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Review on Characteristics and Immune Response against the Proteobacterian *Acinetobacter baumannii* Bouvet & Grimont, 1986

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Abstract: The main cause of death remains infectious diseases, especially in many countries, due for example to the emergence of large numbers of microbial strains that are resistant to many drugs and the increase of new infectious diseases. The previous problem is mostly caused by Gram-negative bacteria. For example, *Acinetobacter baumannii* resistance to drug plays a serious role in the abortive treatment of infectious diseases and cancer. So, to improve effective treatment in contradiction of *A. baumannii*, it is vital to know the origin of bacterial host interfaces, particularly those related to the host's body's defenses. Altered innate immune cells, for example DCs, NK cells, monocytes and macrophages have been recognized as primary influences in protection, in contrast to *A. baumannii*, between them, neutrophils refer to a master immune cells that are essential for controlling infection. Several immunological strategies have been identified to fight *A. baumannii* for example acknowledgment of bacteria through immunocyte done design appreciation receptors, and certainly TLRs, which activate cytokine-containing germicidal mechanisms, oxidative blast and synthesis of chemicals to increase the immune response against germs of pathogens.

Keywords: *Acinetobacter baumannii*, Pathogenicity, Immune response, Biofilm

Introduction

Acinetobacter baumannii belongs to the family Moraxellaceae, Order Pseudomonadales, class Gammaproteobacteria, phylum Proteobacteria of the kingdom Eubacteria (GBIF, 2022). The adequate phylogeny, taxonomy, and clarification of the nomenclature of the genus *Acinetobacter* has been disordered because of the masses of arrangement systems proven via scientists initial on, with over 40 recognized species within the genus (Abdul, 2018; Cameranesi et al., 2018). The greatest clinically significant *Acinetobacter* sp. is *A. baumannii*, due to its connotation with hospice acquired-infections. Others include: *A. calcoaceticus*, *A. grimontii*, *A. junii*, and *A. baylyi*. *A. baumannii* is a Gram-negative non-motile, exactingly aerobic, non-fermentative, coccobacillus, which is notorious for its capacity to tolerate in a diversity of environmental (Perez et al., 2010).

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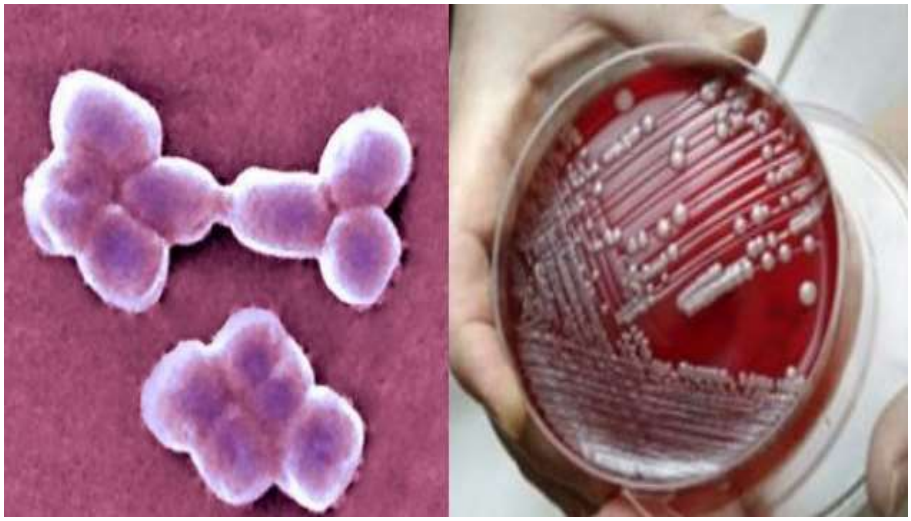


Figure 1: Appearance of *A. baumannii* in microscope and Petri dish (Ehlers et al., 2012).

