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MOLECULAR DYNAMICS STUDY OF INTERACTIONS OF POLYMYXIN B_3 AND ITS ALA-MUTANTS WITH LIPOPOLYSACCHARIDE

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Introduction

Emergence of nosocomial bacterial pathogens (especially Gram-negative bacteria) with multiple resistance against almost all available antibiotics is a growing medical problem [1, 2]. No novel drugs targeting multidrug-resistant Gram-negative bacteria have been developed in recent years [3, 4]. In this context, there has been greatly renewed interest to cyclic lipodecapeptides polymyxins [5-7]. Polymyxins exhibit rapid bactericidal activity [8]. They are specific and highly potent against Gram-negative bacteria [9], but have potential nephrotoxic side effects [7]. So polymyxins are attractive lead compounds to develop analogues with improved microbiological, pharmacological and toxicological properties [5, 10, 11]. A detailed knowledge on the molecular mechanisms of polymyxin interactions with its cell targets is a prerequisite for the purposeful improvement of its therapeutic properties. Polymyxin B_3 (PmB_3) consists of a cyclic heptapeptide ring, together with a tripeptide side chain that is attached to an octanoyl fatty acyl chain (Fig. 1). PmB_3 contains six L-α,γ-diaminobutyric acid (Dab) residues, five of which are positively charged under physiological conditions. The primary cell target of a polymyxin is a lipopolysaccharide (LPS) in the outer membrane of Gram-negative bacteria [12]. Typical LPS molecule is a complex biopolymer composed of three major structural fragments: a variable outer oligosaccharade (or O-antigen), a core oligosaccharide region (both composed of repeating units of various polysaccharides) and the conserved lipid A portion [13]. Lipid A anchors the LPS molecule to the outer membrane. The "classic" *E. coli* lipid A consists of two glucosamines (GlcN I and GlcN II), two phosphate esters and six fatty acid chains (M, L, HM1-4) (Fig. 2). Lipid A is linked to the core oligosaccharide region by two 2-keto-3-deoxyoctanate (Kdo2) residues [13]. The structure of LPS and its interactions with a binding peptide have been revealed in the single case of the X-ray structure of LPS in complex with the integral outer membrane protein FhuA from *E. coli* K-12 [14]. Amongst the most favorable interactions, a subset of four positively charged residues of FhuA has been identified. Three of these four residues formed strong hydrogen bonds with the phosphates of lipid A [14]. Structural scaffold of the four-residue motif appeared to be common to proteins which specifically bind LPS with high affinity: bactericidal/permeability-increasing protein BPI, lactoferrin, lysozyme, *Limuilus* anti-LPS factor LALF as well as polymyxin B [14-16]. Solution structure of PmB as well as structural aspects of PmB-LPS binding have been studied by NMR techniques combined with molecular docking and molecular dynamics simulations and the models of PmB-LPS complex have been proposed [16-20]. The binding site of polymyxin on LPS has been supposed to be Kdo2-lipid A fragment (Fig. 1B). In polymyxin B, the LPS-binding motif has been found to comprise Dab1, Dab5, Dab8 and Dab9 residues but their individual roles and relative contribution to the binding with LPS have not been established] [16-18].

