The peptidoglycan structure of in vitro selected ampicillin-resistant mutant Enterococcus faecium D344M512 and of the susceptible parental strain D344S was determined by reverse phase high performance liquid chromatography and mass spectrometry. The muropeptide monomers were almost identical in the two strains. The substantial majority (99.3%) of the oligomers from the susceptible strain D344S contained the usual d-alanyl $\rightarrow$ d-asparaginyl (or d-aspartyl)-l-lysyl cross-link (d-Ala $\rightarrow$ d-Asx-l-Lys) generated by $\beta$-lactam-sensitive DD-transpeptidation. The remaining oligomers (0.7%) were produced by $\beta$-lactam-insensitive LD-transpeptidation, because they contained l-lys $\rightarrow$ d-asx-l-lys cross-links. The muropeptide oligomers of the ampicillin-resistant mutant D344M512 contained only these l-lys $\rightarrow$ d-asx-l-lys cross-links indicating that resistance was due to the bypass of the $\beta$-lactam-sensitive DD-transpeptidation reaction. The discovery of this novel resistance mechanism indicates that DD-transpeptidases cannot be considered anymore as the sole essential transpeptidase enzymes.

The peptidoglycan of Escherichia coli is generated by polymerization of a precursor composed of N-acetylgalactosamine (GlcNAc) and N-acetylmuramic acid (MurNAc) substituted by d-alanyl-d-asparaginyl (d-alanyl-d-asparaginyl)-l-lysyl pentapeptide stem (d-Ala$_4$-d-iGlu$_3$-d-Ala$_5$-$\rightarrow$ l-lys) (1). The final steps of peptidoglycan synthesis involve polymerization of the glycan strands by glycosyltransferases and cross-linking of the peptide stems by DD-transpeptidases. The latter enzymes catalyze formation of a peptide bond between the $\alpha$-carboxyl of d-Ala at the fourth position of a donor stem and the $\epsilon$-amino group of d-Ala$_2$-pm$_6$ at the third position of an acceptor stem (8, 9). The first step of the transpeptidation reaction leads to the release of the C-terminal d-Ala$_4$ of the donor peptide stem and to the formation of a covalent adduct between the penultimate residue (d-Ala$_3$) and a conserved catalytic serine residue of the DD-transpeptidases (2, 3). Antibiotics of the $\beta$-lactam class, such as penicillin and ampicillin, are structural analogs of the C-terminal d-Ala$_4$-d-Ala$_5$ end of peptidoglycan precursors and act as suicide substrates in a similar acylation reaction (4). The second step of the transpeptidation reaction results in a cross-linking and release of the DD-transpeptidases. In contrast, acylation of the DD-transpeptidases by $\beta$-lactams is nearly irreversible. The DD-transpeptidases are the killing target of the $\beta$-lactams, because transpeptidation is essential to maintain the integrity of the cell wall (2).

The overall structure and mode of synthesis of peptidoglycan is conserved in eubacteria, although variations have been detected, in particular in the sequence of the peptide stem. In the Gram-positive bacteria Enterococcus faecium and Lactobacillus casei, d-iGlu at the second position is amidated, meso-A2 pm$_3$ at the third position is replaced by l-Lys, and the $\epsilon$-amino group of the latter amino acid is substituted by d-Asn or d-Asp (12–14). Consequently, the DD-transpeptidases of E. faecium and L. casei catalyze formation of d-Ala$_4$ $\rightarrow$ d-Asx-l-Lys$_8$ cross-links. Several lines of evidence indicate that the DD-transpeptidase targets of $\beta$-lactam antibiotics are ubiquitous in eubacteria that produce peptidoglycan. First, penicillin-binding proteins have been reproducibly detected based on acylation with radiolabeled penicillin (15, 16). More importantly, analyses of peptidoglycan precursors and of the corresponding biosynthetic enzymes have shown that the C-terminal DD-configuration of residues at the C-terminal positions 4 and 5 of the peptide stem is uniformly conserved (12, 17). This implies conservation of the structural analogy between $\beta$-lactams and the donor substrate of the DD-transpeptidases. Finally, analyses of peptidoglycan structure in a wide range of bacteria have invariably revealed that cross-linking was mainly or exclusively generated by DD-transpeptidase activities that catalyzed peptide bond formation between d-Ala at the fourth position of a donor stem and the amino group of the acceptor (12). In this report,
we showed that emergence of high level ampicillin resistance in an in vitro selected mutant of \textit{E. faecium} was associated with replacement of D-Ala\textsubscript{4} \rightarrow D-Asx\textsubscript{1}-L-Lys\textsubscript{8} by L-Lys\textsubscript{8} \rightarrow D-Asx\textsubscript{1}-L-Lys\textsubscript{8} cross-links establishing for the first time that bacteria can bypass the requirement for \beta-lactam-sensitive DD-transpeptidase activity.

