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PER-7, an Extended-Spectrum β-Lactamase with Increased Activity toward Broad-Spectrum Cephalosporins in *Acinetobacter baumannii*[▽]

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***Acinetobacter baumannii* isolate AP2 was recovered from a bronchial lavage sample of a patient hospitalized in Paris, France. *A. baumannii* AP2 was resistant to all β-lactams, including carbapenems, and expressed the extended-spectrum β-lactamase (ESBL) PER-7, which differs from PER-1 by 4 amino acid substitutions. Compared to PER-1, PER-7 possessed higher-level hydrolytic activities against cephalosporins and aztreonam. The bla_{PER-7} gene was chromosomally located and associated with a mosaic class 1 integron structure. Additionally, isolate AP2 expressed the carbapenem-hydrolyzing oxacillinase OXA-23 and the 16S RNA methylase ArmA, conferring high-level resistance to aminoglycosides.**

Acinetobacter baumannii is an opportunistic pathogen that is an important source of nosocomial infections such as pneumonia and urinary tract and wound infections (2). Treatment of infections due to this microorganism is becoming a serious clinical concern since *A. baumannii* is frequently resistant to multiple antibiotics (21, 22). The main mechanism of resistance to β-lactams in *A. baumannii* corresponds to the production of β-lactamases. In *A. baumannii*, resistance to carbapenems is mostly related to production of metallo-β-lactamases or carbapenem-hydrolyzing oxacillinases (CHDL) (33), while resistance to broad-spectrum cephalosporins mostly results from overexpression of the natural AmpC-type enzyme (4) or from acquisition of extended-spectrum β-lactamases (ESBLs). The ESBL genes that have been identified in *A. baumannii* are bla_{PER-1} and bla_{PER-2}, bla_{GES-11} and bla_{GES-14}, bla_{VEB-1} and bla_{VEB-1a}, and bla_{TEM-92} and $bla_{CTX-M-2}$ (3, 7, 14–16, 20, 27, 28, 30). One study reported the occurrence of a PER-like ESBL in *A. baumannii* in Korea, but nothing is known about its precise hydrolytic properties (19). The bla_{PER-1} gene was first identified in a *Pseudomonas aeruginosa* isolate (17), and then this gene was identified worldwide in many species, including *Alcaligenes faecalis* (13), *Salmonella enterica* (25), *Proteus mirabilis* (18), *Providencia stuartii* (25), *Aeromonas media* (24), *Aeromonas punctata* (39), and *A. baumannii* (27, 30). Several PER-like variants have been identified, corresponding to two subgroups, one consisting of PER-1-like point mutant derivatives (namely, PER-3, PER-4, and PER-5) and one consisting of PER-2 and PER-6, differing by 22 amino acids from each other and showing 85% amino acid identity with PER-1 (9, 20, 35). The bla_{PER-1} gene was found to be part of a composite transposon named Tn*1213* (25). This transposon is made of one copy of IS*Pa12* and one copy of the unrelated IS*Pa13* element (25). The bla_{PER-2} gene was identified in association with one copy of IS*Pa12* upstream of the β-lactamase gene but no copy of IS*Pa13* (25, 35). The bla_{PER-6} gene identified in *Aeromonas allosaccharophila* was located inside a mosaic structure composed of truncated genes encoding mostly proteins of unknown functions (9).

