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STRUCTURE, FUNCTION AND BIOLOGICAL ACTIVITY OF LIPOPOLYSACCHARIDE LIPID A

Bacterial lipopolysaccharides (LPS) are the major outer surface membrane components present in almost all gram-negative bacteria. It consists of poly- or oligosaccharide region that is anchored in the outer membrane by a specific lipid moiety termed lipid A. Recent studies have shown that it is only the lipid A of LPS that has the function of endotoxin. Despite its general structural conservation, lipid A also has considerable structural microheterogeneity which can vary depending on diverse factors including bacterial adaptation to changing environment and external stimuli, incomplete biosynthesis, and breakdown products and/or chemical modifications. Therefore it is more appropriate to consider lipid A as a family of structurally related molecular species with different acylation and phosphorylation patterns rather than as an individual, homogeneous molecule. The studies of structure-function relationship of lipid A, which has the typical structure of E. coli type lipid A backbone, demonstrated that activities differed depending on: 1) the number of phosphoryl and acyl residues, 2) the substituted site of phosphoryl and acyl residues, 3) the chain length of acyl residues, 4) lipid A conformation. Current investigations showed that lipid A and also the integral outer membrane proteins responsible for the final stage of LPS transport are the pinpoints in solving the problem of bacterial drug resistance. The identification of inhibitors that specifically target LPS transport in vitro and more importantly in vivo have a significant potential for the development of novel drugs against multi-drug resistant pathogenic bacteria.

K e y w o r d s: lipid A, lipopolysaccharide, structure, biological activity.

Towards the end of the 19th century Pfeiffer identified a heat-resistant toxin *Vibrio cholera* lysates causing toxic shock in animals. Later, its toxic principle was identified as a lipopolysaccharide (LPS) forming the major component of the external leaflet of outer membrane of gram-negative bacteria and has long since been considered to be tightly associated with the microbial cell [25, 41].

Since the 1950s, the techniques for extracting and purifying LPS have developed. It was shown that purified LPS introduced to experimental animals or humans evokes a number of pathophysiological effects characteristic for severe sepsis, including fever or hypothermia, tachycardia, leucopenia or leukocytosis, hypotention, disseminated intravascular coagulation, local Shwartzman reaction, and multi-organ failure which in most severe situations may cause death. As far as the isolated LPS induces shock and lethality, it has been long considered as a major bacterial mediator of severe Gram-negative sepsis [41, 46].

The prominent role of LPS during infection leads to great efforts for a chemical-analytical elucidation of its LPS structure and for recognition of the biologically active path of this amphiphilic structure. In most bacteria, LPS displays a common structural architecture that includes three domains: a lipophilic moiety termed lipid A (the term lipid A was introduced in order to distinguish it from a further LPS-associated lipid B, which was later identified

as phosphatidylethanolamine), a hydrophilic glycan called the O-specific polysaccharide (also known as O-chain or O-antigen), and a joining core oligosaccharide (OS). The core OS can be further separated into two regions, one proximal to lipid A (inner core OS), and another one distal from lipid A but proximal to the O-antigen (outer core OS). The inner core OS contains at least one residue of 3-deoxy-D-manno-oct-2-ulosonic acid (Kdo) and several heptoses. Kdo is rarely found in other glycans and, therefore, can be considered as a marker for the presence of LPS. The inner core OS can often be decorated with other substituents, usually present in non-stoichiometric amounts. These are phosphate (P), diphosphate, 2-aminoethyl phosphate (PEtN) or 2-aminoethyl diphosphate, uronic acids as D-galacturonic, and 4-amino-4-deoxy-L-arabinose (L-Ara4N). Whereas the carbohydrate chain is oriented outwards and interacts with the external environment, including the defense mechanism of animal or plant host species, the lipid A is embedded in the outer leaflet of the outer membrane and anchors the LPS molecules through electrostatic and hydrophobic interactions [6, 21, 30, 31].

