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LISTERIA MONOCYTOGENES: MECHANISMS OF PATHOGENESIS AND ANTIMICROBIAL RESISTANCE

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Listeria monocytogenes is nonspore-forming, gram-positive rods, it is a widespread bacterium; it can survive for a long time in different environments such as food, soil, water, and feces causing adverse health impacts in both animals and humans. Because of its pathogenesis mechanism combined with its ubiquity, It's considereda serious concern. Invasive listeriosis could be without symptoms until 1-4 weeks after infection. It causes serious complications especially in pregnant women, newborn babies, and people with weakened immunity if left untreated. An example of its outbreak what happened in South Africa in January 2018, which resulted in 180 deaths.

Attention is conferred on L.monocytogene from being able to adapt to many types of stresses. Moreover, it can activate specific genes during the life cycle allowing it to replicate within many host cell types during its infection.

In our review, we will highlight the pathogenicity of L.monocytogenes, with emphasis on its antimicrobial resistance.

Keywords:*Antimicrobials, adhesion, invasive, Listeria monocytogenes, pathogenesis, phagosome.*

INTRODUCTION

Listeria monocytogenes is Gram-positive rods, nonspore-forming and facultative anaerobe bacterium. *Listeria monocytogenes* adapts well in stressful environmental conditions, it is able to overcome different degrees of acidity, osmolarity and oxygen differences[1-4]. *Listeria monocytogenes* has 3 lifestyles: 1) Intracellular where it moves based on actin-based motility for cell-to-cell spread, 2) Extracellular in the environment as a free-living, flagellum-propelled bacterium, and finally 3) Extracellular as a part of a biofilm community. It is worth mentioning that even during its saprophytic existence, *L. monocytogenes* has the ability to use carbon sources to produce gene products which ensure its survival in this environment[1-4].

Over the last few decades, *Listeria monocytogenes* has been responsible for foodborne diseases. It is considered a causative agent of listeriosis and one of the leading foodborne pathogens and has been implicated in numerous outbreaks. It was recognized as a foodborne human pathogen in 1981[1-4]. For healthy people, the ingestion of highly contaminated food causes gastroenteritis, while for elderly individuals, pregnant women, children/newborns, and immunocompromised patients, even low levels of food contamination could be cause in septicemia and encephalitis, infection of the fetus resulting in abortion or stillbirth[1-4].

Actually, the process of intestinal phase of infection is very complicated and not fully understood. In addition, transmission to the brain or to the fetus is not completely clear.

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However, the Mechanism of Pathogenicity is well understood, it could be summarized as will be shown.

Mechanism of Pathogenicity

Adhesion and internalization into host cells

Following ingestion of contaminated food with *L.monocytogenes*, these bacteria colonize the intestine causing gastroenteritis. It is considered as invasive bacterium that infects many types of cells. Molecular and cell biological methods showed that *L.monocytogene* has developed many virulence factors to emulate proteins of the host cell and therefore controlling the cellular processes[5&6]. The entry process of *L.monocytogene* into epithelial cells is regulated by two bacterial surface proteins that called Internalin A (InlA) and Internalin B (InlB)[7-9]. InlA is a LPXTG motif (Leu-Pro-any-Thr-Gly) that is covalently anchored to the peptidoglycan by the sortase SrtA, and it uses E-cadherin, which is present on the host cell surface, as a receptor. Some of surface proteins bound non-covalently with peptidoglycan by GW modules. InlB includes three GW modules in its C-terminal domain and interacts with lipoteichoic acids by them. InlB binds to the host cell surface by the receptor tyrosine kinase Met. (Fig. 1) [1&7-9].