A. baumannii is considered as one of the greatest demanding pathogens to treat (Evans et al., 2013). It is one of the universally significant nosocomial pathogens (Smani et al., 2012). It is the subsequent highest public Gram-negative nosocomial bacilli next to *Pseudomonas* species seen in clinical samples (Cerezales et al., 2018). Antibiotics not only kill the bacteria, but also affect the host's immune response (Ankomah & Levin, 2014). It's useful to know in what way the body immunity is resistant to this bacteria. Description of the cellular and molecular bases of the response of the body's defenses could afford ways for the improvement of immunological or substitute therapies, in contrast to *A. baumannii* (Morais et al., 2020). This article reviews the limited present concepts regarding the response of the body's defenses to disease through this disease, so the potential healing goals to be implemented in coming approaches for controlling *A. baumannii* infection will be addressed. This is useful to know by what means body's defenses is resistant to these microbes (Romero-Calle et al., 2019).

Categorization of the molecular and cellular bases of the protected defense probably offers apparatuses to advance of immunological or substitutional therapies against *A. baumannii* (García-Patiño et al., 2017). In the present article, the recent information regarding the pathogenesis and immune reaction through this contagion and debate potential healing goals for their implementation in future strategies for controlling *A. baumannii* infection is given.

Factors of Virulence

Several factors of bacterial virulence have been identified. Despite the recent phenotypic and genomic analyzes of bacteria, moderately limited virulence have been recognized in *A. baumannii*, related to those in other G-ve pathogens (Cho & Blaser, 2012).

Lipopolysaccharides (LPS) and Capsular Polysaccharides

Away from outer membrane proteins (Omp), the *A. baumannii* covering is connected with several factors that donate to pathogenicity. Amongst these, capsular exopolysaccharides and LPS are *A. baumannii* pathogenicity influences. Particularly, numerous isolates from patients with *A. baumannii* infections definite surface capsular polysaccharides and contain a preserved gene group, called the K locus, which may regulate invention of capsular polysaccharides (Murray et al., 2020). An accidental transposon screening to recognize genes important for development in an incendiary exudative liquid principal to the proof of identity of the ptk and epsA genes, which are foretold to be required for capsule polymerization and assemblage (Nielsen et al., 2021).

Phospholipase Enzyme

Phospholipase is a hydrolysis enzyme necessary for metabolism of phospholipid and is a virulence factor in several bacteria, for example *P. aeruginosa*, *Legionella monocytogenes* and *Clostridium perfringens* (Kon et al., 2021). Three important classes of enzyme, such as phospholipase C (PLC), phospholipase A (PLA) and phospholipase D (PLD) have been definite established on the cleavage location. PLA hydrolyzes fatty acids from the glycerol (Nielsen et al., 2021), while PLC chops the phosphorylated head collection from the phospholipid. PLD is a transphosphatidylase that only cleaves off the head cluster. Poverty of phospholipids affects the solidity of cell membranes, and the smitten head group can affect with cellular indicating, resultant in alterations in the host immune response (Singh et al., 2019).

Outer Membrane Proteins (OMP)

OmpA, previously Omp38 of outer membrane, is the greatest overflow outer membrane protein of *A. baumannii* (Botelho-Nevers et al., 2013), and one of the supreme well-regarded as factors of virulence. Protein A is greatly preserved, through 83 of 100 and three medical isolates displaying more than 99% characteristics of sequence, by furthermost different taking 85% exact likeness of sequence (Ofek & Doyle, 2012). For instance, OmpA has frequently been encouraged, such as a primary goal for vaccine development. As cited by Mihu & Martinez (2011), β barrels at outer membrane, with a hole length of 2 nm are made by protein A and extension of circular C-terminal periplasmic, accepting molecules up to 500 Da (Lindblom et al., 2015). In contrast to other key porins, for instance OmpA of *A. baumannii*, it is believed that it contributes to the total decrease in outer membrane penetrability of *A. baumannii* (Wang et al., 2017). Up to the present time, only domain of the periplasmic of C-terminal has been crystalized (1.6 Å) and through Asp271 and Arg286 binding to diaminopimelate often, revealed to directly interact with peptidoglycan (Kröger et al., 2017). This interaction is assumed to stimulate the OMPs packing into vesicles (OMVs) of outer membrane. However, this has until now selected established, also might remain only as a result of changed tissue homeostasis in mutant of an outer