After "lipid A" was first described by Westphal and Luderitz [23], as an endotoxically active principle of the bacterial lipopolysaccharide it soon became an important target of research in microbiology, immunology, and related fields. However, more time was required until this particular molecule became attractive to organic chemists. This was due to a little knowledge present on the structural features of lipid A, mainly owing to the difficulties in the purification of this amphiphilic and intrinsically heterogeneous molecule for sufficient chemical characterization [31]. The improved extraction methods and the discovery that the lipid component can be cleaved from the rest of the molecule by mild acidic hydrolysis lead to unraveling of its detailed structure. Modern mass spectrometric methods, especially with matrix assisted laser desorption/ionization (MALDI) and electrospray ionization, have provided an invaluable aid [11]. Lipid A is a unique and distinctive phosphoglycolipid, the structure of which is highly conserved among bacterial species. First the structure of lipid A from *Escherichia coli* was established in 1954 [40], the details of which were updated in 1983 [7, 33]. One year later [8] *E. coli* type lipid A was successfully synthesized.

Lipid A from various gram-negative bacteria studied to date (Fig.) [31, 44] contains D-gluco-configured pyranosidic hexosamine residues (or 2,3-diamino-2,3-dideoxy-D-glucose), which are present as β(1→6)-linked dimers. The disaccharide contains α-glycosidic and non-glycosidic phosphoryl groups in the 1 and 4' positions, and (R)-3-hydroxy fatty acids in the O-2, O-3, O-2' and O-3' positions in ester and amide linkages, two of which are usually further acylated at their 3-hydroxyl group. In the lipid A of the most studied *E. coli* established, the hydroxy fatty acids are C14 in chain length and the hydroxyl groups of the two (R)-3-hydroxy fatty acids of the distal GlcN-residue (GlcN II), and not those of the GlcN residue at the reducing side (GlcN I), are acylated by non-hydroxy fatty acids (12:0 and 14:0). Some molecular species contain an additional fatty acid attached to the amide-linked 3-hydroxy acid and the phosphate group may be substituted with ethanolamine phosphate (of GlcN I).

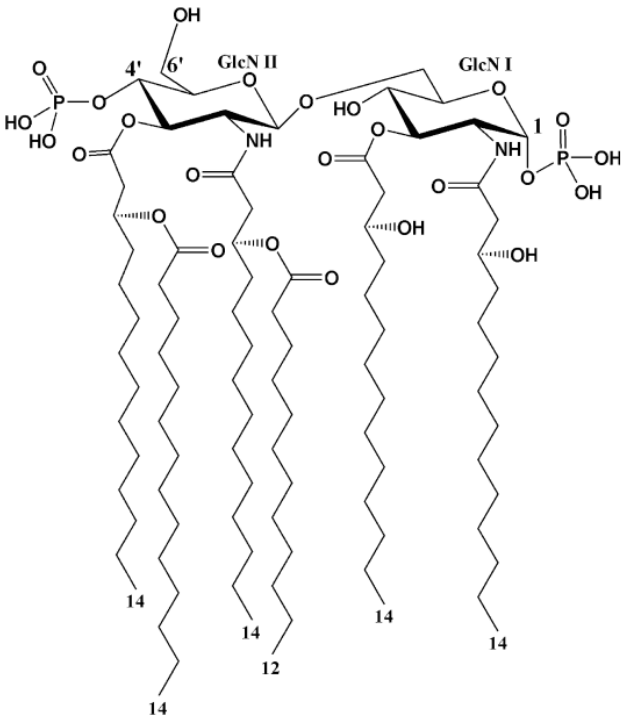

Fig. Structure of lipid A of *E. coli*

Despite its general structural conservation, lipid A also is characterized by considerable structural microheterogeneity which can vary depending on different factors including bacterial adaptation to changing environment and external stimuli, incomplete biosynthesis, break-down products and/or chemical modifications. Therefore, a number of new variants of lipid A structures were isolated and structurally evaluated in the LPS of many bacteria. It was shown that the differences concern the type of hexosamine present, the degree of phosphorylation, the presence of phosphate substituents, and importantly the nature, chain length, number, and position of the acyl groups.

While β(1→6)linked glucosamine disaccharide is common, the similarly bound 2,3-diamino-2,3-dideoxy-D-glucopyranose (GlcN3N) disaccharide skeleton was identified in several bacterial species, such as *Aquifex pyrophylus*, *Brucella abortus*, *Bacteriovorax stolpii*, *Caulobacter crescentus*, *Bradyrhizobium elkanii*, *Bartonella henselae* and *Legionella pneumophila* [31]. The main structural variant of *Campylobacter jejuni* contains a hybrid of a carbohydrate skeleton represented by disaccharide βGlcN3N(1→6)GlcN; two other variants of lipid A are characterized by the presence of disaccharide GlcN or GlcN3N [38].