Invasion

Upon the association of *L.monocytogene* surface proteins with their receptors on the host cell surface, the filamentous actin concentrates at the site of bacterial internalization. Many actin regulators that are important for internalization depend on the cadherin of the junctional actin cytoskeleton. Actin-related protein 2/3 (ARP2/3) complex is considered one of these regulators, it is necessary for actin assembly at the entry site. In addition to cortactin (a member of the actin-binding protein family which promotes activity of ARP2/3 at cadherin adhesions), actin polymerization mediates the expansion of lately formed adhesion contact sites that result in creating phagocytic cups surrounding the entering bacterium[9&10]. It's believed that clathrin (a protein that plays a role in the formation of coated vesicles) recruitment precedes the local actin rearrangements that are required for *L.monocytogene* internalization where clathrin recruits the proteins that are involved in the actin rearrangements such as adaptor proteins Dab2, Huntingtin Interacting Protein 1 Related (Hip1R), and myosin VI[11-14]. Indeed, Actin is not the only protein that is required for *L.monocytogene* entry. Recent studies indicate that septins, GTP-binding proteins, have an important role in creating phagocytic cup and *L.monocytogene* entry. (Fig. 2) [15&16] .

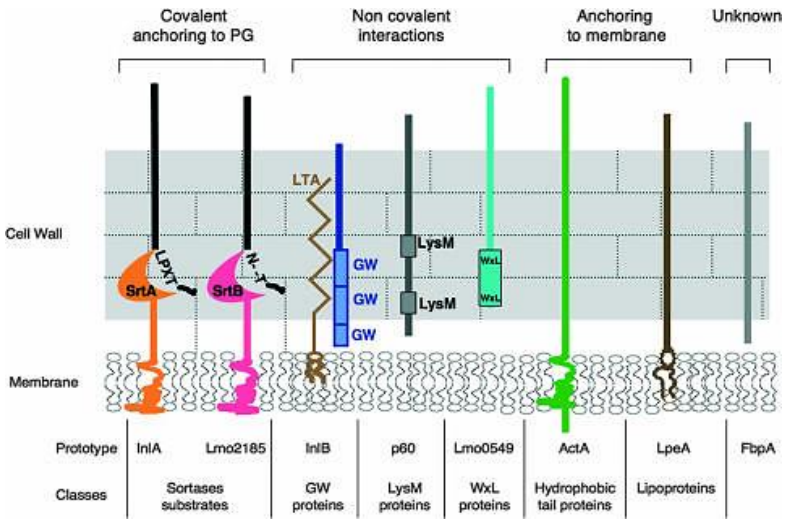

Fig.1: Different types of surface proteins found in *L.monocytogene* [9]*:*

***LPXT** and **NXXTX**: Proteins Covalently Linked to the Peptidoglycan;* **SrtA**: *Sortase A,* **SrtB**: *Sortase B;* ***GW, WxL** and* **LysM**: Proteins with Noncovalent Association to the Cell Wall*;* **LTAs**: lipoteichoic acids, **LysM**: lysin motif domain*;* **InlA**: Internalin A*;* **InlB**: Internalin B.

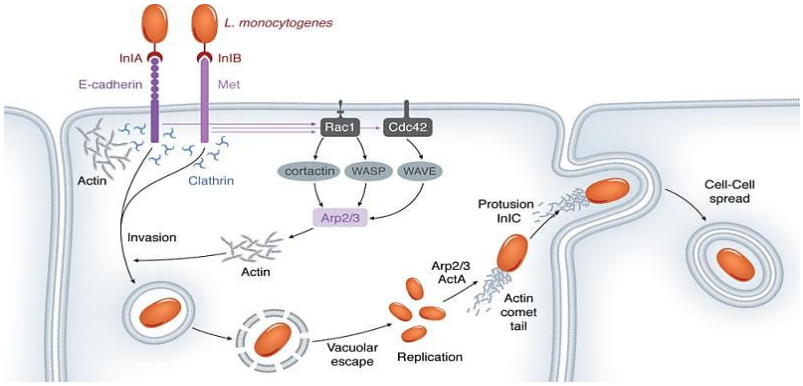

Fig.2: Virulence factors and pathogenesis of *L.monocytogene* [10]:
E-cadherin and **Met**: receptors, **Cdc42** mediates activation of **WASP** (Wiskott-Aldrich syndrome protein)*;* **Rac1** (Rac Family Small GTPase 1) activates **WAVE** (**WASP** Verprolin homologous proteins)*;* **ARP2/3**: Actin-related protein 2/3*;* **cortactin:** a member of the actin-binding protein family that promotes activity of ARP2/3 at cadherin adhesions.