**EXPERIMENTAL PROCEDURES**

\textbf{Strains and Growth Conditions—} \textit{E. faecium} D344S is highly susceptible to ampicillin and derives from \textit{E. faecium} D344 (18) by a spontaneous deletion of \textit{pbp5} encoding the low-affinity penicillin-binding protein. \textsuperscript{5} This strain was chosen to avoid selection of ampicillin resistance because of penicillin-binding protein 5 alterations (19). \textit{E. faecium} D344M512 is a spontaneous mutant of D344S obtained by five serial selection steps on agar containing increasing concentrations of ampicillin. All cultures were performed at 37 °C in brain heart infusion (Difco Laboratories, Detroit, MI) agar or broth without shaking. Minimal inhibitory concentrations of ampicillin (Bristol-Myers, Paris, France) were determined by the agar dilution method.

\textbf{Peptidoglycan Structure Analysis—} Peptidoglycan was obtained after 4\% sodium dodecyl sulfate treatment at 100 °C. The pellet was treated with Pronase (200 \textmu g/ml) for 16 h at 37 \textdegree C in 10 mM Tris-Cl, pH 7.4, and then after centrifugation (40,000 \times g, 4 \textdegree C), the pellet was treated with trypsin (200 \textmu g/ml) for 16 h at 37 \textdegree C in 20 mM potassium phosphate buffer (pH 7.8) to remove the contaminating proteins from the protease-resistant proteoglycan. The pellet was washed twice with water and treated with lysozyme and mutanolysin, and muropeptides were resolved by reverse-phase high performance liquid chromatography (HPLC) and identified by mass spectrometry (MS) as described.

\textbf{Fragmentation Analysis of Selected Muropeptides—} The structure of muropeptides B and E of D344M512 was determined by MS/MS performed on singly and doubly charged molecules with argon as collision gas (21) using a Waters 600 MS-HPLC pump system and a Waters PDA 996 liquid chromatograph with a diode array detector system coupled to a Finnigan TSQ 7000 triple quadrupole mass spectrometer (San Jose, CA). Muropeptides 11 and 13 of D344S and muropeptides 8, C, D, G, and H of D344M512 were purified by reverse-phase high pressure liquid chromatography and analyzed by MS/MS using the nanoelectrospray source kit for the Finnigam TSQ 7000 Protonona A/S pressure liquid chromatography and identified by MS/MS (21, 22).

\textbf{RESULTS}

\textbf{Characteristics of D344S and D344M512—} The minimal inhibitory concentration of ampicillin for the parental strain D344S was 0.06 \textmu g/ml. Growth of the ampicillin-resistant mutant D344M512 was not inhibited at the highest drug concentration tested (minimal inhibitory concentrations > 2000 \textmu g/ml).

\textbf{Muropeptide Composition of Peptidoglycan from D344S and D344M512—} The peaks in the HPLC muropeptide profiles of \textit{E. faecium} D344S (Fig. 1A) and D344M512 (Fig. 1B) were identified, and their relative amounts were determined (Table I). Monomers were eluted first between 49 and 69 min followed by oligomers (68–84 min). The monomers accounted for the same proportion of all muropeptides in the two strains (37–38\%), and the monomer profiles were almost identical (peaks 1–10). The molecular mass and deduced structure of these monomers were in accordance with previous analyses of different strains of \textit{E. faecium} (13, 14). The oligomer profile of the parental strain D344S was also in agreement with previous studies (13, 14). In contrast, the peptidoglycan of D344M512 contained a novel oligomer muropeptide species (peaks A–M). The muropeptide profiles of D344M512 grown in the absence of antibiotic (Fig. 1B) or in the presence of 32 \textmu g/ml ampicillin (data not shown) were very similar indicating that cross-linking of these novel oligomers was not inhibited by the drug.