membrane A (Morris et al., 2019). OMPA, especially intense addicted to Omvs through regular growing and in vivo diseases (Zgurskaya et al., 2015). Protein A interaction on the surface cell of microbes or OMVs through cells of eukaryotic prompts cytotoxicity, done adhesion, then binding toward death receptors of eukaryotic cell surface (Park et al., 2012). Besides, OmpA are cytotoxic characteristic moderate's series of added traits of virulence (Yu et al., 2018).

An increase in information of new OMPs donating for pathogenesis of *A. baumannii* have seen at recent years. Omp34 (also named Omp34-36) is greatly preserved in *A. baumannii* (Lindblom et al., 2015). Omp34 is like to OmpA, prompts apoptosis in cells of eukaryotic over and done with caspase-dependent technic and autophagy suppression, encouraging persistence to bacteria in the auto-phagosome (Hannan et al., 2012).

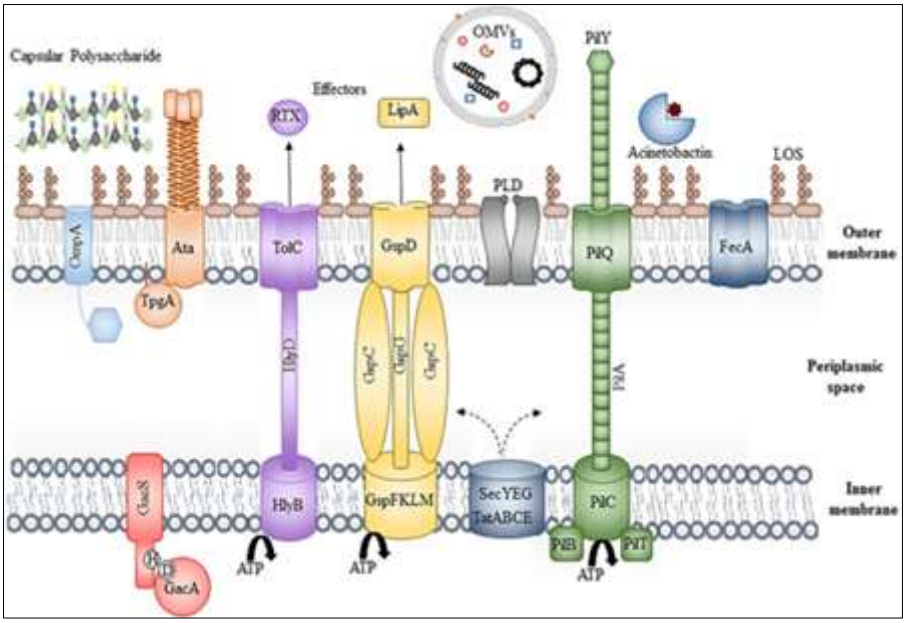


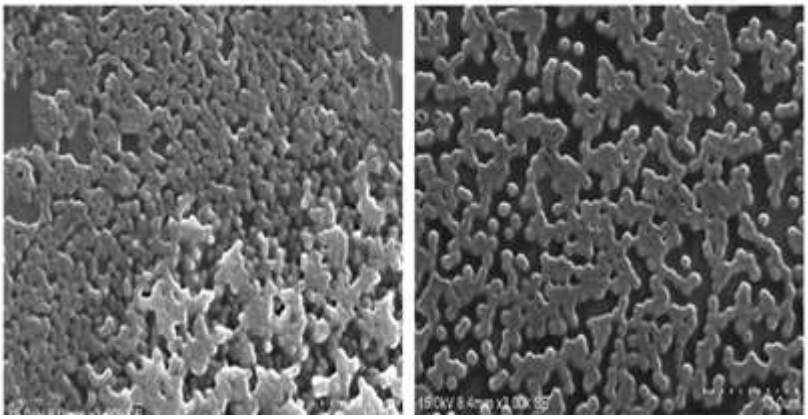
Figure 2: *Acinetobacter* cell virulence factors, consisting of outer membrane; OmpA, schemes type, phospholipase D (PLD), iron attainment systems (Acinetobactin and FecA) and internal membrane, GacA/GacS and outer factors, such as lipid oligosaccharide, capsular polysaccharide and outer membrane vesicles (Morris et al., 2019).