Escape from phagosomes

After the successful entry into the host cell, the *L.monocytogene*is internalized within a primary vacuole. To escape from vacuole, *L.monocytogene* produces listeriolysin O (LLO) (Cholesterol-dependent cytolysins) and two of phospholipases C: phosphatidylinositol specific phospholipase C (PI-PLC) and phosphatidylcholine specific phospholipase C (PC-PLC), both of them are involved combined with LLO in destroying the lipid bilayer membrane of phagosome. Although the first suggestion of LLO role was in pore forming. Recent studies also showed that *L.monocytogene* causes mitochondrial fragmentation of the host cell because of calcium influx through these pores. It is worth mentioning that the premature releasing of PC-PLC into the cytosol of the host cell can be dangerous to bacterium. So, *L.monocytogene* increases the pH inside the vacuole, causing inhibition in the activity of metalloprotease and PC-PLC inactivation[17-20] .

Intercellular Spread

L.monocytogene starts its intracellular replication after its escape from the vacuole using hexose phosphates as a rich source of carbon through hexose phosphate transporter Hpt, which can be controlled by the transcriptional activator of virulence genes (PrfA). Soon after that, the reticulated actin filaments surround *L.monocytogene* and initially concentrate round one pole of the bacterium to rearrange later into comet-like tails; this is because of the ActA (Actin assembly-inducing *protein)* polymerization in a polar way that resulting in one-way propelling of bacterium cell through the cytoplasm[21&22]

ActA consists of 3 functional regions: the N-terminal part which promotes the actin filament nucleation via the interaction with the Arp2/3 complex, C-terminal part contributes in noncovalently linking of protein to the bacterial cell wall, and central part includes proline-rich repeats which is required to link the multiple molecules of VASP. The phosphoprotein VASP molecules modulate the actin filaments by reducing the rates of actin y-branching by the Arp2/3 complex this would increase the actin-based motility. On the other hand, VASP is considered as normal ligand of profilin which in turn promotes the actin polymerization[23-28] .

L.monocytogene uses the actin-based motility to spread from cell to cell resulting in pseudopod-like protrusions forming from the infected cell to neighboring cells. Later, the protrusions are internalized by the recipient cell allowing the bacteria to spread in its cytoplasm in double-membrane vacuole that is called secondary vacuoles[24]. The protrusion formation requires the intervention of Listeria proteins that control properties of the plasma membrane of the host cell. In fact, the actomyosin network may prevent the movement of *L.monocytogene* by creating cortical tension resists its propelling. The Cortical tension depends on the adaptor protein called Tuba by the sixth SH3 domain (SH3-6) which is the target of InlC, a member of the internalin family; this affects its interaction with the cytoskeletal protein N-WASP allowing protrusion forming. (Fig. 3) [29&30]

