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Bacterial Endotoxins: Biological Properties and Mechanisms (Review)

Aya Raad Salih
Department of Microbial Biotechnology/ College of Biotechnology, AL-Nahrain University, Baghdad, Iraq, aya.raad@nahrainuniv.edu.iq

Noor Dheyaa Hameed
Department of Microbial Biotechnology/ College of Biotechnology, AL-Nahrain University, Baghdad, Iraq, noor.dheyaa@nahrainuniv.edu.iq

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Abstract: Gram-negative bacteria produce endotoxins (lipopolysaccharides, or LPS), which are pathogenic chemicals linked to the onset of Gram-negative shock. When endotoxins interact with the cells that are susceptible to lipopolysaccharides, they produce endogenous mediators such tumor necrosis factor alpha (TNFt). TNFt is the main mediator of the fatal impact of endotoxins, while macrophages are cells that mediate the hazardous actions of LPS. The several processes with endotoxin are bacterially sensitized would be covered in this review article.

Key words: Bacterial endotoxins, Carnitine congeners, Lipopolysaccharide (LPS), Tumour necrosis factor alpha (TNFo0

I. Introduction

Gram-negative bacteria's outer membrane is made up of endotoxins. When given to experimental animals, thus the isolated endotoxins cause a wide range of physiologic reactions, some of which are also seen in Gram-negative septic shock [1]. The Gram-negative bacterial disease could be

noticed using the endotoxins as an important biomarker and the disease therapy consist on this diagnostic [2].

For the safety and quality of pharmaceutical and medical products, the endotoxin identification is also important, such in medical implants, biological (like insulin), and parenteral and injectable medications need to be sterile [3]. However, if Gram-negative bacteria are present and killed during the sterilization process, endotoxins may be released [4]. The organ failure and fever were caused by endotoxins if they enter the bloodstream, as well as at least one mg of endotoxins could be lethal [5]. To the safety of product, it must be tested for the existence of endotoxins. The chemical makeup of endotoxins, which are amphiphilic compounds, varies greatly throughout bacterial strains. A lipid component comprising disaccharide phosphates, fatty acids, and a core polysaccharide chain make up the typical structure of endotoxins, which weigh about 10 kDa (fig. 1) [6].

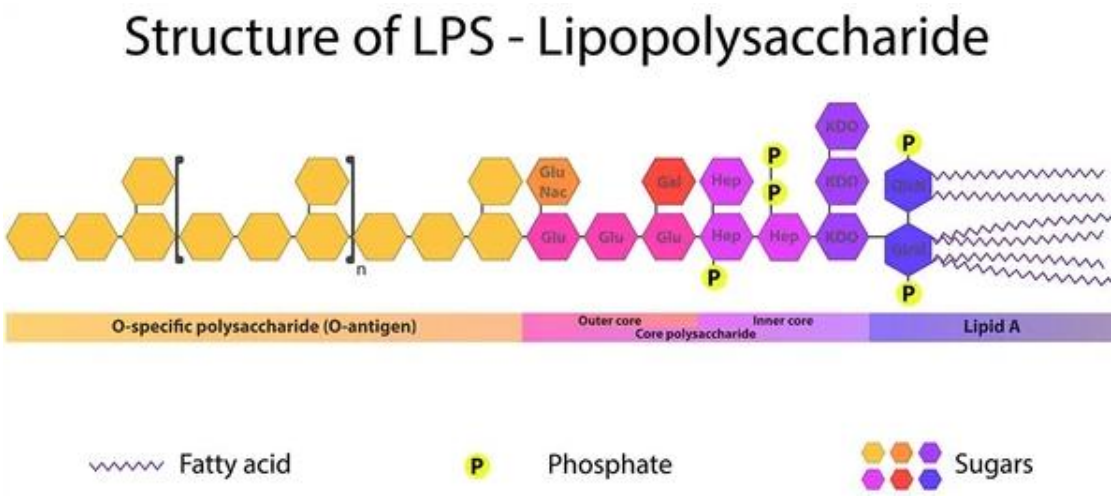

Fig. 1: General structure of LPS endotoxins.

II. Endotoxins are lipopolysaccharides (LPS).

The lipid A, the core oligosaccharide, and the O-specific polysaccharide—make up LPS were connected covalently in Enterobacteriaceae and many other Gram-negative bacteria [7]. The parent bacterial strain's serological specificity is determined by the structure and composition of its O-polysaccharide, which varies greatly across Gram-negative bacteria. Because a certain core structure is shared by many bacterial species, the structure and composition of the core oligosaccharide are less varied [8] . Since many Gram-negative bacteria share a similar structure and makeup, the lipid A is the physically component of the lipopolysaccharide molecule. Each of the three immunogenic components of it could causes the production of antibodies that engage selectively with unique epitopes in the corresponding region [9]. The lipid A is the only component of LPS that has biological activity; the polysaccharide has no harmful properties [5]. Some endotoxins, such those that induce the tumor could be advantageous to the host, although they are not necessarily toxic [6]. Instead of being direct impacts of the LPS molecule, some LPS activity are indirectly generated by endogenous mediators that are created after endotoxins contact with cells that are susceptible to LPS. Turnout necrosis factor alpha (TNF) is a key mediator of the activity of endotoxins that mediate the actions of LPS [7].