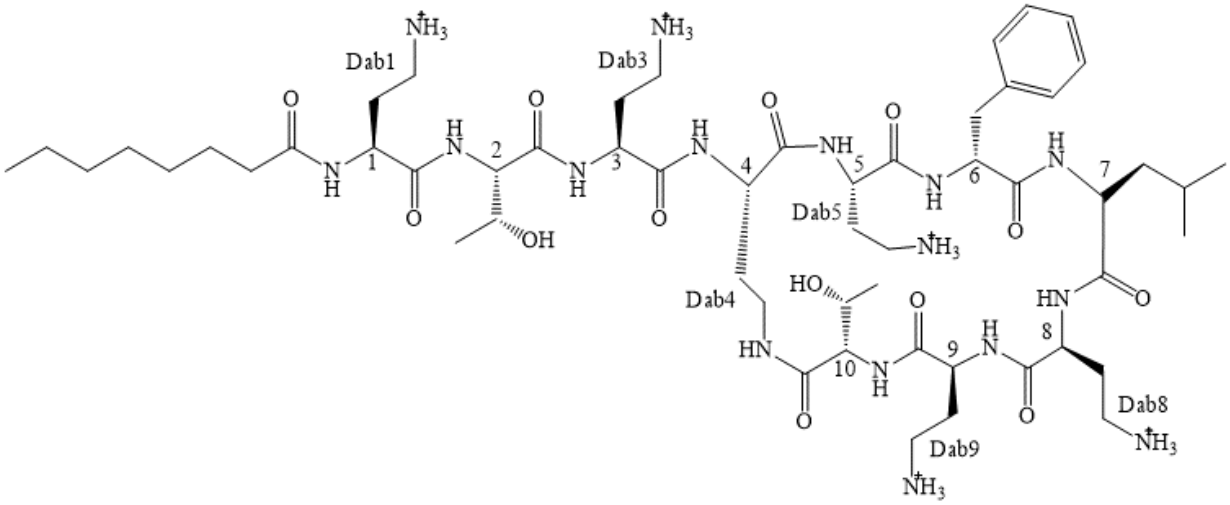

Fig. 1. Chemical structures of polymyxin B_3 (PmB_3).

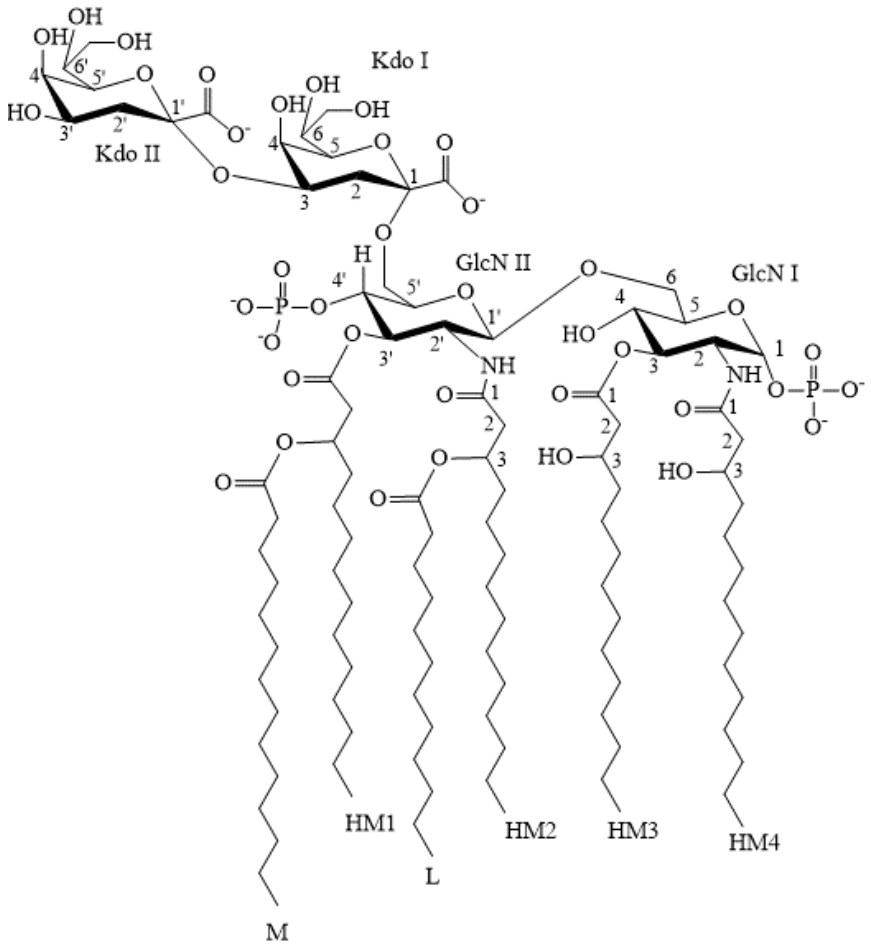

Fig. 2. Chemical structures of lipid A from *E. coli* K12 (Kdo2-lipid A).
M – myristoyl, HM1-4 – hydroxymyristoyl, L – lauroyl.