Biofilm Formation

Injury associated with biofilms over a specific location long before separation (Schwechheimer & Kuehn, 2015). The separate biofilms then cause infection via the urinary system or the bloodstream, as well as a lack of blood flow (Doran et al., 2016; Abdul et al., 2019). On the contrary, biofilms have the ability to resist harsh environmental conditions and immune systems as well as anti-bacterial agents than planktonic bacteria. Therefore, the removal and destruction of biological membranes is a serious challenge (Lin et al., 2020), causing in biofilms producing a extensive variety of sub-acute or chronic infections which are actual stimulating to

eradicate (Chiang et al., 2018). *A. baumannii* has been selected as a "red-alert" human pathogen because of its capacity to purchase confrontation to all presently accessible antimicrobial causes (Lee et al., 2017). However, *A. baumannii* infections are attractive increasingly significant in medical repetition and are a universal health concern, moderately little is famous about the factors prompting its pathogenesis. Sections of indication explicated external membrane protein A (OmpA), phospholipids and extracellular polysaccharides (Abdul et al., 2019).

Such a relationship may describe the capability of *A. baumannii* to disseminate and persevere with human host plus medical environments even in the existence of antibiotics in a wide range (Hall & Hall, 2020). Abdi-Ali et al. (2014) established that loss of lipopolysaccharide (LPS) takes significant result on traits of multiple virulence; include production of slime layers via *A. baumannii*.



A B

Figure 3: *A. baumannii* biofilm in scanning electron micrograph images. (A), strong biofilm development; (B), moderate biofilm formation (Yang et al., 2019).

Antibiotic Resistance

The speedy appearance of multiple, drug-resistant strains of *Acinetobacter* highpoints the organism's capacity to adapt rapidly to careful alterations in environmental stresses. The regulation of the organism's inherent resistance mechanisms along with the attainment of external elements joked a critical part in the organism's quick path to attractive a multidrug-resistant pathogen (Ellington et al., 2017).

This possibility of 'switching' their genomic makeup is due in part to the rapidity with which *Acinetobacter* acquires resistance factors when below the influence of antimicrobials, possibly in high-danger environments, such as in hospital intensive care units (Hassan et al., 2014), where broad-spectrum antibiotics are used indiscriminately. The analyses showed similarity in the genetic sequence that most of the resistance genes are located in the *Acinetobacter* AYE strain that was recently obtained from the bacteria *Escherichia* (Axente et al., 2017).

A. baumannii resistance to antibiotics managers are by means of via wholly of main appliances of drug resistance recognized to happen in bacteria counting active efflux, enzyme disabled, goal place modification, and reduced medicine inflow. In addition, a monovalent cation mostly establishes in our skin, NaCl has newly been related with heightened *A. baumannii* multidrug resistance (Draughn et al., 2018).

As stated by Chang et al. (2018), *A. baumannii* can adjust its opposition to drugs by detecting NaCl with surroundings. *A. baumannii* is fewer sensitive to antibacterial means in species of Enterobacteriaceae (Bulens et al., 2018).

The antimicrob reluctance properties of *A. baumannii* are partial attributable to the reduced penetrability of OMP. Omp A is most traditional *A. baumannii* proteins. The possibility of Ag can motivate multiple reaction of the adaptive immune response (Chang & Lin, 2011). *A. baumannii*-MDR is established worldwide, and do not typical description of *A. baumannii*. In addition, most reports define *A. baumannii*-MDR as strong to at least three for the subsequent five antibiotics: carbapenems, ampicillin/sulbactam, cephalosporins, amino-glycosides and fluoroquinlone (Katchanov et al., 2018).