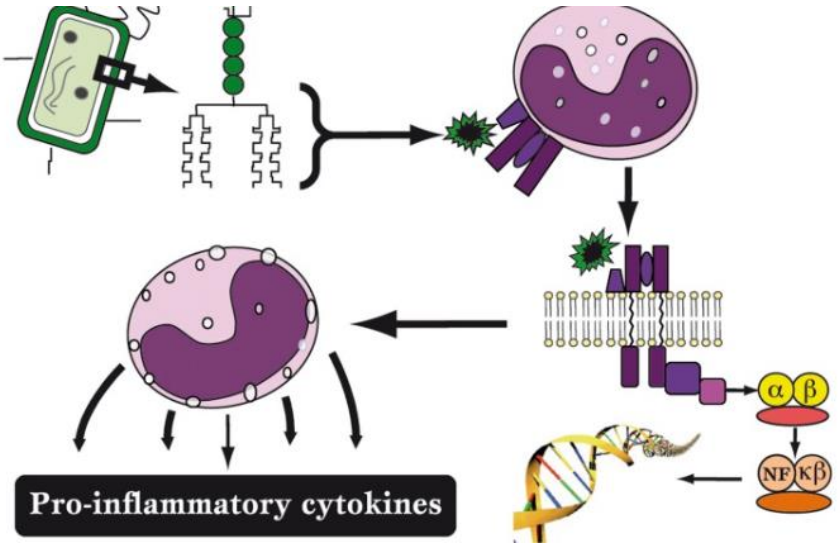

Figure 2 The pathophysiology of lipopolysaccharide

Figure 2 shows the pathophysiology of lipopolysaccharide (LPS) "endotoxin." Beyond the peptidoglycan layer, gram-negative bacteria have a lipopolysaccharide (LPS) membrane [8].

The bacterial membrane continuously shears LPS, also known as "endotoxin," into the surrounding serum and interstitial fluid. The Lipid-A, which is very pro-inflammatory, and the O-antigen and Core protein, which have minimal immunogenic effect, are produced when LPS breaks down [9]. As the Lipid-A initiates intracellular pathways by binding to tissue macrophages' and serum monocytes' CD14/TLR4/MD2 receptor, a complicated, multi-step intracellular mechanism activates the NF-κβ protein family, which then moves to the nucleus and starts the synthesis of cytokines [10] .

III. The activity of endotoxin

There are several host plasma proteins that can bind LPS, which can affect (increase or decrease) the action of endotoxins. These consist of LPS-binding protein (LBP)lb, lipoproteins (HDL and LDL), and, additionally, certain antibodies that may existed in the particular host [11]. Bacterial proteins (like Omp A) that the released LPS may impacted on the harmful microorganism in the event of endotoxin brought on by inflammation [12]. Endotoxin sensitivity is genetically determined; humans and rabbits are extremely sensitive, whereas guinea pigs, mice and rats were significantly less effective [13].

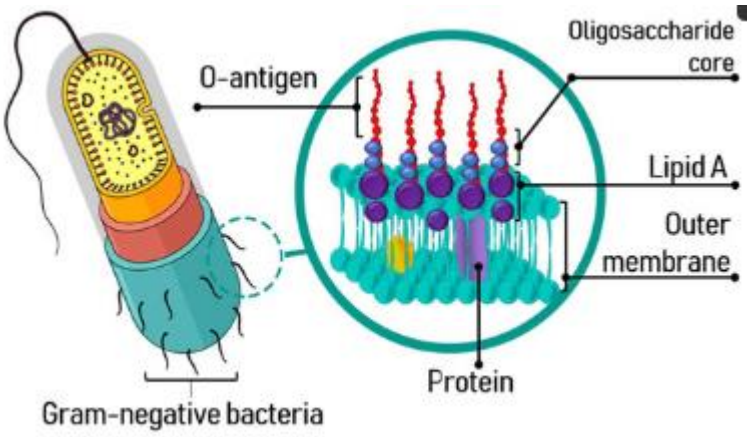

Figure 3 Endotoxin of Gram-negative bacteria [14] **.**

IV. The hypersensitivity of Endotoxin

The endotoxin sensitivity has long been recognized that several experimental settings can significantly increase the sensitivity of healthy, normal animals [15]. Therefore, giving

hepatotoxic substances like D-galactosamine to the experimental animals will make them more susceptible to the deadly effects of endotoxins. [16]. When the mice treated with muramyl dipeptide (MDP), a partial peptidoglycan structure, may similarly have a notable level of sensitization [17]. Additionally, the hyperthermic environment, hypophysectomy, or adrenalectomy will all significantly increase the susceptibility to endotoxins [18]. Several developing tumors were also observed to increase the sensitivity of mice to endotoxins, thus, it was demonstrated that the EMT6 sarcoma developing in BALB/C mice and Lewis lung cancer in C57BL/6 mice significantly increased the animals' sensitivity to endotoxins [19]. It has been demonstrated that both Gram-positive23 and Gram-negative microorganisms make mice more vulnerable to the deadly effects of endotoxins. Particularly noteworthy is the bacterial sensitization [20].