There are few important exceptions to the types of fatty acid present in lipid A. For example, in the lipid A of *Helicobacter pylori* in comparison to that of *E. coli*, there are four rather than six fatty acids with a longer average chain-length (16–18) [16]. In *Rhodobacter sphaeroides* [26] and *R. capsulatus* [6] the amide-linked fatty acids of the disaccharide backbone are 3-oxo-tetradecanoate, while some species contain 2-hydroxy acids. *Agrobacterium* and *Rhizobiaceae* species, which are plant pathogens and symbionts, respectively, tend to have

pentacyl units with four C12 to C20 3-hydroxy acids and one very long chain (ω-1)-hydroxy acid such as 27-hydroxyoctacosanoic acid (sometimes with 3-hydroxy-butyric acid linked in turn), attached to one of the 3-hydroxyl groups [2].

Lipid A from marine cyanobacteria of the genus *Synechococcus* differs significantly from those of all other species as it consist of tri- and tetraacylated structures with hydroxy (odd-chain) and non-hydroxy fatty acids connected to the diglucosamine backbone, lacks phosphate and contains a single galacturonic acid. Whether these represent primitive structures were formed in the result of adaptation to the marine environment is a matter of speculation [1].

A number of unusual features are inherent to lipid A of *Francisella* species which exists partly in a free form, i.e. not linked to Kdo, core sugars and O-specific chain. Moreover in comparison to the lipid A from *E. coli*, the phosphate group in the 1-position of the β-(1–6)-linked diglucosamine unit is replaced by α-linked galactosamine and there is no phosphate in the 4'-position, while the fatty acid components are C18 and C16 in chain-length [17].

Lipopolysaccharide of *Pantoea agglomerans* [36] is constructed with at least two kinds of lipid A of different levels of acylation. One is the same as that of *E. coli* type 4$^{'}$-monophosphoryl hexa-acyl lipid A and the other is the *Salmonella minnesota* type 4$^{'}$-monophosphoryl hepta-acyl lipid A.

The fatty acid composition is influenced by the temperature of culture growing: *E. coli* and *S. enterica* grown at low temperatures (10–15 ^{0}C), incorporates unsaturated fatty acids into lipid A [42].

Modification of lipid A by palmitoylation catalyzed by PagP has been demonstrated in such bacterial species as *S. enterica*, *E. coli*, *Legionalla pneumophila*, *Bordetella bronchiseptica*, and *Yersinia pseudotuberculosis*. The introduction of palmitate 16:0 is under control of the PhoP/PhoQ signal transduction system, which responds to the presence of antimicrobial peptides and is activated by low concentration of Mg^{2+} [22]. *S. enterica* mutants that are unable to add palmitate to lipid A, are sensitive to certain cationic antimicrobial peptides, including representatives of amphipatic α-helical (C18G) and β-sheet (protegrin) structural classes but excluding polymyxin. In *B. bronchiseptica* palmitoylation of lipid A at O-3$^{'}$ [45] is required for the persistent colonization of the respiratory tract and for the resistance to antibody-mediated complement lysis [3].

In contrast to *Y. pseudotuberculosis*, in which palmitoylated lipid A species predominate at the body temperature of the infected warm-blooded host, the plague pathogen *Y. pestis* cannot incorporate the 16:0 group into lipid A but can remodel the acylation pattern in a temperature-dependent manner [15]. When grown at 26 ^{0}C, *Y. pestis* expresses a hexaacyl lipid A containing an unsaturated secondary fatty acid 16:1, whereas at 37 ^{0}C mainly a tetraacyl lipid A (lipid IVA) is synthesized. The latter is poorly recognized by TLR4 on the immune cells of the mammalian host, and thus the systemic infection is allowed.

The most common polar substituents of lipid A phosphate groups, which are typically present in nonstoichiometric amounts, are secondary phosphate (with the formation of a diphosphate group), hydrogen, heptose, galacturonic acid, phosphoethanolamine and 4-amino-4-deoxy-L-arabinose (L-Ara4N) [9]. Charged groups allow bacteria to modulate the surface charge and vary depending on the growth conditions. A considerable amount of anionic

groups in the zone of lipid A–core-oligosaccharide are linked by electrostatic interactions with divalent cations (Mg^{2+} and Ca^{2+}), which contribute to binding of LPS molecules with each other. This largely stabilizes the outer membrane and reduces its permeability, creating an effective protective barrier.