Recently, a series of PmB_3 alanine scanning analogues was experimentally examined to determine the contribution of each amino acid position to LPS binding and antimicrobial activity [21]. All Ala-substituted analogues for Dab side chains showed greatly reduced binding affinity indicating an important role of Dab side residues in polymyxin-LPS binding. However, the binding energetics and details of intermolecular interactions in the complexes remained beyond the scope of the study.

In this paper, the molecular aspects of PmB_3-LPS binding and its energetics were studied in more detail by molecular dynamics. Understanding the peculiarities of molecular interactions of polymyxins with its primary target on the outer membrane of Gram-negative bacteria may assist in the designing of novel polymyxin-like lipopeptides.

Materials and methods

All computations were performed in YASARA [22]. *Initial structures.* Coordinates of polymyxin B_3 were taken from NMR solution structure of polymyxin B_1 when bound to *E. coli* LPS [17]. The coordinates of the lipid A portion of LPS (including two 2-keto-3-deoxyoctanate (Kdo) residues) were derived from the X-ray crystallographic structure of LPS in complex with the integral outer membrane protein FhuA from E. coli K-12 (1QFF) [14]. PmB_3 was manually docked onto the Kdo2-lipid A to reproduce as close as possible the structure of complex PmB-LPS from NMR solution experiment [17, 18]. Then the complex was energy-minimized in a periodic simulation cell filled with TIP3P water molecules. The simulation cell was 1 nm larger than the complex along all three axes. Na^+ and Cl^- counterions were added to neutralize the system and to reach ion mass fraction 0.9% NaCl [23]. The AMBER03 force field [24] was used with a 1.05 nm force cutoff. To treat longrange electrostatic interactions the Particle Mesh Ewald algorithm [25] was used. After a short steepest descent minimization, the procedure continued by simulated annealing minimization started at 298 K, velocities were scaled down by 0.9 every 10th step until the energy improved by less than 0.05 kJ/mol per atom during 200 steps.

Local docking. The further refinement of PmB_3 location on LPS was carried out by local docking by means of AutoDock Vina program with standard parameters [26]. The above optimized PmB-LPS complex was placed in the center of 0.9x0.9x0.9 nm simulation cell. The structures of Kdo2-lipid A and PmB_3 were kept rigid whereas polymyxin's residues Dab 1, Dab 3, Dab 5, Dab 8 та Dab 9 were flexible. The output structure of the complex was used as a starting point for alanine scanning procedure as

well as for molecular dynamics simulations of PmB_3–LPS complex.

Alanine scanning. The complex of PmB_3 with Kdo2-lipid A was firstly minimized as described above. The water molecules located at a distance more than 0.6 nm from the complex were deleted and the system was energy-minimized again. Then water shell was temporarily removed from the cell. All atoms of the complex with a distance more than 0.8 nm from the center of polymyxin residue to be mutated were fixed. Dab side residues of PmB_3 were consequentially substituted by alanine and the water shell was added again. Water molecules with distance less than 0.3 nm from new mutant were deleted. Environment of the mutated residue was energy-minimized. Then all water molecules were deleted and potential and solvation energies of the complex, the receptor (Kdo2-lipid A) and the ligand (PmB_3) were calculated.

Molecular dynamics. The complexes of PmB_3 or its Ala-mutants with Kdo2-lipid were placed in a periodic simulation cell which was filled with TIP3P water molecules. The systems were minimized as described above. The simulation cell was 1 nm larger than the complex along all three axes. Na^+ and Cl^- counterions were added to neutralize the system and to reach ion mass fraction 0.9% NaCl [23]. The AMBER03 force field [24] was used with a 1.05 nm force cutoff. The solute charges were assigned based on the AMBER03 force field [24], using GAFF/AM1BCC [27, 28] for the LPS fragment and N-terminal fatty acyl chain of polymyxin B_3. To treat longrange electrostatic interactions the Particle Mesh Ewald algorithm [25] was used. The molecular dynamics simulations were run in NPT ensemble at 300 K and pH 7.0 using a multiple time-step of 1.25 fs for intra-molecular and 2.5 fs for inter-molecular forces. The Root Mean Square Deviations (RMSD), Root Mean Square Fluctuations (RMSF), mean hydrogen bond lengths and the H-bond probabilities were calculated by the use of macros *md_analyze*.

