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Role of *rmpA, wabG, uge, Ycfm, fimh1, EntB, Ybt-irp2 and kfu* genes in pathogenicity of *Klebsiella pneumoniae*: An overview.

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Abstract : *Klebsiella pneumoniae* is one of the most important pathogenic bacteria, its gram negative, bacilli, non-motile and causative agent of many diseases, such as pneumonia, urinary tract infections, bacteremia, burns and wounds infections and pyogenic liver abscesses. Pathogenicity of *K. pneumoniae subsp. pneumoniae* is due to many virulence genes can encoded many virulence factors that allow it to attack the immune system of mammalians and cause many kind of diseases, some of these virulence factors are: biofilm formation, hypermucoviscosity, capsule synthesis, adhesions, iron uptake and lipopolysaccharides formation.
Objective:The aim of this study was to an overview study about the role of some gens in pathogenicity of *K.pneumoniae.*
Conclusions: The study concluded that *rmpA, wabG , uge , Ycfm , fimh1, EntB , Ybt-irp2 and kfu* genes have an important role in classic pathogenicity of *K. pneumoniae.*
Keywords : Klebsiella pneumoniae, rmpA, wabG, uge, Ycfm , fimh1, EntB , Ybt-irp2 and kfu genes.

Introduction

Carl Friedlände (1847- 1887) is the first German microbiologist and pathologistisolate*Klebsiella* from human with lunginfections in 1882, therefore this bacterium was called Friedlander's bacillus,then named *Klebsiella* in 1886 by Brieg (Polish Biologist), later,especiallyat the beginning of the nineteenth century Edwin Klebs (German microbiologist 1834-1913) is the first one isolate and named *K.pneumoniae* from human with respiratory tract infection[1].

Klebsiella pneumoniae is one of the family *Enterobacteriaceae,* Phylum:*Proteobacteria,* Class:*Gamma proteobacteria* and order :*Enterobacteriales*, its Gram-negative bacilli, rods (0.4-0.7 x 2-4 μm), non-motile,lactose fermenting, negative for oxidase and indole test and urease positive , which have a polysaccharide capsule that produce sticky and large colonies when cultured on an classical media like nutrient agar and selective media like MacConkey agar[2].

Klebsiella pneumoniae isbroadly spread in nature, taking place both as saprophytes in soil, vegetation and water as commensals in human and animal intestine[3]. All strains of *K. pneumoniae* are pathogenic to humans and animals, in which they are both a frequent cause of re-emerging cause of severe community-acquired infections and nosocomial infections[4].It was known as a saprophyte bacteria, it can colonizing in the skin, nasopharynx and human gastrointestinal tract and able to cause urinary tract infections, bacteremia , wound and burns infection and other disease[1].

Klebsiella pneumoniae can produce many virulence factors, these factors can play an important role in pathogenicity such as: fimbriae, outer membrane lipoprotein, siderophores and capsular polysaccharides[5]. Infection by *K. pneumoniae* can spread between person-to-person through respiratory tract and led to cause pneumonia, and may be transmitted to the blood to cause blood infection (bacteremia), infections by *K.pneumoniae* are most predominant in hospitals transmitted by objects contaminated and people's hands , others spread way of *K. pneumoniae* infections through surgery wounds , ventilators and catheters are highly prone to catching this deadly infection[6].

Klebsiella pneumoniae can encoding many virulence factors that permit it to attack the host of innate immunity and cause infection of human, these factors are: production of capsule , attachment factors, production of hypermucoviscosity, formation of biofilm and iron up take systems[7,8,9].Identical or distinct diseases are unexplored because the genetic construction of *K.pneumoniae* remains practically unknown[10].Environmental changes that reflect of pathogenic bacterial clones to their new lifestyle may effect on evolution to increased virulence[11,12].