Phosphate groups may also be substituted by other components. For example, two residues GalA substitute both phosphate groups in GlcN3N in the disaccharide skeleton of lipid A in hyperthermophilic bacteria *Aquifex pyrophilus* [19].

It was shown [13] that lipid A of *Neisseria meningitides*, a bacterium responsible for meningococcal infection, carries two PPEtN groups at 1 and 4' of disaccharide skeleton. In lipid A of a tularemia microorganism *Franciella tulariensis*, one (in position 4') or both phosphate groups are missing, which may account for its low LPS bioactivity. Moreover, lipid A of *F. tulariensis* ssp. *novicida* contains galactosamine-1-phosphate at the position 1 [18, 39].

Why today the attention of investigators is captured by the lipid A studies, its structure, biosynthetic processes, modification, obtaining of individual components? It is due to the observation of its responsibility for a large variety of biological activities of an LPS molecule [6, 30] in particular, for many toxic effects of infections with gram-negative bacteria. Because of its conserved structure in diverse pathogens, it is recognized as a pathogen-associated molecule by a specific receptor, Toll-like receptor 4 (TLR4), present on immune cells (monocytes, macrophages, neutrophils, and dendritic cells especially) and stimulating them to secrete pro-inflammatory cytokines. At high concentrations, lipid A induces high fever, increased heart rate, and in the worst cases can lead to septic shock and death by lung or kidney failure. However, lipid A is also an active immunomodulator, able to induce non-specific resistance to both bacterial and viral infections at low concentrations [9].

An essential role in understanding of lipid A structure-activity relationships was played by the studies on successful chemical synthesis of lipid A and its partial structures. Such compounds as *E. coli*-type lipid A (compound 506, LA-15-PP) and precursor Ia (compound 406, LA-14-PP, or lipid IVa) [37] were synthesized. It was shown that the biological activity of lipid A and its partial structures depends on the phosphorylation and acylation pattern of the hexosamine disaccharide. Maximal monokine-inducing activity is displayed by the biphosphorylated lipid A possessing six acyl residues, which structurally corresponds to *E. coli*-type lipid A (compound 506). Partial structures lacking any of these components, structures containing different constituents, or structures with a different distribution of constituents are either less or not active in inducing monokines. Although the α-glycosyl phosphate group is an important constituent for the expression of lipid A biological activity, an introduction of an oxyethyl linkage has no considerable effect on the activity.

Later numerous data on comparative studies of lipids A structure and their biological activity permit the authors to conclude that the bisphosphorylated hexaacylated disaccharide lipid A with an asymmetric (4 + 2) distribution of the acyl groups represents the most active structure for human cells [6, 21, 30, 34]. Various modifications of lipid A structure largely affect LPS bioactivity. The deletion of a single fatty acid, resulting in a pentaacyl form of lipid A, or the introduction of an additional acyl residue (hepta-acyl lipid A) reduced biological activity (induction of the synthesis of interleukin-1 by human

monocytes) by 10^2 times. The tetra-acyl derivative—a precursor of lipid A known as the "compound 406"—did not induce the production of cytokines by human monocytes [9].

The *E. coli* type hexa-acyl lipid A from *P. agglomerans* showed the highest activity so far known, including endogeneous TNF induction, whereas the *Salmonella* type hepta-acyl lipid A activity was slightly lower [36].

A significant role in the manifestation of endotoxic properties is played by fatty acids of particular length. Lipids A with short carbon chains of fatty acid are less toxic or have no toxicity compared to lipids A containing long chains of fatty acids. Thus, lipid A from *Marinomonas vaga* ATCC 27119 [12] is characterized by a pentaacyl-type structure, which is composed of only short chain fatty acids, in particular, 3-hydroxydecanoic and 3-hydroxydodecanoic acids, and shows low toxicity: LD_{50} comprises 1.46 μg/mouse. Lipids A of *Enterobacteriaceae* representatives, which include 3-hydroxytetradecanoic acid, are characterized by high toxicity [29, 37]. However, the LPS from *Rhodobacter capsulatus*, which lipid A contains two 3-hydroxytetradecanoic acids, two 3-hydroxydecanoic acids, and one 3-hydroxydodecenoic acid (i.e., only 5 fatty acids), express no endotoxic activity. Lipid A of *Salmonella minnesota*, which includes a nonstoichiometric seventh— hexadecanoic— fatty acid that acylates 3OHC14:0 at the position 2 of the reducing GlcNI and LPS of *Rhodocyclus gelatinosus*, the lipid A of which contains fatty acids with short carbon chains (C = 10) showing a high toxicity and pyrogenicity [31].