\textbf{Figure 1. HPLC muropeptide profiles of D344S (A) and ampicillin-resistant mutant D344M512 (B).} Purified peptidoglycan was digested with lysozyme and mutanolysin, and muropeptides were resolved by reverse-phase high pressure liquid chromatography. Numbers and letters correspond to peaks identified in Table I.

\footnotesize{\textsuperscript{2} J.-L. Mainardi, M. Arthur, and L. Gutmann, unpublished results.}
This observation and previous analyses of muropeptides from E. faecium indicated that aspartate-branched muropeptides harbored the D-Ala₄ cross-link or a donor tripeptide stem and an acceptor tetrapeptide stem and an acceptor tetrapeptide stem with an L-Lys₃ cross-link generated by DD-transpeptidation. The most prevalent dimer of D344M512, muropeptide E (referred to as Asp-tri-Asn-tri, dimer B because it eluted 1.2 min before dimer B and differed by one mass unit from dimer B.

Structure of Dimers E, C, B, and A of Mutant D344M512—

The molecular composition was determined by reverse-phase HPLC, mass spectrometry, and MS/MS. The relative amounts of the compounds are expressed as percentages calculated from the UV absorbance of peaks in HPLC elution profiles of D344S (Fig. 1A) and D344M512 (Fig. 1B).

| Peak number<sup>a</sup> | Proposed structure<sup>c</sup> | Mass [M + H]<sup>+</sup> | Amounts<sup>b</sup> |
|------------------------|-----------------------------|------------------|------------------|
|                        |                             | Observed         | Calculated       | D344S | D344M512 |
| Monomers               |                             |                  |                  |
| 1                      | ds-di                       | 669.4            | 37.2             | 37.8  |
| 2                      | ds-tri                      | 826.5            | 0.5              | 0.3   |
| 3                      | ds-tetra                    | 897.5            | 6.3              | 5.8   |
| 4                      | ds-Asp-tri                  | 941.7            | 2.5              |
| 5                      | ds-Asn-tri                  | 940.6            | 1.7              |
| 6                      | ds-Asp-tetra                | 1012.5           | 16.2             |
| 7                      | ds-Asn-tetra                | 1011.3           | 19.5             |
| 8                      | ds-Asn-penta                | 1082.6           | 3.9              |
| 9                      | ds(AC)-Asp-tri              | 983.7            | 3.6              |
| 10                     | ds(AC)-Asn-tri              | 982.7            | 2.5              |
| Dimers and trimers     |                             |                  |                  |
| A                      | Bis-ds-tri-Asp-tri          | 1749.7           | 62.8             |
| B                      | Bis-ds-tri-Asn-tri          | 1748.8           | 62.2             |
| C                      | Bis-ds-Asp-Asn-tri          | 1803.7           | 8.0              |
| 11                     | Bis-ds-tri-Acetyl-Asn-tri   | 1819.7           | 0.2              |
| D                      | Bis-ds-Acetyl-Asn-tetra     | 1819.0           | 3.5              |
| E                      | Bis-ds-Asn-tri-Asn-tetra    | 1862.8           | 2.5              |
| F                      | Bis-ds-Asn-tri-Asn-tetra    | 1934.0           | 17.6             |
| G                      | Bis-ds-Asn-tri-Acetyl-Asn-tetra | 1933.1     | 7.3              |
| H                      | Bis-ds-Acetyl-Asn-tri       | 2004.7           | 1.8              |
| I                      | Bis-ds-Acetyl-Asn-tetra     | 2004.7           | 2.2              |
| J                      | Bis-ds-Acetyl-Asn-tetra     | 2005.0           | 1.3              |
| K                      | Bis-ds-Asn-tri-Asn-tetra    | 2004.9           | 5.5              |
| L                      | Bis-ds-Acetyl-Asn-tetra     | 2005.9           | 0.7              |
| M                      | Bis-ds-Asn-Asn-Acetyl-Asn   | 2016.0           | 0.7              |
| N                      | Bis-ds-Asn-Acetyl-Asn       | 2017.0           | 0.7              |