Likewise to MDR, PDR are definite in several means, most proper description of *A. baumannii*-PDR is a bacterium hardy to wholly line antibiotics that have healing possibility transversely *A. baumannii* (Hood et al., 2010). In the same way as MDR, PDR has been defined through a variety of methods. The most appropriate description is that *A. baumannii*-PDR is a kind of resistance to all first-line antimicrobial agents with cross-sectional therapeutic for pathogenic organisms such as *A. baumannii* (Hood et al., 2010).

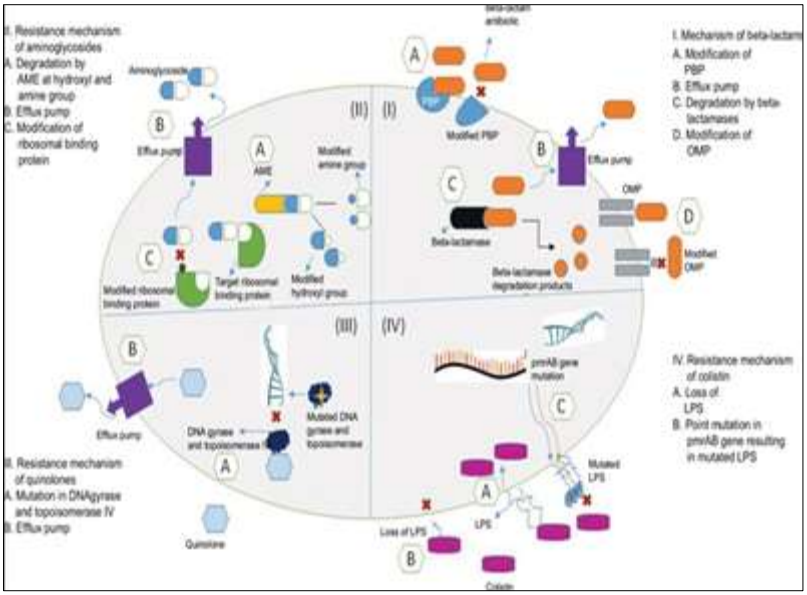


Figure 4: *A. baumannii* resistance mechanism including beta-lactams, aminoglycosides, quinolones and colistin, AME (aminoglycoside modifying enzyme), LPS, PBP (penicillin-binding protein) and OMP (Yan et al., 2017).

Immune Responses

Innate (Neutrophils and Macrophages) Immune Response

The status of neutrophils in response to *A. baumannii* is observed for the first time in relation to the improved occurrence of this pathogen in patients with neutropenia. Though, it took another ten years for some scholars to prove its prominence in fighting respiratory infections caused by *Acinetobacter* (Kabbaj et al., 2013). Immune cells act as antimicrobial agents that defend the body (Agoba et al., 2018). Phagocytosis is facilitated via TLR stimulation, IgG obliteration, or cell mediated response (CMR) necessary (Ghajavand et al., 2015). Once phagocytosed, quick killing relies on reactive oxygen species ROS and granular fusion, which leads to the release of a huge number of antibacterial molecules, defenses into phagocytosis (Pieterse et al., 2016). However, neutrophils ability on destroying *A. baumannii* is controversial, as certain laboratory studies have demonstrated that their co-culture does not affect the capability of either (Underhill & Goodridge, 2012). Alternatively, *A. baumannii* specially adheres to neutrophils, in a manner dependent on IL-8, enhancing their proliferation (Dakal et al., 2016), but some are demonstrated in vitro phagocytosis destroy *A. baumannii*, an outcome constant in vivo readings (Yin & Heit, 2018). The reason for such discrepancies in reporting is mostly led to trial facts. Simply, one strain of *A. baumannii*, ATCC 19606, was tested for one hour after infection, *A. baumanii* and *A. pitii*, above a period, assure the significance of compound strains exam.