Klebsiella pneumoniae cause a variety of infections, in individuals who are immunocompromised or have a pre-present primary disease; typically urinary tract infections, pneumonias and soft tissue infections in those predisposed due to diabetes mellitus, and there were two types of *Klebsiella* infections that predominate which are result in airway or urinary tract infections with many following insert of a medical device, likeCatheterization, *K. pneumoniae* remains an causative agent of catheter-associated urinary tract infections[13].*Klebsiella pneumoniae* epidemiology of infections has evolved in the antibiotic date, with most infections, mainly in developed western countries, occurring with long-period care services in hospitals[14].Infections of soft tissue , considered originally in liver abscesses, have become recognized with more aggressive infections that have been found to affect the lungs the parotid gland the brain and the kidneys[15].

Klebsiella pneumoniae is a significant opportunistic pathogen producing nosocomial infections, generally in hospital locations because of the use of antimicrobial agents among immunocompromised individuals[16].

Recently *K. pneumoniae* strains have expected increased disrepute because of their tendency for obtaining antimicrobial resistance determinants, Therefore, treatment has become more challenging[17,18].Because of the increased ability of *K.*pneumoniae to resist different types of antibiotics when transmitted to another site of infections become difficult to be treated[19,20].

Objective: The aim of this study was to an overview study about the role of some gens in pathogenicity of *K.pneumoniae*: Genes responsible for biosynthesis of capsule, genes responsible for adhesions and biofilm formation and genes responsible for iron uptake.

Virulence genesin *Klebsiellapneumoniae*

Klebsiella pneumoniae strains exhibit different virulence factors such as capsular polysaccharides (CPS), lipopolysaccharide (LPS), iron-scavenging systems (siderophores), adhesins , hypermucoviscosity and outer membrane lipoprotein[21].

1.Genes responsible for biosynthesis of capsule

The capsule is an important virulence factor to govern pathogenesis, which protects the bacteria from phagocytosis and bactericidal effects of serum factors[22].Capsule of *K.pneumoniae* is a crucial virulence factor which avoids killing of the pathogen by the host immune system, structurally the capsule is a thick acidic polysaccharide layer composed of repeating four to six sugar subunits,serologically there are about 97 unique capsular antigens (K antigens), but the capsular antigens K1 and K2 considered mainly virulent strains of *K.pneumoniae* there forthey are greatest well-studied[23,24].Capsular protection against phagocytosis by preventing the admission of the complement factor C3b on the bacterial surface.Disability to produced capsule make the strain to be reduced for virulence in a mouse model and increase killing by immune system[25]. Recently, assembly of CPS by *Klebsiella pneumoniae* was organized by glucose concentrations and external iron via the regulation of cyclic adeno monophosphate (cAMP) dependent carbon catabolize repression (CCR) and ferric uptake regulator (Fur), respectively[26,27]. Lipopolysaccharide consists of three parts: O-specific antigen, core oligosaccharide, and lipid A , in smooth lipopolysaccharide the core region is conceptually divided

into two parts: an outer core that provides the attachment site for bacteria and O antigen with lipid A proximal inner core[28]. Additionally lipopolysaccharide O-antigen involved in activation of dendritic cell and in the relationship of the bacterium with eukaryotic cells[29].

A large amount of capsular polysaccharide clinically produced by *Klebsiella pneumoniae* strains, these materials usually can resistance to engulfment by specialized phagocytes also give a mucoid phenotype to the bacteria[30]. Investigation of several virulence factors has been frequently related to the capsule genes like,*rmpA*,*wabG*and *uge*genes, the results of these studies demonstrated that these genes are responsible for the generation of hypermucoviscosity phenotype and biosynthesis of capsule of *Klebsiella pneumoniae*[31].

1.1. *rmpA, wabG* and*Uge genes*

There are many genes that control in biosynthesis of capsule in *Klebsiella pneumoniae*:*uge* gene (codes for uridine diphosphate galacturonate 4-epimerase, express both capsule polysaccharide (K antigen) on the surface and smooth lipopolysaccharide (LPS) with O antigen molecules, therefore, isessential for *Klebsiella pneumoniae* virulence, *wabG* gene(an important role in biosynthesis of virulence and core lipopolysaccharide) and *rmpA* gene(responsible for regulator of mucoid phenotype A of capsule), these factors contribute to virulence and are responsible for invasion , pathogenicity and colonization for *Klebsiella pneumoniae*[32].Sometime *Klebsiella pneumoniae* also exhibits large amounts of mucopolysaccharide mas of capsular and extra capsular polysaccharides to produce more virulent hypermucoviscosity strain[7]. The *rmpA* generesponsible for phenotype of hypermucoviscosity in culture media, this phenomenon could be useful in diagnosis of putative virulence isolates of *Klebsiella pneumoniae* in the early identification of tissue abscess disease caused by *Klebsiella pneumoniae* infection[33].The strains with the hypermucoviscosity phenotype establish extremely high viscosity, determined by a string test of the colony cultured in the laboratory[16,34].