Analysis of these rather contradictory data suggests that not only the carbon chain length of a fatty acid, but also other factors, in particular, the amount of fatty acids, the presence of phosphorus residues, carbohydrate components of lipid A play an important role in the manifestation of endotoxic activity. Thus, it was shown that the monosaccharide form of lipid A is less active (activity is reduced more than 10^7 times) than the disaccharide one. It was shown [10] that 3'-O-deacylation of *Salmonella* lipid A reduces its ability to stimulate human TLR4-MD2 receptor complex.

The beneficial therapeutic effects of *Pantoea* LPS, which were not observed with other LPS, are not explainable by the structure of its lipid A. *P. agglomerans* LPS is composed mainly of low molecular weight (5 kDa) LPS and, to a lower extent, of 30–60 kDa high molecular weight LPS, whereas the *E. coli* LPS tested was composed largely of high molecular weight LPS.

The authors [20] have constructed an *E. coli* mutant and its derivatives and demonstrated that these progeny strains contained modified forms of lipid A with markedly decreased capacity to induce inflammatory response in human and mouse cells. These mutant strains may be used for expressing therapeutic recombinant proteins or targeted drugs without elimination of LPS.

The results of several LPS structure-function studies have shown that polysaccharide chain length and composition of LPS can also significantly influence biological activity. Thus, there is a possibility that composition and polysaccharide chain length are attributable to the biological activity of its lipid A and it seen as a beneficial therapeutic effects.

It is known that lipid A due to peculiar chemical structure harbors the "endotoxic principle" of LPS and is responsible for the expression of pathophysiological effects. Chemically modified lipid A can be endotoxically inactive but may express strong antagonistic activity against LPS, a property

that can be utilized in antisepsis treatment. The authors [29] showed that these different biological activities are directly correlated with the molecular shape of lipid A. Only hexaacyl lipid A with a conical/concave shape, the cross-section of the hydrophobic region being larger than that of the hydrophilic region, exhibited strong interleukin-6 (IL-6)-inducing capacity. Most strikingly, a correlation between a cylindrical molecular shape of lipid A and antagonistic activity was established: IL-6 induction of enterobacterial LPS inhibited by cylindrically shaped lipid A except for the compounds with a reduced head group charge. The antagonistic activity is interpreted by assuming that lipid A molecules intercalate into the cytoplasmic membrane of mononuclear cells, and subsequently block the putative signaling protein by the lipid A with cylindrical shape.

A certain conformation of lipid A, the so-called endotoxically active conformation corresponding to cubic and hexagonal supramolecular structures like *E. coli*, *S. minnesota*, *R. gelatinosus* plays a significant role in the manifestation of high biological activity of LPS, while lamellar conformation like those of *Rhodobacter capsulatus*, *Chromobacterium violaceum* and *Rhodospirillum rubrum* were completely endotoxically inactive [14, 27].

LPS plays an essential role in drug resistance of gram-negative bacteria which are becoming a global health threat. LPS in the complex with proteins-porins forms in the outer membrane a permeation barrier, which prevents hydrophobic antibiotics from entering the organisms. It indicates the antibiotic resistance may be due to peculiarities of LPS structure, in particularly the presence in lipid A negatively charged groups which are targets for antibacterial substances of a polycationic nature used in the treatment of bacterial infections. It is known [31, 35], that the substituents at 4'-phosphate of glucosamine II are responsible for the bacterial resistance to some polycationic antibiotics, in particular, polymyxins. If the OH group at the 4'-phosphate of glucosamine II is not substituted, polymyxin is attached to the group and these bacteria will be susceptible to polymixin. If the OH group carries substituents such as 4-amino-4-deoxy-L-arabinose, polymyxin cannot join and such bacterium will be resistant to polymyxins. These data indicate that the presence in lipid A of certain bacterial substituents is able to alter the biological properties not only of LPS but also of the whole bacterial cell.