A. baumannii AP2 was isolated from a bronchial sample of a 30-year-old patient hospitalized at the intensive care unit of the Necker-Enfants Malades University hospital (Paris, France) in April 2010. Identification of *A. baumannii* AP2 was performed by using the API32GN system (bioMérieux, Marcy l'Etoile, France) and was confirmed by 16S rRNA gene sequencing as described previously (6). *A. baumannii* AP2 was resistant to penicillins, β-lactamase inhibitor-penicillin combinations, broad-spectrum cephalosporins, aztreonam, and carbapenems (Table 1) (5). Synergy between ceftazidime and clavulanic acid suggested the production of an ESBL. In addition, *A. baumannii* AP2 was resistant to aminoglycosides, fluoroquinolones, sulfonamides, and tetracycline and showed susceptibility only to colistin (MIC of 0.5 μg/ml). Whole-cell DNA of *A. baumannii* isolate AP2 was extracted as described previously (23). This DNA was used as a template under standard PCR conditions (37) with a series of primers designed for the detection of class A β-lactamase genes (bla_{TEM}, bla_{SHV}, bla_{PER-1}, bla_{VEB-1}, bla_{GES-1}, and bla_{CTX-M}) (3, 26, 30, 31, 34), of the intrinsic bla_{ampC} gene (10), of class B β-lactamase genes (bla_{IMP}, bla_{VIM}, bla_{SIM}, and bla_{NDM}), and of class D β-lactamase genes (bla_{OXA-23}, bla_{OXA-40}, bla_{OXA-51}, bla_{OXA-58}, and $bla_{OXA-143}$) (11, 27, 28, 32). Detection of the IS*Aba1* element upstream of the bla_{ampC} and bla_{OXA-51} genes was performed as described previously (10). *A. baumannii* AP2 harbored a bla_{OXA-51}-like naturally occurring gene, and further sequencing revealed that it corresponded to bla_{OXA-64}, also known as $bla_{OXA-Ab-2}$ (32). The IS*Aba1* element was not identified upstream of the intrinsic $bla_{OXA-Ab-2}$ and bla_{ampC} genes in *A. baumannii* AP2, suggesting that both genes were not overexpressed. *A. baumannii* isolate AP2 harbored the bla_{OXA-23} CHDL gene, encoding resistance to carbapenems, and possessed a bla_{PER}-like gene that corresponded to the novel bla_{PER-7} gene variant (see below). In addition, *A. baumannii* AP2

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TABLE 1. MICs of β-lactams for *A. baumannii* strain AP2, *E. coli* pTOPO-PER-1, *E. coli* pTOPO-PER-6, and *E. coli* pTOPO-PER-7 in *E. coli* TOP10 or *E. coli* HB4 reference strains[a]

β-Lactams	MIC (μg/ml)								
	A. baumannii isolate AP2	*E. coli* TOP10 (pTOPO-PER-1)	*E. coli* TOP10 (pTOPO-PER-6)	*E. coli* TOP10 (pTOPO-PER-7)	*E. coli* TOP10	*E. coli* HB4 (pTOPO-PER-1)	*E. coli* HB4 (pTOPO-PER-6)	*E. coli* HB4 (pTOPO-PER-7)	*E. coli* HB4
Amoxicillin	>256	>256	>256	>256	2	>256	>256	>256	8
Amoxicillin-CLA	>256	4	4	8	2	32	64	64	8
Ticarcillin	>256	>256	>256	>256	2	>256	>256	>256	4
Ticarcillin-CLA	>256	16	16	16	2	32	32	32	4
Piperacillin	>256	32	256	256	1	128	256	256	4
Piperacillin-TZP	128	8	16	16	1	16	32	32	4
Cephalothin	>256	>256	>256	>256	4	>256	>256	>256	64
Cefuroxime	>256	>256	>256	>256	2	>256	>256	>256	16
Cefoxitin	64	2	2	2	2	>256	>256	>256	>256
Cefotaxime	>256	8	16	32	0.06	64	64	64	0.38
Cefotaxime-CLA	0.5	0.03	0.06	0.12	0.06	0.5	0.5	0.5	0.38
Ceftazidime	>256	>256	>256	>256	0.12	>256	>256	>256	4
Cefepime	>256	4	4	4	0.06	32	32	32	0.75
Cefepime-CLA	1	0.06	0.06	0.12	0.06	0.5	0.5	1	0.75
Cefpirome	>256	16	8	16	0.06	>32	>32	>32	0.5
Aztreonam	>256	128	128	256	0.03	>256	>256	>256	4
Meropenem	>32	0.03	0.03	0.03	0.03	0.5	1	0.5	0.25
Ertapenem	ND	0.03	0.06	0.03	0.03	1	4	1.5	1
Imipenem	>32	0.12	0.12	0.12	0.12	0.5	4	1.5	0.25
Imipenem-CLA	>32	0.12	0.12	0.12	0.12	0.5	1	0.5	0.25

[a] CLA, clavulanic acid (4 μg/ml); TZB, tazobactam (4 μg/ml); ND, not determined.

harbored the 16S RNA methylase *armA* gene, conferring high-level resistance to all aminoglycosides.