wabG gene is the best one of these genes because it hasmain role in lipopolysaccharide biosynthesis of *K. pneumoniae*, the lipopolysaccharide is one of the mainimmune molecules in bacteria and important structural of the outer membrane[35]. *Klebsiella pneumoniae* oftenexpresses on its surface both O antigen with smooth lipopolysaccharide and capsule polysaccharide called (K antigen), these antigens are responsible for bacterial pathogenicity , the most external component of lipopolysaccharide is O antigen, and it composed of multi repeating units of oligosaccharide polymers, because the high chemical differential in O antigen structures lead to the genetic variation in genes involved in biosynthesis of O antigen and bacterial capsule, these genes are located in the so-called *wabG* cluster. *Uge* gene is located outside of the lipopolysaccharides bacterial antigen O1 (*wb*), capsular polysaccharide K2 (wac_{K12}) gene clusters and lipopolysaccharides-core (*waa*) , and found in most *Klebsiella* strains. The most external component of lipopolysaccharides is O antigen, and it composed of a repeating units of oligosaccharide, on the other hand, there was high chemical variability reported in O antigens of *K. pneumoniae* , this chemical variability lead to genetic variation in biosynthesis of O antigen, these chemical variation are located in type of cluster called *wb*[36]. The genes involved core lipopolysaccharides biosynthesis in *Enterobacteriaceae*are found in cluster called *waa* (*rfa*) gene[37]. Analysis of the structures of core lipopolysaccharides demonstrated that the 1st outer core residue could be galacturonic acid (GalA) residue or glucose (Gluc)[38].

2. Genes responsible for Adhesions and biofilm formation

Many microorganisms especially *K. pneumoniae* have the ability to adapt to environmental changes, this phenomenon is important for multiplication and survival both in the environment and colonization of the host[21].*Klebsiella pneumoniae* hasstructures of protein that identifya varied range of molecular designs involving under groups of virulence factors like fimbria encodes by *fimh* gene and outer membrane lipoprotein encodes by *ycfm* gene , these structures enables the bacteria from attachment and biofilm formation in host cell[2].Bacterial DNAoften able to expression *ycfm gene* , which encodes outer membrane lipoprotein, is significantly induced in *Klebsiella pneumoniae* attachment and biofilms formation is also induced by many stress conditions[39].

2.1. *Ycfm* and *fimh1* genes

Ycfm belongs to the family of *YhcN*, which consist of proteins structures with 9 paralogous, low-molecular mas with unclear function in *K. pneumoniae* and other gram negative bacteria[40]. *Ycfm* family may be have evolved from a common ancestor that is thought to have important roles in attachment and colony

formation by contact cell with cell, intercellular signaling and self-identification , *ycfm* induced about 12-fold in *Klebsiella pneumoniae* cells of biofilm compared to other cells like Phytoplankton cells . *Ycfm* contain high numbers of amino acids(85 amino acid) is also response to general cellular stress, for example: during extreme conditions like changes in pH between 3 to 8[41]. *FimH* gene especially *fim H1* encoding one of the most important virulence factors called fimbriae, are important factor for the attachment of *Klebsiella pneumoniae* toepithelial cells throw the first steps of invasion ,they are also required for colonization of the tissues and for infection of the body[42]. Type 1 fimbriae are existing in many bacteria in the family *enterobacteriaceae* and are one of the important fimbrial adhesins[43]. Because of *K.pneumoniae* has attachment factors such as type 1 fimbriae and outer membrane lipoprotein , therefor its capable of strong attachment to both in living tissues and nonliving objects this feature enabled the bacteria from colonization within the host tissue and are involved in the 1st stage of adhesions and formation of biofilm[42].