<sup>a</sup> The values are presented as a percentage of the sum of all peaks presented in the Table.<br><sup>b</sup> Muropeptide peak designation as in Fig. 1.<br><sup>c</sup> Ds, disaccharide (N-acetylgulosamine-β-1,4-N-acetylmuramic acid); Bis, dimeric form; Ter, trimeric form; di, dipeptide (L-alanyl-D-isoglutamine); tri, tripeptide (L-alanyl-D-isoglutamyl-L-lysine); tetra, tetrapeptide (L-alanyl-D-isoglutamyl-L-lysyl-D-alanine); penta, pentapeptide (L-alanyl-D-isoglutamyl-L-lysyl-D-alanyl-D-alanine); Asn, D-asparagine; Asp, D-aspartate; AC, O-acetylation on both N-acetylmuramic acids of the dimer.

<sup>d</sup> Assignment of Asp and Asn residues to either stem peptide is arbitrary.

<sup>e</sup> D-aspartate instead of an asparagine residue on the e-amino group of the L-lys₃ of the donor peptide stem (Asp-tri-Asn-tri) (Fig. 3) was a tri-Asn-dimer tripeptide containing the unusual L-Lys₃ → D-Asn-L-Lys₃ cross-link and an unsubstituted L-Lys₃ in the donor stem peptide (Fig. 3). Dimer A (Mₐ 1748.7) was most probably the D-aspartate-containing analog of dimer B because it eluted 1.2 min before dimer B and differed by one mass unit from dimer B.

Structure of Dimers D and G of D344M512 Compared with That of Dimers 11 and 13 of D344S—Comparison of the muropeptides from D344S and D344M512 revealed the presence of dimers that had similar molecular masses but did not elute exactly with the same retention times. For example, muropeptide 13 (see above) and G present in D344S and D344M512, respectively, had a molecular mass of 1932.5 and 1932.0 and a retention time of 75.4 and 76.4 min (Table 1, Fig. 1). For this pair of muropeptides, the observed mass was consistent with two alternative structures containing either a donor tetrapeptide stem and an acceptor tripeptide stem with a D-Ala₄ → D-Asx-L-Lys₃ cross-link or a donor tripeptide stem and an acceptor tetrapeptide stem with a L-Lys₃ → D-Asx-L-Lys₃ cross-link (Fig. 3). The two structures were differentiated on the basis of the presence or absence of a C-terminal alanine residue. The complete anal-
yses of the MS/MS fragmentation pattern of muropeptides 13 of D344S and G of D344M512 are presented in Figs. 2 and 6, respectively, whereas Fig. 7 provides a comparison of the relevant portions of the two patterns. Muropeptide G of D344M512 contained an alanine residue that was not engaged in the cross-bridge (Figs. 6 and 7). In particular, the peak at m/z 1641.6 resulted from the loss of one alanine residue at the C-terminal end of the acceptor tetrapeptide stem after the loss of an additional asparagine residue gave an ion at m/z 1616.1. The loss of both GlcNAc residues gave an ion at m/z 1527.4; the loss of an additional asparagine residue gave an ion at m/z 1412.9. The loss of GlcNAc-MurNAc and of an alanine residue gave an ion at m/z 1382.0; the loss of an additional GlcNAc residue gave an ion at m/z 1179.0; the loss of an additional isoglutamine residue gave an ion at m/z 1050.7; the loss of additional lysine, asparagine, and alanine residues gave an ion at m/z 720.0; the loss of additional asparagine, lysine, and isoglutamine residues gave an ion at m/z 349.4. The ion at m/z 331.4 corresponds to the tripeptide alanyl-asparaginyl-lysine.