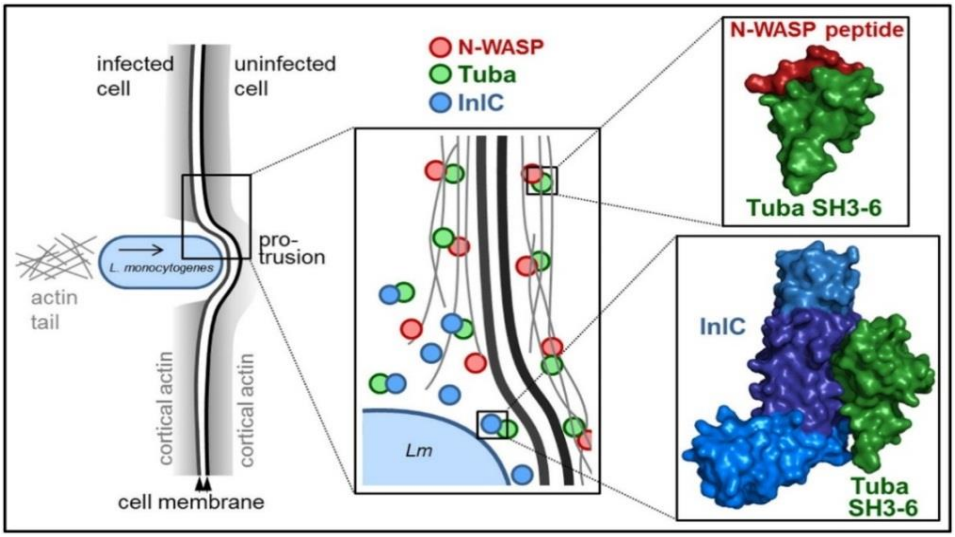

Fig.3: Structural details of Tuba recruitment by InlC of *L.monocytogenes*[30]:

InlC targets the sixth or C-terminal SH3 domain **(SH3-6)** of the adaptor protein called Tuba causing disruption in the interaction with the cytoskeletal protein **N-WASP**. This made it possible to form a protrusion through mobile listeria and cell-to-cell propagation.

Escape from the secondary vacuole

Again, *L.monocytogene* have to penetrate the secondary vacuoles and this requires bacterial proteins such as LLO, PC-PLC, PI-PLC and metalloprotease that lyse the double membrane (Mpl). This causes releasing of into the newly cytoplasm of the infected cell where they initiate a new cycle[24&31].

Antibiotic resistance in *L.monocytogenes*

The multiple resistances of *L.monocytogene* were connected to of movable genetic elements available, such as self-transferable plasmids, conjugative transposons. In addition, many studies showed that efflux pumps, such as multidrug resistance (MdrL) and Listeria drug efflux (Lde), are involved in the multiple drug resistance[2&32&33]. It was indicated that *L.monocytogene* used the conjugation as a main process to be resistant to antibiotic. Conjugation studies showed that Enterococci and Streptococci are the main sources of resistance genes for *L.monocytogenes*. Plasmid pIP501, *Streptococcus agalactiae* plasmid, was transferable to *L.monocytogene* by conjugation, and transfer back to *Streprococcus*. It confers resistance against chloramphenicol, macrolides, lincosamides and streptogramins. pAMβ1 is another plasmid, it was transferred by conjugation between *Enterococcus faecalis* to *L.monocytogene* resulting in conferring the resistance against erythromycin[2&34&35]

Resistance to penicillin and cephalosporin

Penicillin-binding proteins of *L.monocytogene*are are responsible for the construction of the bacterial cell wall, and they are considered as targets of beta-lactam agents. Ampicillin inhibits mainly PBP1 and PBP2 in addition to its effective activity in inhibition of PBP3 and PBP4. Cephalosporins, particularly cefotaxime and ceftazidime, does not inhibit the PBP3. So, even though other important PBPs could be inhibited by cephalosporins such as PBP2 and PBP4, the active PBP3 insures the cell wall construction. This hypothesis was supported by the observed low correlation of monobactams and most cephalosporins for this protein and high affinity between the MICs of b-lactams for it. There are other proteins involved in resistance to cephalosporins, one of them is O-acetyltransferase OatA which modificates the murein of peptidoglycan thus giving resistance against cefotaxime and gallidermin. Lmo2522 is also protein involved in peptidoglycan modification, but it confers a low resistance to cephalosporins[36-38]

Resistance to aminoglycosides

The gene that confers resistance to streptomycin has been detected in *L.monocytogenes*, called aad6 that encodes the 6-N-streptomycin adenylyl transferase. The resistance to gentamicin is uncommon, and hasn't been recorded in normal Listeria

strains[39]. The transposition of Tn3706 which contains aac6'-aph2, gentamicin-resistance gene, happened on the plasmid pIP501. This plasmid is transferable from Streptococcus to Listeria and again, transfer back to Streptococcus. Also, the presence of efflux pump is associated with resistance to benzalkonium chloride[40&38].