Networks are a significant mechanism through which neutrophils controller pathogens, whereas their creation in reaction to *A. baumannii* is also provocative (Konig & Andrade, 2016; Yin & Heit, 2018). The networks are a network of chromatin, saturated with peptides and antimicrobial proteins, including neutrophil elastase, myeloperoxidase, then LL-37 correspondingly (Dakal et al., 2016). Bacterial infection control networks have been connected, but *A. baumannii* is described to impede its development (Kamoshida et al., 2015). This inhibition mechanism has not been completely clarified and established in vivo, although neutrophil cell wall receptors CD11b and CD11a have been concerned in experiential summary bond of *A. baumannii* to neutrophils (Lindblom et al., 2015). That cytokines like IL-8 (TNF-α) need stimulating plus chemically attractive belongings on neutrophils, it is noteworthy are TNF-α triggers attention-reliant on belongings, counting cytokine announcement and MAP kinase stimulation, apoptosis (Kamoshida et al., 2016). Additional host elements like Wip1, neutrophil phosphatase and serum amyloid A and P container control neutrophil passage and pro-inflammatory emission (Sun et al., 2016). Character of macrophages in *A. baumannii* contagion is similarly important. As for its reduction in zebra fish (*Danio rerio*), there is no significant result. In mouse replicas, macrophage give generously decreases pro-inflammatory cytokines plus rises bacterial loads when tried in combination with supplementation (Kamoshida et al., 2016). Tongue and roof of mouth macrophages form major line of protection in contrast to *A. baumannii* in the lungs, plus they have the ability to dependent phagocytosis by microfilaments and microtubules of bacteria, and to stimulate great plains of

interleukins-6, TNF-α, and the inflammatory protein macrophage-2. This is a strong chemical attraction to neutrophils, in added interleukins-1β and interleukins-10 produced at later period opinions (Okshevsky & Meyer, 2015). They can phagocytize microbes now in place of slight as 10 minutes (Thorley et al., 2007; Okshevsky & Meyer, 2015).

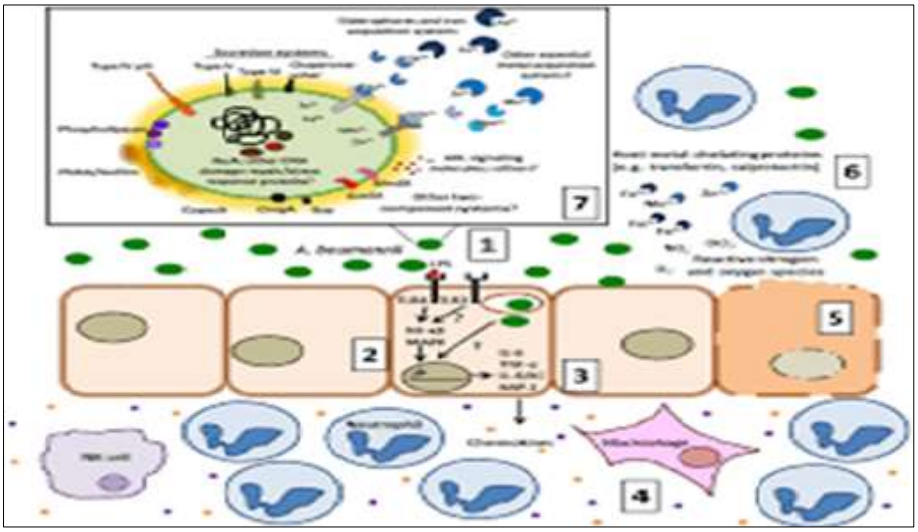


Figure 5: Interaction between *A. baumannii* and the host.
1- Attachment of the bacteria to the host cells causing inflammatory response. 2- Initiation immune response by TLR4 recognition of LPS. 3- Pro-inflammatory mediators including IL-6 and TNF-a as well as chemokines KC/IL-8 and MIP-2. 4- Chemokines activate granulocytes and lymphocytes. 5- *A. baumannii* infection causes the host cells to apoptosis. 6- ROS/RNS production and antimicrobial peptides. 7- Other virulence factors contributed in *A. baumannii* pathogenesis. (Mortensen & Skaar, 2012).