Shotgun cloning using HindIII-restricted genomic DNA and HindIII-restricted pBK-CMV plasmid was performed as described previously (17). Recombinant plasmids were selected onto Trypticase soy (TS) agar plates containing ceftazidime (2 μg/ml) and kanamycin (30 μg/ml). The resulting recombinant *Escherichia coli* strain (pBK-PER-7) displayed an ESBL phenotype with high-level resistance to broad-spectrum cephalosporins and aztreonam and remained susceptible to cefoxitin and carbapenems. In addition, it was resistant to sulfonamides and chloramphenicol and showed reduced susceptibility to rifampin, but it remained susceptible to fluoroquinolones, aminoglycosides, and tetracycline. Sequence analysis of the cloned DNA fragment identified the $bla_{\text{PER-7}}$ gene. Compared to PER-1, PER-7 exhibited four amino acid substitutions, Q119E, V245I, R246K, and A294T (1). The last three substitutions had previously been identified in PER-6.

Sequencing of the insert of recombinant plasmid pBK-PER-7 revealed that an IS*CR1* element (38) was present immediately upstream of the $bla_{\text{PER-7}}$ gene, but no additional IS*CR1* copy was identified downstream of $bla_{\text{PER-7}}$. IS*CR1* possessed, at its right extremity, promoter sequences named $P_{\text{CR1-1}}$ (made of the −35 [TAAACG] and −10 [TAAGAT] regions) that were previously shown to be responsible for the expression of $bla_{\text{CTX-M}}$ and *qnrA* genes (36). The similar genetic context (the distance separating the *ori*IS extremity of IS*CR1* from the $bla_{\text{PER-7}}$ start codon being only 74 bp) that we identified in *A. baumannii* AP strongly suggests that $bla_{\text{PER-7}}$ expression might be also under the control of $P_{\text{CR1-1}}$.

Further analysis of the IS*CR1* left extremity (according to Fig. 1) identified a class 1 integron that contained two gene cassettes, namely, *arr-2* and *cmlA7*, that encode resistance to rifampin and chloramphenicol, respectively. The 3′ conserved sequence (3′CS) extremity was made of a fusion of *qacEΔ1* and *sul1*, but the *orf5* gene, usually described as being associated with a class 1 integron, was absent, as previously described, with the complex class 1 integron associated with IS*CR1* (38).

Downstream of the $bla_{\text{PER-7}}$ gene, a gene encoding a hypothetical protein followed by a gene encoding a putative electron transfer flavoprotein-ubiquinone oxidoreductase previously found on the chromosome of *A. baumannii* AYE (8) were identified, further reinforcing the hypothesis of a chromosomal location for the IS*CR1*-$bla_{\text{PER-7}}$-associated complex class 1 integron (Fig. 1).

In order to evaluate and compare the spectra of hydrolysis of PER-1, PER-6, and PER-7, the corresponding genes were amplified using the degenerated primers PERextS and specific primers PER-1extAS and PER-6extAS as described previously (9). A $bla_{\text{PER-7}}$ amplicon was obtained with primers PERextS and PER-1extAS. The obtained PCR fragment was purified with a QIAquick column (Qiagen, Courtaboeuf, France) and cloned into the pTOPO vector (Qiagen, Courtaboeuf, France). The three genes were respectively cloned in the same vector and expressed in *E. coli* TOP10. It gave rise to the recombinant *E. coli* TOP10(pPER-1), *E. coli* TOP10(pPER-6),

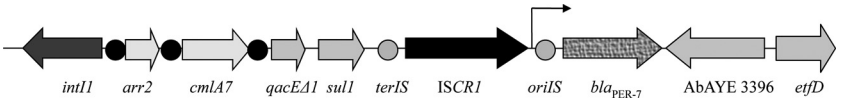

FIG. 1. Schematic map representing the genetic structure surrounding the $bla_{\text{PER-7}}$ gene. The genes and their corresponding transcriptional orientations are indicated by horizontal arrows. The 59-base elements are indicated by a black circle. The replication origin *ori*IS and terminus *ter*IS of IS*CR1* are indicated by a gray circle. AbAYE, *A. baumannii* AYE.

TABLE 2. Kinetic parameter values for β-lactamase PER-7[a]

Substrate	K_m (μM)		k_{cat} (s^{-1})		k_{cat}/K_m (mM^{-1}/s^{-1})	
	PER-7	PER-6	PER-7	PER-6	PER-7	PER-6
Benzypenicillin	90	200	15	5	170	25
Amoxicillin	150	NA	5	NA	30	NA
Ticarcillin	25	9	1	0.4	40	50
Piperacillin	10	4	0.3	0.1	30	25
Cephalothin	100	55	20	8	200	145
Cephaloridine	550	NA	130	NA	240	NA
Cefoxitin	0.08[b]	NA	ND	ND	ND	ND
Cefotaxime	1,000	900	100	40	100	45
Ceftazidime	3,000	1,000	120	10	40	10
Cefepime	2,300	2,000	70	10	30	5
Aztreonam	90	40	10	3	110	75
Imipenem	100	1.5	0.05	0.006	0.5	4
Meropenem	5[b]	10	ND	0.004	ND	0.4

[a] Data are the means of results from three independent experiments. The standard deviations were within 10% of the means. Data for PER-6 are from Girlich et al. (9). ND, not determinable; NH, no detectable hydrolysis; NA, not available.