The authors [24] observed that in response to environments signals (low concentrations of Mg^{2+}, a PhoPQ-activating signal), wild types of *E. coli* and *S. enterica* modified lipids A including in its structure 4-amino-4-deoxy-L-arabinose and phosphoetnanolamine, which promote bacterial resistance to cationic antimicrobial peptides (in particular, polymyxin B).

Due to the presence in the lipid A of 4-amino-4-deoxy-L-arabinose the lipopolysaccharides of *Burkholderia cenocepacia* displays a unique resistance to antimicrobial peptides and others antibiotics. Mutants of *B. cenocepacia* with defects in 4-amino-4-deoxy-L-arabinose synthesis are characterized by increased sensitivity towads two classes of antibiotics: polymixin and mellitin [5]. The authors believe that the LPS structural transformations, which take place after linking of 4-amino-4-deoxy-L-arabinose molecule to lipid A, determine the LPS transport and its correct assemblage on outer membrane.

Therefore the recent trend in solving the problem of antibiotic-resistance concerns LPS transport proteins which are the attractive drug targets, as the

impairment of LPS transport kills most of the Gram-negative bacteria [28, 32]. And really the authors [4, 43] showed that seven LPS transport proteins (that is, LptA-LptG) form a transenvelope protein complex are responsible for the transport of LPS from the inner to the outer membrane, the mechanism of which is poorly understood. They have reported the first crystal structure of the unique integral membrane LPS translocon LptD-LptE complex. LptD forms a novel 26-stranded β-barrel, which is to our knowledge the largest β-barrel reported so far. LptE adopts a roll-like structure located inside the barrel of LptD to form an unprecedented two-protein 'barrel and plug' architecture. The structure, molecular dynamics simulations and functional assays suggest that the hydrophilic O-antigen and the core oligosaccharide of the LPS may pass through the barrel and the lipid A of the LPS may be inserted into the outer leaflet of the outer membrane through a lateral opening between strands β1 and β26 of LptD. The development of new tools may be needed to dissect the molecular mechanism of transport and to define what individual role each of these seven proteins play in this process. These find do not only provide help for the understanding of important aspects of bacterial outer membrane biogenesis but also have a significant potential for the development of novel drugs against multi-drug resistant pathogenic bacteria.

Summary. On the stated above data it is possible to make the following conclusions:

1) the paramount role in studies of structure-function relationships of lipids A belongs the further elucidation of peculiarities of its structure;

2) it is more appropriate to consider lipid A as a family of structurally related molecular species with different acylation and phosphorylation patterns rather than as an individual, homogeneous molecule;

3) the studies of structure-function relationship of lipid A, which has the typical structure of *E. coli* type lipid A backbone, demonstrated that activities differed depending on: 1) the number of phosphoryl and acyl residues, 2) the substituted site of phosphoryl and acyl residues, 3) the chain length of acyl residues;

4) the existence of lipid A-containing LPS in the most ancient and primitive gram-negative bacteria demonstrates that it is absolutely required for their survival, shielding them from a variety of aggressive conditions. It is not produced simply to aggravate humans;

5) endotoxin-induced disease almost always results from a complex interaction of the endotoxin with host mediator systems. The prevention of tissue damage may be accomplished by blocking the biological effects of toxins. One of these ways is obtaining modified lipid A forms which are nontoxic, nonpyrogenic but retaining the immunomodulative activity. Such modified forms may be good candidates for the development of new immunomodulators which may be used to prevent gram-negative septic shock and related disorders by blocking the toxic effect of LPS by competing for its binding sites;

6) today many current antibiotics are becoming useless, causing hundreds of thousands of deaths each year. Bacteria are able to infect their hosts because they hide themselves from the immune system by changing the structure of LPS. The studies of authors [4, 43] reveals how the bacteria construct this camouflage and opens the door to blocking the process through new class of

antibiotics. The identification the path and gate used by the bacteria to transport the barrier building blocks to the outer surface is really very important. These investigations have demonstrated that the bacteria would die if the gate is locked. And the key role of LPS in this process is not disputed. Therefore the all-round studies of lipopolysaccharides of gram-negative bacteria and in particular of its lipid A, and also the integral proteins responsible for the final stage of LPS transport are the pinpoints in solving the problem of drug-resistant bacteria. Today the high-priority task of creating new medical treatment includes finding special substances (for example proteins), able to block the building of bacterial cell envelope and as a result to cause the bacterial death. The identification of inhibitors that specifically target LPS transport *in vitro* and more importantly *in vivo* may represent important tools to dissect the transport pathway.