Fig. 2. MS/MS spectrum and schematic representation of muropeptide 13 with an [M + H]+ ion at m/z 1933.5. The loss of one GlcNAc residue gave an ion at m/z 1730.2; the loss of an additional asparagine residue gave an ion at m/z 1616.1. The loss of both GlcNAc residues gave an ion at m/z 1527.4; the loss of an additional asparagine residue gave an ion at m/z 1412.9. The loss of GlcNAc-MurNAc and of an alanine residue gave an ion at m/z 1382.0; the loss of an additional GlcNAc residue gave an ion at m/z 1179.0; the loss of an additional isoglutamine residue gave an ion at m/z 1050.7; the loss of additional lysine, asparagine, and alanine residues gave an ion at m/z 720.0; the loss of additional asparagine, lysine, and isoglutamine residues gave an ion at m/z 349.4. The ion at m/z 331.4 corresponds to the tripeptide alanyl-asparaginyl-lysine.

Fig. 3. Proposed structures of the main muropeptide dimers of D344S and D344M512. Muropeptide designations refer to peaks of the chromatogram in Fig. 1. a, % of total muropeptides; b, Rt, retention time (min); c, assignment of Asp to either stem peptide is arbitrary.
of one N-acetylglucosamine residue (m/z 1730.5). Similarly, the peak at m/z 1437.9 was because of the loss of one alanine residue at the C-terminal end of the tetrapeptide stem after the loss of both N-acetylglucosamine residues (m/z 1527.3). The loss of the alanine residue was also found from another major fragmentation product (m/z 1178.7) yielding ions at m/z 1089.6 (Fig. 6). Thus, muropeptide G had a cross-link through an asparagine between two lysine residues (Fig. 3). In contrast, the fragmentation profile of muropeptide 13 of D344M512 did not reveal the presence of any structure generated by the cleavage of a C-terminal alanine residue confirming that the C-terminal d-alanine of the donor tetrapeptide stem was participating in the formation of a D-Ala₄→d-Asn-L-Lys₃ cross-link. Using the same approach, muropeptides 11 of D344S (Mᵣ
1818.7) and D of D344M512 (Mr 1818.0) were found to correspond to a tetra-Asn-tri dimer with a D-Ala4 D-Asn-L-Lys3 cross-link and to a tri-Asn-tetra dimer with a L-Lys3 D-Asn-L-Lys3 cross-link, respectively (data not shown).

Analogs of Dimer G—Dimer F eluted slightly before dimer G (retention time 74.8 versus 76.4 min, respectively) and differed from dimer G by one molecular mass unit (Mr 1933.0 versus 1932.1). Based on a previous comparison of dimers E and C (see FIG. 6. MS/MS spectrum and schematic representation of muropeptide G with an [M + H]+ ion at m/z 1933.1. Major fragmentation products are because of the loss of one GlcNAc residue (the peak at m/z 1933.1 gave an ion at m/z 1730.5) or the loss of both GlcNAc residues (the peak at m/z 1933.1 gave an ion at m/z 1527.3). The loss of GlcNAc-MurNAc and of one alanine residue gave an ion at m/z 1382.2; the loss of an additional GlcNAc residue gave an ion at m/z 1178.7; the loss of an additional isoglutamine residue gave an ion at m/z 1050.7; the loss of additional lysine, alanine, and asparagine residues gave an ion at m/z 719.6; the loss of an additional asparagine, lysine, and isoglutamine residues gave an ion at m/z 349.5. The peaks at m/z 1641.6, 1437.9, and 1089.6, issued from ions at m/z 1730.5, 1527.3, and 1178.6, respectively, correspond to the loss of the C-terminal alanine of the acceptor tetrapeptide stem peptide.