V. Mechanisms of endotoxin

The ability of bacteria to increase the sensitivity to endotoxins is not exclusive to *S. typhimurium*; it is a widespread phenomenon seen in both live and dead Gram-positive and Gram-negative bacteria [21]. It is discovered that bacterially hypersensitive mice release significantly more TNF0 than healthy animals, when it is demonstrated that giving mice *Propionibacterium* aches or *S. typhimurium* causes their TNF production to increase by 1,500 and 200 times, respectively, in response to an LPS challenge [22]. The TNF is the main mediator of LPS's fatal action, hypersensitivity in animals sensitized to bacteria might be explained only by LPS's overproduction of TNF0 [23]. However, an excess of TNF0 is not the only reason why mice treated with bacteria have a high endotoxin sensitivity [22]. Mice exposed to the lethal defect of bacteria are also shown to be hypersensitive to TNF0's activities. Therefore, an excess of TNF0 are the starter of hypersensitivity which observed in mice [23]. Since Gram-negative bacteria also produce endotoxins, their ability to induce hypersensitivity is particularly interesting. The current findings provide for a better understanding of the dangerous effects of Gram-negative infections by demonstrating that these bacteria not only create endotoxins but also sensitize the harmful action [24] . When the processed with bacteria become sensitized to the deadly activity of LPS through the mediation of IFN2.Consequently, giving the animals more pre-treated with bacteria anti-IFNy monoclonal antibodies prevented the higher producing of TNF0 and eliminated the emergence of sensitization to the deadly action of LPS [25].

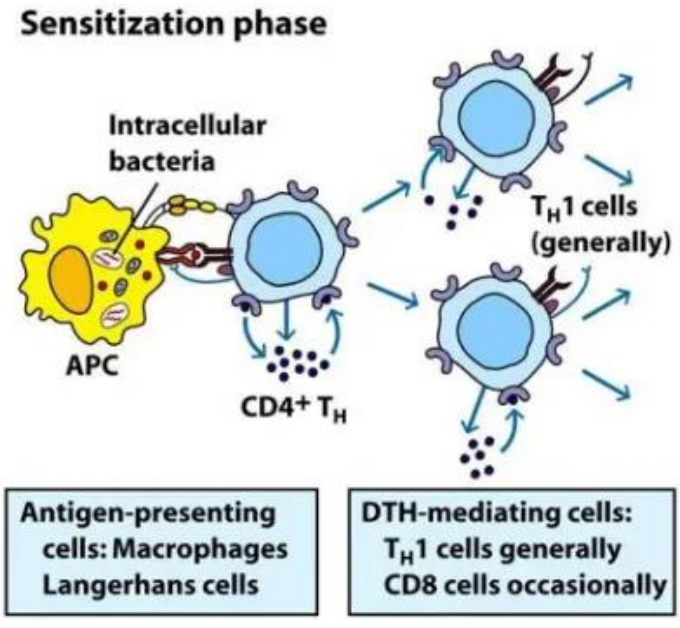

Figure 4 Type IV Hypersensitivity (Sensitization Phase) [24]

VI. The sensitization of endotoxin

One of the mediators of the bacterial sensitization is interferon gamma: The process by which bacteria make an organism more sensitive to endotoxins has lately become better understood [25]. Significant levels of interferon gamma (IFN) have been observed in the serum of mice treated with Gram-positive or Gram-negative bacteria [26]. All mouse strains that are susceptible to endotoxins produce IFN2 after being treated with bacteria. However, it was noted that IFNy production is not triggered by a comparable bacterial infection of mice with LPS-resistant (lpsd) strains [27]. This finding implied that the lack of IFNy production in lpsd mice may be the cause of their incapacity to get sensitized to germs. This possibility was thoroughly examined, and it was shown that IFN2 mediates the sensitization of bacterially treated animals to the deadly activity of LPS [28]. In order to prevent endotoxin shock, anti-IFNy monoclonal antibodies were administered to mice that had previously received bacterial treatment [29]. This prevented the overproduction of TNF0 and eliminated the development of LPS activity. Some research have been looking for effective treatments and preventative measures for endotoxin shock ever before LPS was identified as the primary damage component of Gram-negative bacteria [30]. The antibodies that target specific regions of the LPS molecule that are shared by medicinally significant Gram-negative bacteria have drawn particular attention. Additional strategies include the LPS uses the receptor antagonists and antibodies to the LPS receptor [31].

VII. Conclusion

According to this review, an endotoxin is a complex lipopolysaccharide that is present in the outer cell wall of gram-negative bacteria. It is composed of three primary regions: lipid A, core polysaccharide, and O-specific antigen. It causes toxic effects such sepsis, septic shock, fever, and multi-organ failure.

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