[b] K_m was obtained as a K_i value.

and *E. coli* TOP10(pPER-7) strains, expressing PER-1, PER-6, and PER-7, respectively. In order to compare the catalytic properties of PER-1, PER-6, and PER-7, the corresponding genes were cloned and expressed in *E. coli* TOP10 under the control of an identical promoter. Then, these recombinant plasmids were electroporated into *E. coli* HB4 in order to evaluate the impact of their production in an *E. coli* background that corresponds to a porin-deficient strain. As expected, expression of the bla_{PER-1}, bla_{PER-6}, and bla_{PER-7} genes in *E. coli* TOP10 conferred resistance to penicillins, to broad-spectrum cephalosporins, and to monobactams (Table 1). In *E. coli* HB4 lacking porins OmpF and OmpC (12), expression of both the bla_{PER-6} and the bla_{PER-7} genes conferred reduced susceptibility to carbapenems, whereas that of bla_{PER-1} did not. Noteworthy, the MICs of imipenem, meropenem, and ertapenem were higher for PER-6 than for PER-7, suggesting a weaker carbapenemase activity for PER-7. In contrast, the MICs of cefotaxime and aztreonam were higher for *E. coli* expressing PER-7 than for *E. coli* expressing either PER-6 or PER-1.

In order to characterize more precisely whether PER-7 might possess specific catalytic properties, a kinetic study was conducted as described previously (29). *E. coli* DH10B (pPER-7) produced a β-lactamase with a pI value of 6.1, whereas the pI values of PER-1 and PER-6 are 5.4 and 6.4, respectively (9, 17). PER-7 was purified (>90% as estimated by SDS-PAGE analysis) from *E. coli* TOP10 pTOPO-PER-7 crude extract by using a two-step chromatography process (a anion exchange at pH 7.5 followed by an anion exchange at pH 6.9 using a Q Sepharose column).

β-Lactamase PER-7 had a broad-spectrum hydrolysis profile, including penicillins, broad-spectrum cephalosporins, and to a lesser extent carbapenems (Table 2). PER-7 was less susceptible to inhibition by clavulanic acid and tazobactam than PER-6. The 50 percent inhibitory concentrations (IC_{50}s) of clavulanic acid were 3 and 0.3 μM for PER-7 and PER-6, respectively, and those of tazobactam were 1 and 2 μM for PER-7 and PER-6, respectively. Since a synergy image was observed *in vitro* between cefoxitin and ceftazidime, IC_{50}s were also measured using cefoxitin as an inhibitor. The IC_{50} for cefoxitin was at 2 μM. PER-7 showed higher catalytic efficiencies (k_{cat}/K_m) for cefotaxime, ceftazidime, cefepime, and aztreonam than PER-6 (Table 2). Overall, PER-7 showed higher K_m values (lower affinity) for most substrates. The k_{cat}/K_m values for cefotaxime and ceftazidime, respectively, were slightly higher for PER-7 than for PER-6. Hydrolysis of imipenem was detected, but at lower rate than that observed for PER-6. In fact, the K_m value for imipenem was 100-fold higher for PER-7 than for PER-6, evidencing the lower affinity of PER-6 for that substrate. In contrast, no significant hydrolysis was detected for meropenem.

This study identified a novel PER-type β-lactamase whose gene was identified inside a novel genetic structure. PER-7, as already observed for PER-6 identified in *A. allosaccharophila* from the aquatic environment, exhibited a weak but significant carbapenemase activity. The level of that activity remained quite low; thus, it cannot provide resistance to carbapenems by itself, but we showed that it may confer resistance or intermediate susceptibility to *E. coli* once associated with poor outer membrane permeability. This result may explain the high level of resistance to carbapenems of *A. baumannii* AP2 that coproduced PER-7 and OXA-23. This work further demonstrates that bla_{PER}-like gene acquisition may be linked to a variety of genetic elements (Fig. 1), and the involvement of IS*CR1* is especially noteworthy, since that peculiar insertion (IS) element seems to be significantly involved in the genetic plasticity of *A. baumannii*.

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