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СТРУКТУРА, ФУНКЦІЯ ТА БІОЛОГІЧНА АКТИВНІСТЬ ЛІПІДУ А ЛІПОПОЛІСАХАРИДУ

Резюме

Бактеріальні ліпополісахариди (ЛПС) є основними компонентами зовнішньої мембрани і присутні майже у всіх грамнегативних бактерій. Вони складаються із полі- або олігосахаридної частини, яка закріплюється в зовнішній мембрані специфічною ліпідною частиною, що має назву ліпід А. Нещодавніми дослідженнями показано, що саме ліпід А ЛПС виконує функцію ендотоксину. Незважаючи на загальний структурний консерватизм, ліпід А характеризується також значною структурною гетерогенністю, яка може варіювати в залежності від різних факторів, включаючи бактеріальну адаптацію до умов оточуючого середовища, яке змінюється, неповний біосинтез та руйнуючі продукти і/або хімічну модифікацію як результат методу ізолювання ліпіду А, який був використаний. Тому більш прийнятним вважається розглядати ліпід А як родину структурно споріднених молекулярних видів з різним ацилюванням та фосфорилюванням, аніж як індивідуальні гомогенні молекули. Вивчення структурно-функціональних взаємовідносин ліпіду А, який має типовий для *E. coli* тип структури ліпіду А, свідчить, що активності різняться в залежності від: 1) кількості фосфорильних і ацильних залишків; 2) місця їх заміщення; 3) довжини ланцюга ацильних залишків; 4) конформації ліпіду А. Сучасні дослідження свідчать, що ліпід А та інтегральні білки зовнішньої мембрани, відповідальні за термінальну стадію транспорту ЛПС, є важливими у вирішенні проблеми стійкості бактерій до лікарських препаратів. Ідентифікація інгібіторів, які є специфічною мішенню транспорту ЛПС *in vitro* і, що більш важливо, *in vivo* має значну перспективу для розробки нових препаратів проти множинної стійкості патогенних бактерій.

Ключові слова: ліпід А, ліпополісахарид, структура, біологічна активність.

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СТРУКТУРА, ФУНКЦИЯ И БИОЛОГИЧЕСКАЯ АКТИВНОСТЬ ЛИПИДА А ЛИПОПОЛИСАХАРИДА

Резюме

Бактериальные липополисахариды (ЛПС) являются основными компонентами внешней мембраны и присутствуют почти во всех грамотрицательных бактериях. Они состоят из поли- или олигосахаридной части, которая заякоривается во внешней мембране специфической липидной частью, называемой липидом А. Недавними исследованиями показано, что именно липид А ЛПС выполняет функцию эндотоксина. Несмотря на общий структурный консерватизм, липид А характеризуется также значительной структурной гетерогенностью, которая может варьировать в зависимости от различных факторов, включая бактериальную адаптацию к изменяющимся условиям окружающей среды, неполный биосинтез и разрушающие продукты, и/или химическую модификацию как результат использованного метода изолирования липида А. Поэтому более приемлемым является рассматривать липид А скорее как семейство структурно родственных молекулярных видов с различным ацилированием и фосфорилированием, а не как индивидуальные гомогенные молекулы. Изучение структурно-функциональных отношений липида А, который имеет типичный для *E. coli* тип структуры липида А, свидетельствует, что активности различаются в зависимости от: 1) количества фосфорильных и ацильных остатков; 2) места их замещения; 3) длины цепи ацильных остатков; 4) конформации липида А. Современные исследования свидетельствуют, что липид А и интегральные белки внешней мембраны, ответственные за терминальную стадию транспорта ЛПС, являются основополагающими в решении проблемы устойчивости бактерий к лекарственным препаратам. Идентификация ингибиторов, которые являются специфической мишенью транспорта ЛПС *in vitro* и, что более важно, *in vivo* имеет значительную перспективу для разработки новых препаратов против множественной устойчивости патогенных бактерий.

Ключевые слова: липид А, липополисахарид, структура, биологическая активность.

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