by Naval Medical University Basic Medical Research Youth Launch Fund (No. 2025QN086) and Deep Blue Talent Program of No. 905 Hospital of PLA Navy.

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