Resistance to tetracyclines

The resistant to tetracycline usually depends on *tet(M)* gene that is associated with Tn1545-Tn916 of conjugative transposons contributing genetic transfer between *Enterococcus*, *Streptococcus* and *Listeria*. *tet(S)* gene is also present in resistant *L.monocytogene* and acquired by Tn6000 from Enterococcus casseliflavus[2&38&41&42] .

Resistance to macrolides

The mechanism of macrolides resistance occurs because of rRNA methylases that are encoded by the *erm* genes. These enzymes contribute to methylate the adenine base causing non-linking the macrolides to the 50S ribosomal subunit. Clarithromycin and azithromycin are considered more effective on *L.monocytogene* than erythromycin and spiramycin. Although clarithromycin has the most therapeutic activity, but azithromycin is still active after discontinue therapy because of its long half-life[38&43].

Resistance to quinolones

There are two types of quinolones resistance: mutations and acquisition genes. The mutations occur in DNA gyrase and/or DNA topoisomerase IV causing inhibition in quinolones binding to these enzymes. It was observed that two of efflux pumps, mdrL and lde, are involved in the resistance of *L.monocytogene* to quinolones. In addition, it was suggested that the mutation in the fluoroquinolone efflux regulator (fepR) is responsible partly for the resistance to ciprofloxacin [36&44&45]

Besides, there is a quinolones resistance caused by plasmid-mediated mechanisms. Qnr is one of these plasmids. Qnr proteins protect target enzymes (DNA gyrase and topoisomerase IV) from quinolones action reducing the rate of double-stranded breaks in DNA, so inhibits the progress of DNA replication[46]. The second plasmid is acetylating aminoglycoside acetyltransferase (AAC(6′)-Ib variant, AAC(6′)-Ib-cr) that has Trp102Arg and Asp179Tyr (two unique amino acids) mutations. It catalyzes the acetylation of iprofloxacin and norfloxacin decreasing their activity[45&47] .

Conclusion

Recently, the genetic studies gave us a lot of new information on the mechanisms of action of this bacterium in the host and the extent of antibiotic resistance. It would be interesting to search further into the antibiotic resistance gene patterns and its ability to acquire resistance from other bacterial species, which is due to the molecular basis of differences between strains resulting in new virulence factors and pathogenic mechanisms. In fact, understanding the pathogenesis *of L. monocytogenes* can give us a good perception about the microbial virulence and the development of better therapeutic agents. Therefore, we have reviewed the pathogenesis mechanism of *L. monocytogenes*, as well as the treatment regimens that would be efficient in the control of the disease.

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Listeria monocytogenes: آليات الإمراضية ومقاومة مضادات الميكروبات

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جراثيمListeria monocytogenes هي عصيات موجبة الغرام غير متبوغة، تنتشر بشكل واسع في بيئات مختلفة كالطعام والتربة والماء والبراز ولفترات طويلة مما ينتج عنه آثار صحية ضارة لكل من الحيوانات والبشر. تُعتبر مصدر قلق كبير وذلك بسبب آليتها الامراضية من جهة بالإضافة الى انتشارها الواسع في كل مكان من جهة أخرى. يمكن أن تكون الليستريات الغازية بدون أعراض لمدة تتراوح بين ١–٤ أسابيع بعد التعرض للإصابة. تسبب مضاعفات خطيرة خاصة عند النساء الحوامل والأطفال حديثي الولادة والأشخاص الذين يعانون من ضعف المناعة إذا تركوا دون علاج. نذكر كمثال على تفشي المرض ما حدث في جنوب إفريقيا في يناير ٢٠١٨، والذي أدى لوفاة ١٨٠شخص. ينصب الاهتمام على L. monocytogene كونها قادرة على التكيف مع العديد من أنواع الاجهادات. كما يمكنها تنشيط جينات معينة خلال دورة الحياة مما يسمح لها بالتكاثر داخل العديد من أنواع الخلايا المضيفة أثناء الإصابة. سنسلط الضوء في مقالتنا على إمراضية L. monocytogenes مع التركيز على مقاومتها لمضادات الميكروبات.