Role of Other Immune Cells against *A. baumannii* Infection

Natural killer cells (NKs) are significant protection device versus microorganism's infections both outside and inside cells. However, its function on *A. baumannii* infection is still not fully defined (Thorley et al., 2007).

NKs are one of the types of immune cells that operate in the soon defense rejoinder period versus *A. baumannii* expending for the natural killer in the pneumonia classic intervene in the removal of the bacteria. The instrument by which NKs participate to control *A. baumannii* pneumonia indirectly depends on formation for chemical attractant KC that volunteers neutrophils to place of contagion (Azcutia et al., 2018). DCs were single Ag-PCs connecting the immune system. *A. baumannii* outer membrane A triggers DCs by their dependence, which induces development, NF-B signaling, led to either CD4 + T-helper1, TC rejoinders or initial programmed cell death (Lindblom et al., 2015). By targeting mitochondria and producing dendritic cell (DC), reactive oxygen species (ROS) is dying off, in line with the device of deed of OmpAs, suggesting which *A. baumannii* might

justice the TC rejoinder across the cell kind (Qiu et al., 2012). Mast cells are guardians of the mucous layers, sensing and responding to invading pathogens. It has been demonstrated that pulmonary mast cells conceal interleukin-8 tumor necrosis factor-α in reaction to bacteria, which enhances neutrophil employing in situ (Wong et al., 2017).

Complement-Mediated Killing

Supplemental arbitrated killing is essential innate non-cellular invulnerable ingredient, containing of a group of solvable agents that act in stream chain that promotes either bacterial cell lysis or increased phagocytosis. There are three ways at statement of accompaniment issues on cell wall, though an alternate complementary pathway in human serum is required to kill *A. baumannii* (Gupta et al., 2018). Confrontation is repeatedly told in medical isolates of bacteria plus in vitro blood confrontation, probably related to additional intense illness (García-Patiño et al., 2017).

The alternative complementary way is controlled by agent H, solvable element of importance for recognizing steward bacteria symbols (Lee et al., 2007). Substitutional action complementary passage induces C3 entrusting on inner of blood-susceptible bacteria, although there are variations on issue H binding to bacteria and later reserve C3 statement, which increases serum resistance in *A. baumannii*. Previously, reports indicated that element H was binding with the bacteria OMPs, enhancing blood opposition (Arora et al., 2019), while some reports the identification of factor H bound in their blood opposition isolates (Blaum et al., 2015) has not been reached, and this indicates that acquisition of factor H is not the only culprit.

In addition, it has also been demonstrated that *A. baumannii*, cip A plasminogen-binding protein degrades fibrin networks and inhibits the alternative complementary pathway through C3b cleavage, by mechanisms that have not yet been fully addressed (Miętka et al., 2016). In line function of cip A in complementary confrontation, alterations of cip A removal is high likely killed by human blood (Viehman et al., 2014).

Genes convoluted in the bacteria cover homeostasis are too involved in blood impedance, such as inactivation of TCS bfmS, that controls capsule plus tablet bio formation, pointers to blood impedance (Cserhalmi et al., 2019; Sandholm, 2019).

Soluble Excrete Factors

The inflammatory immune fluids are produced in reply to *A. baumannii* mainly by NF-B action, whereas all immune fluids drives various stimulators such as activation of caspase 1, 11 results in discharge of interleukin-1β, 18 of the affected pulmonary tract epithelium, thus causing skin injury (Li et al., 2016). However, IL-7 increases agranulogenesis and stimulates discharge of interleukin-8, inducing the drugs peptide LL-37 (Koenigs et al., 2015). Through discharge of interleukin-8, TNF-α, is employed plus motivated but, interleukin-33 suppresses IL-8 emission, besides, recognized to aid neutrophil trek and motivation (Geisinger et al., 2019).