Binding energy. Binding energy was calculated as a difference of potential and solvation energies for ligand and receptor in the bound (in the complex) and in the unbound states (at infinite distance). Solvation energy included Van der Waals and Coulomb energies of interactions between the solute and solvent molecules. The entropic component of the solvation energy was approximated by an entropic term proportional to the solvent accessible surface area. The solvation energy was calculated using the boundary element method implemented in YASARA. The boundary between solvent (dielectric constant 78) and solute (dielectric constant 1) was formed by the solute molecular surface, constructed with a solvent probe radius of 1.4 Å.

Results and discussion

The complex of native polymyxin B_3 with lipopolysaccharide obtained as a result of the docking is presented in fig. 3. It was this structure of the complex that served as a starting point for an Ala-scanning as well as a reference structure for the subsequent comparative analysis of Ala-mutants of polymyxin.

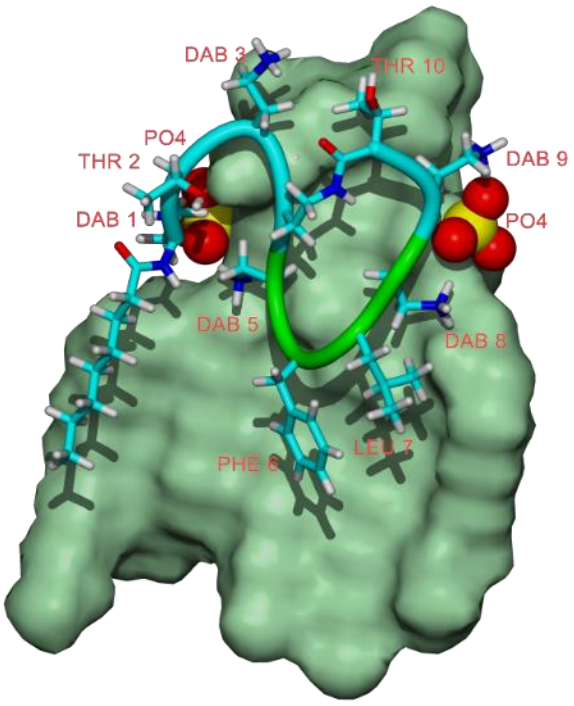

Fig. 3. PmB_3–LPS complex. PmB_3 is depicted as a combined tube and stick model for peptide backbone and side chains, correspondingly. Regions of polymyxin's turn-like secondary structure are green colored. LPS is shown as a space-filling model, its molecular surface, excluding PO4 phosphate groups, is colored in light-green.

To analyze at atomic level the structural consequence of Ala1, Ala3, Ala5, Ala8 and Ala9 mutations in PmB_3–LPS complex and their influence on the binding energetics of the complexes molecular dynamic simulations of these systems were carried out in water solution at physiological conditions.

Values of root mean square deviations of backbone C_α atoms (RMSD C_α) of polymyxin and its derivatives in dependence on the simulation time are shown in fig. 4. The values of RMSD C_α characterize a structure stability and a simulation integrity. For the complex of unmodified PmB_3 with LPS, there were observed insignificant fluctuations of RMSD C_α near the mean value (after 8 ns) being the minimal amongst all complexes studied (fig. 4). For Ala-mutants, in contrast to unmodified PmB_3, RMSDs of C_α atoms showed continuous increase and/or irregular fluctuations with large amplitude, revealing sustained changes in their structures and resulting in the less close contacts within the complex, the increase of the values of binding energies (fig. 5) and as a consequence the notable loss in stability of Ala-mutants complexes with LPS.