FIG. 7. Comparison of the MS/MS fragmentation patterns of muropeptide G ([M + H]+ ion at m/z 1933.1) of D344M512 and muropeptide 13 ([M + H]+ ion at m/z 1933.5) of D344S. For both muropeptides, loss of one or both GlcNAc residues gave ions at m/z 1730.5 and 1527.3, respectively. From the latter peak, loss of one MurNAc residue and the N-terminal alanine residue gave peaks at m/z 1178.6 (D344M512) or 1179.3 (D344S). Loss of the C-terminal alanine from the acceptor tetrapeptide stem peptide of muropeptide G produced peaks at m/z 1641.6, 1437.9, and 1089.6 that were issued from ions at m/z 1730.5, 1527.3, and 1178.6, respectively. These peaks were absent from the fragmentation pattern of muropeptide 13.
above), most likely dimers F and G differed only by the presence of a d-asparagine or a d-aspartate residue. Finally, MS/MS analysis of muropeptide H revealed an Asn-tri-Asn-penta dimer containing the L-Lys₃ → D-Asn-L-Lys₃ cross-link present in the other dimers of D344M512 (data not shown).

Overview of the Oligomers from D344S and D344M512—All the oligomers of mutant D344M512 that were analyzed contained the unusual L-Lys₃ → D-Asx-L-Lys₃ cross-link instead of the d-Ala₄ → D-Asx-L-Lys₃ cross-link present in the parental susceptible strain. Despite this major difference, the cross-linked peptidoglycan generated by DD-transpeptidation in D344S or by LD-transpeptidation in D344M512 displayed striking similarities. In particular, triptide stems were detected at the acceptor position in the majority of the oligomer muropeptides from both strains (Table 1 and Fig. 3). Moreover, L-Lys₃ in the muropeptides of both strains was more frequently substituted by D-Asn than by D-Asp. Finally, as mentioned above, the extent of the cross-link was similar in D344S and D344M512 because oligomers, mainly dimers, represented 62–63% of the muropeptides (Table I).

Further Attempts to Find Common Muropeptides Oligomers in D344S and D344M512—As shown in Fig. 1 and Table I, all the major muropeptide oligomers of D344M512 that were produced in sufficient amount for structural analysis contained the unusual L-Lys₃ → D-Asx-L-Lys₃ cross-link. Further analysis of very minor peaks did not provide any evidence for the presence of muropeptide containing the usual d-Ala₄ → D-Asx-L-Lys₃ cross-link present in D344S (data not shown). In contrast, further analysis of minor peaks of D344S revealed two dimers (A and B) that contained the unusual L-Lys₃ → D-Asx-L-Lys₃ cross-link. These peaks were very minor components of the peptidoglycan of D344S accounting for only 0.7% of the total muropeptides (Table I and Fig. 1A). Thus, the unusual L-Lys₃ → D-Asx-L-Lys₃ cross-links preexisted in the parental strain.

Further Characterization of Monomer Muropeptides—Five monomers (peaks 4, 5, 9, and 10) present in the muropeptide profiles of D344S and D344M512 had not been fully characterized in previous studies of the E. faecium peptidoglycan. MS/MS analysis indicated that muropeptide 5 was a monomer containing a triptide stem with a d-asparagine branched on L-Lys₃ whereas muropeptide 4, which eluted 1.2 min before muropeptide 5 and differed by one mass unit, was the d-aspartate-containing analog of muropeptide 5. Based on the 42 mass unit difference, muropeptide 10 differed from muropeptide 5 by O-acetylation of the MurNAc residue. In agreement, peak 10 had the same retention time and molecular mass as the O-acetylated form of muropeptide 5.

Despite the wide distribution of these resistant mechanisms in pathogenic bacteria, β-lactams are still the most broadly used antibiotic class because several strategies have been successfully developed to overcome resistance, including modification of β-lactam structure to prevent hydrolysis by β-lactamase, association of β-lactams with β-lactamase inhibitors, and design of new drugs that display increased affinity for DD-transpeptidases from resistant bacteria. The emergence of resistance by LD-transpeptidase bypass mechanism described in this study is worrisome because it is expected to confer cross-resistance to all β-lactams.

Acknowledgment—We thank C. Harcour for secretarial assistance.

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Novel Mechanism of β-Lactam Resistance Due to Bypass of DD-Transpeptidation in Enterococcus faecium

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J. Biol. Chem. 2000, 275:16490-16496.
doi: 10.1074/jbc.M909877199 originally published online March 19, 2000

Access the most updated version of this article at doi: 10.1074/jbc.M909877199

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