Epithelialization, neutrophils besides discharge a host for drugs, counting human β- preservation two plus three, cathlicidin LL-37 and CD14 to enhance toll like R-4 actions by myeloid distinction agent two tie (Lindblom et al., 2015). That it is unlikely (Tejera-Alhambra et al., 2016). Notably, merely lower oesophageal sphincter LOS-lacking *A. baumannii* showed hypersensitivity of antibiotics LL-37, although aim is careful LOS (Navegantes et al., 2017; Arora et al., 2019).

Adaptive Immune Response (AIR)

Humoral immunity has been extensively traveled in an effort to scheme an active and harmless inoculation, although there is little information regarding the influence of bacteria of adaptive immune response to controlling plus resolving *A. baumannii* infection. A group of microbial antigens (Ags) are planned like applicants for inoculation improvement (Kobayashi, 2008; Bertheloot & Latz, 2017). Now, OmpA stands out like one of top species, due to their great immunity in men (Kobayashi, 2008; Kumar et al., 2018), in addition to their widespread prevalence like harmful agent amid numerous various strains of *A. baumanii* (Kobayashi, 2008). Anti-specific induction of *A. baumaii* antibodies (Abs) through contagion is told, demonstrating that OmpA are main Ag capable of improving the response of the humeral Ab. By a diabetics mice, which had beforehand been exposed is disposed host of *A. baumannii* contagion (Powers & Trent, 2018). In addition, it has been established that this one of apparatuses by that averse-OmpA drugs uses defense is through microbial shadowing, results macrophage-arbitrated over-phagocytosis. A similar study to indicate this defense granted was self-determining of supplement stimulation (Kobayashi, 2008). Vaccination in reunified OmpA no unique consequences in manufacture of particular IgG1 Abs plus stimulation to spleen cells producing IfN, IL-4 and IL-17 in Ag-particular mode. However, besides with Ag amount dependent, results about vaccination generate different forms of cytokines. As a result, with little quantities (3 micrograms) of the Ag, the IFN/ IL-4 outline was touched, but vaccination in greater quantities of reunified OmpA (100 micrograms) leads to the IL-4 shape, which is properties of Th2 reactions (Bertheloot & Latz, 2017).

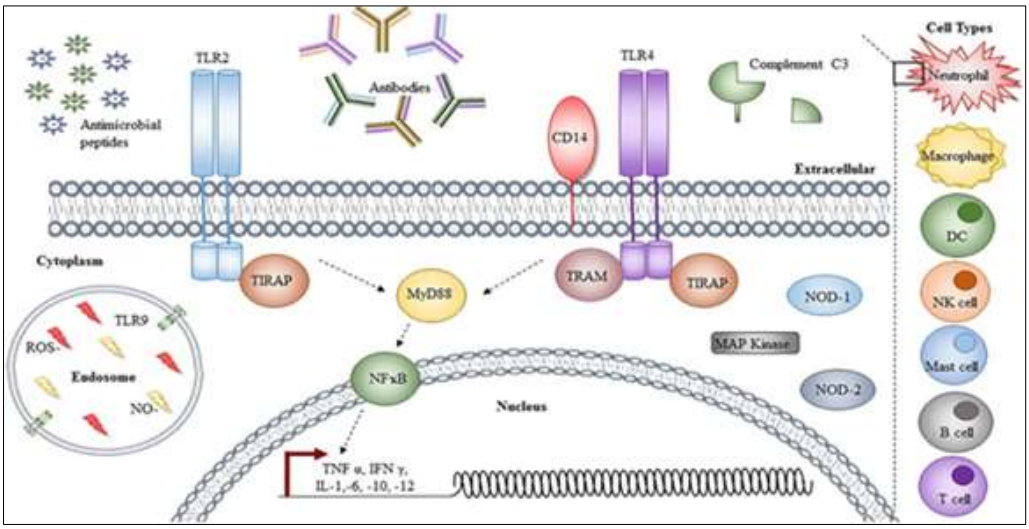


Figure 6: *Acinetobacter* and immune responses through toll-like receptor (TLR) pathways signalling (Yang et al., 2019).

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