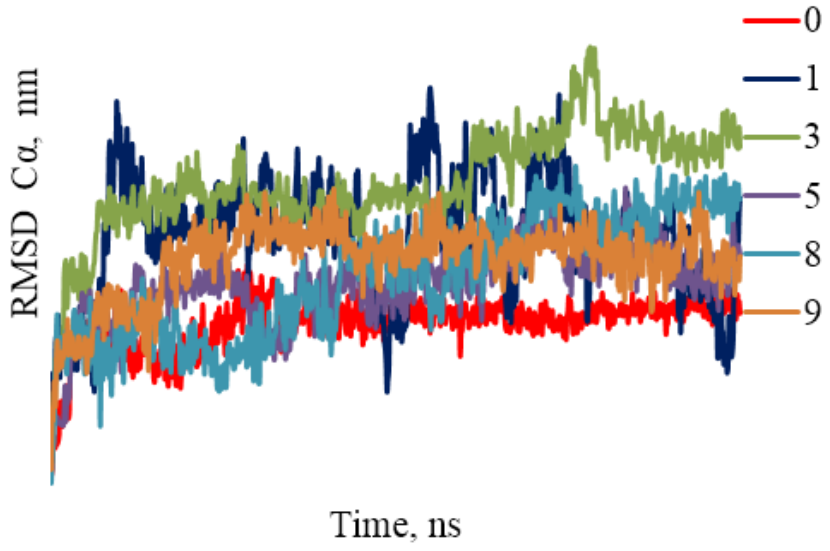

Fig. 4. RMSD of C_α atoms from initial structures of the complexes of PmB_3 and its Ala-mutants with LPS: 0 – PmB_3; 1 – Ala1-PmB_3; 3 – Ala3-PmB_3; 5 – Ala5-PmB_3; 8 – Ala8-PmB_3 and 9 – Ala9-PmB_3.

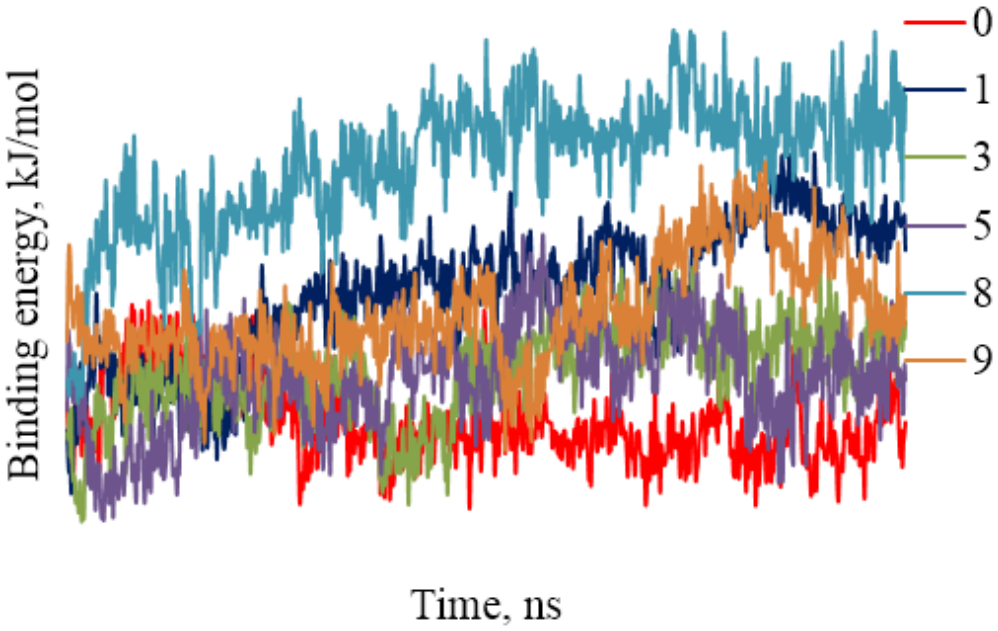

Fig. 5. Binding energies of the complexes of PmB_3 and its Ala-mutants with LPS: 0 – PmB_3; 1 – Ala1-PmB_3; 3 – Ala3-PmB_3; 5 – Ala5-PmB_3; 8 – Ala8-PmB_3 and 9 – Ala9-PmB_3.

Amino acid residues of PmB_3 bound to LPS showed quite predictably considerable reduction in mobility compared to the free peptide (red solid line versus red dashed line in fig. 6). Especially it concerns the residues that comprise LPS-binding motif: values of RMSF for Dab1, Dab5, Dab8 and Dab9 residues decreased threefold.

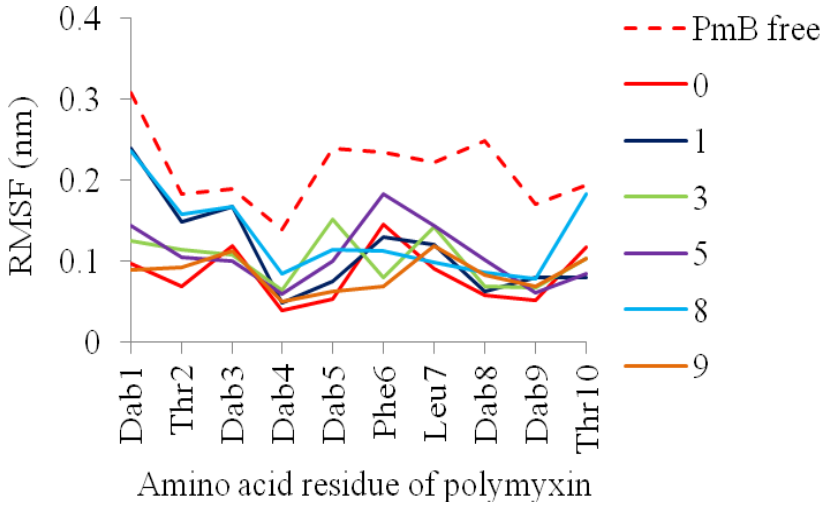

Fig. 6. RMSF of amino acid residues of PmB_3 and its Ala-mutants in complex with LPS: 0 – PmB_3; 1 – Ala1-PmB_3; 3 – Ala3-PmB_3; 5 – Ala5-PmB_3; 8 – Ala8-PmB_3 and 9 – Ala9-PmB_3.

In PmB_3-LPS complex, Ala-mutations disturb the characteristic H-bond network not only near the mutatated residue but within the entire interface of the complex. As can be seen from table 1, where the H-bonds formed in complexes of PmB_3 and its Ala-mutants with LPS as well as their parameters (mean "donor...acceptor of H-bond" inter-atomic distances and H-bond

Table 1. Hydrogen bonds in complexes of PmB_3 and its Ala-mutants with LPS

	Hydrogen bonds	Distance N···O, Å	Probability
PmB_3			
	Dab1-NH···O3-P	2.933	0.522
	Dab1-NH···O4-P	3.116	0.336
	Dab8-NH···O1-HM4	3.058	0.795
	Dab9-NH···O3-P	3.015	0.117
	Dab9-NH···O4-P	2.822	0.785
	Dab9-NH···O1B-KdoII	3.292	0.700
Ala1-PmB_3			
	Dab5-NH···O2-P	3.018	0.572
	Dab8-NH···O4-P	2.895	0.466
	Dab9-NH···O1A-KdoII	3.047	0.596
Ala3-PmB_3			
	Dab1-NH···O4-P	2.749	0.917
	Dab8-NH···O1-HM4	2.901	0.707
	Dab9-NH···O3-P	2.737	0.953
	Thr10-OH···O8-KdoI	3.005	0.764
Ala5-PmB_3			
	Dab1-NH···O3-P	2.759	0.868
	Dab9-NH···O2-P	2.905	0.424
	Dab9-NH···O3-P	2.825	0.452
	Dab8-NH···O3-HM4	3.028	0.773
	Dab9-NH···O1A-KdoII	3.024	0.846
Ala8-PmB_3			
	Dab9-NH···O3-P	2.799	0.954
Ala 9-PmB_3			
	Dab1-NH···O4-P	2.746	0.934
	Dab8-NH···O1-HM2	2.888	0.907

probabilities) are represented, Dab1, Dab8 and Dab9 amino acid residues of PmB_3 form rather strong H-bonds (average N···O distance was less 0.3 nm). Amongst them, H-bonds formed by residues Dab9 (with 1-phosphate and KdoII) and Dab8 (with fatty acid chain HM4) were the most stable in the course of MD simulations. Ala-mutations of these residues maximally destabilize PmB_3-LPS complex: the values of binding energy for these mutants showed increase and large-amplitude irregular fluctuations (fig. 5).

Conclusions

The structural and energetic aspects of PmB_3-LPS binding have been studied by alanine scanning and molecular dynamics simulations. Ala-mutations of polymyxin's residues Dab1, Dab3, Dab5, Dab8 and Dab9 in the PmB_3-LPS complex caused sustained structural changes which resulted in the notable loss in stability of LPS complexes with Ala-mutants of PmB_3. Hydrogen bonding of polymyxin B with the lipopolysaccharide is an important factor of the stability of PmB_3-LPS complex. The mutations disturb the characteristic hydrogen-bond network of PmB_3-LPS complex. Ala-mutations of Dab1, Dab8 and Dab9 amino acid residues of PmB_3 destabilized PmB_3-LPS complex to a greater extent: the values of binding energy for these mutants showed increase and large-amplitude irregular fluctuations.

Detailed knowledge of the peculiarities of molecular interactions of polymyxins with its primary target on the outer membrane of Gram-negative bacteria is a prerequisite of a purposeful design of novel polymyxin-like lipopeptides.

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Lisnyak Yu. V.

Introduction. Emergence of nosocomial bacterial pathogens (especially Gram-negative bacteria) with multiple resistance against almost all available antibiotics is a growing medical problem. No novel drugs targeting multidrug-resistant Gram-negative bacteria have been developed in recent years. In this context, there has been greatly renewed interest to cyclic lipodecapeptides polymyxins. Polymyxins exhibit rapid bactericidal activity, they are specific and highly potent against Gram-negative bacteria, but have potential nephrotoxic side effects. So polymyxins are attractive lead compounds to develop analogues with improved microbiological, pharmacological and toxicological properties. A detailed knowledge of the molecular mechanisms of polymyxin interactions with its cell targets is a prerequisite for the purposeful improvement of its therapeutic properties. The primary cell target of a polymyxin is a lipopolysaccharide (LPS) in the outer membrane of Gram-negative bacteria. The binding site of polymyxin on LPS has been supposed to be Kdo2-lipid A fragment. **Methods.** For all molecular modeling and molecular dynamics simulation experiments the YASARA suite of programs was used. Complex of antimicrobial peptide polymyxin B_3 (PmB_3) with Kdo2-lipid A portion of E. coli lipopolysaccharide was constructed by rigid docking with flexible side chains of the peptide. By alanine scanning of polymyxin B_3 bound to LPS followed by simulated annealing minimization of the complexes in explicit water environment, the molecular aspects of PmB_3-LPS binding have been studied by 20 ns molecular dynamics simulations at 298 K and pH 7.0. The AMBER03 force field was used with a 1.05 nm force cutoff. To treat long range electrostatic interactions the Particle Mesh Ewald algorithm was used. **Results.** Ala-mutations of polymyxin's residues Dab1, Dab3, Dab5, Dab8 and Dab9 in the PmB_3-LPS complex caused sustained structural changes resulting in the notable loss in stability of LPS complexes with Ala-mutants of PmB_3. The mutations disturbed the characteristic hydrogen-bond network of PmB_3-LPS complex. Ala-mutations of Dab1, Dab8 and Dab9 amino acid residues of PmB_3 destabilized PmB_3-LPS complex to a greater extent: the values of binding energy for these mutants showed increase and large-amplitude irregular fluctuations.
Conclusions. Hydrogen bonding of polymyxin B with the lipopolysaccharide is an important factor of the stability of PmB_3-LPS complex. Detailed knowledge of the peculiarities of molecular interactions of polymyxins with its primary target on the outer membrane of Gram-negative bacteria is a prerequisite of a purposeful design of novel polymyxin-like lipopeptides.
Keywords: polymyxin, lipopolysaccharide, lipid A, docking, molecular modeling.