In*Klebsiella pneumoniae* and other of some bacteria, fimbriae type 1(heteropolymeric surface organelles responsible for the D-mannose-sensitive adhesion)play a critical role through many infections in patients with respiratory tract infection and urinary tract infections due to mannose bacterial receptors on the epithelium host cells lead to formation of bacterial aggregations in the host cells[44].

Fimbriae (especially type1) are fluffy and adhesive surface structures frequently present in all members of the family *Enterobacteriaceae*[43]. During the stage of colonization the expression of bacterial adhesions is a signify when many mechanical forces such as salivary secretion act to avoid or hamper bacterial attack within the host[45].The *fimH* adhesion enables the pathogens to attach and then colonization to the epithelium tissues by identifying mannose-containing glycoproteins which are existent on many mammalian host tissues, for instance the surface of the urinary tract[46]. Due to the mannose binding pocket existent within the fimbrial tip adhesin, FimH; Type 1 fimbriae bind to mannosylated glycoconjugants on the surfaces of various epithelial cell kinds[47].*Klebsiella pneumoniae* type 1 fimbriae have an effect on creation of intracellular biofilm communities resemble to those formerly observed in *E. coli*. The formation of intracellular biofilm communities enables the organisms to evade the host defenses[48].

The initiation of biofilm production is the attachment of the bacteria to a surface, in many enterobacteria the attachment is facilitated by the presence of fimbriae and outer membrane lipoprotein, the bacteria within the biofilm are protected from inhibition by typically concentrations of antibiotics and innate host defense mechanisms, although several antibiotics are able to penetrate *K. pneumoniae* biofilm, but are quickly broken down[49]. After biofilm formation bacteria remain to multiply finally becoming a large collection of cells in a matrix that may be composed of protein,polysaccharides, and/or DNA, thebacterial growth in biofilms is important component of many infections, mostly cystic fibrosis lung infections, chronic wounds and endocarditis[50].

Investigation of the role of *K. pneumoniae* type 1 fimbriae and outer membrane lipoprotein in facilitating biofilm production *in vivo* has also been examined,deletion of type 1 fimbriae on an abiotic surface, does not affect the biofilm formation ,actually during biofilm formation expression of type 1 fimbriae is down controlled[9].

3. Genes responsible for iron uptake

Siderophores: in Greek know as iron carriers , defined as a compounds with low molecular weight (400 - 1500 Dalton) and it is bio-molecules secreted by microorganisms in response to iron starvation , these compounds are synthesized by bacteria and other microorganisms like fungi and actinomycetes when grow under little ironic stress , structurally siderophores consist of are iron binding proteins , the role of these compounds is to scavenge iron from the host and convert it to the mineral which is available and essential to the bacterial cell, all studies demonstrated that there is a strong relationship (A positive relationship) between siderophores production and virulence of bacteria[51]. There were three types of siderophore systems are most prevalent in *Enterobacteriaceae*: enterobactin, yersiniabactin and aerobactin , the synonym for enterobactin is (enterochelin) is an important catecholate and is produced by more than 91% of gram negative bacterial isolates[52]. Enterobactin or yersiniabactin have high affinity with Fe^{+3} ,on the contrary, aerobactin is synthesis by a small numbers of gram negative bacteria strains and has a lower affinity for free Fe^{+3} [53]. Yersiniabactin is the first siderophore discovered in bacteria, in particular (*Yersinia*), also yersiniabactin found in many isolates of gram negative bacteria, yersiniabactin genes can horizontal transfer from bacteria to other[54]. The locus of

yersiniabactin is located within island with high pathogenicity, which is responsible for dangerous disease caused by pathogenic bacteria like respiratory tract infection[55].

Many types of bacteria can produce siderophores includes: *E. coli,, Klebsiella pneumoniae,Salmonella* , *Vibrio cholera* and others, and there were four main types of siderophores according to their structures: carboxylate , hydroxamate, salicylate and catecholate , and about 500 classes of siderophores have been discovered so far , these compounds play major role in solubilization of iron from organic substances or minerals[51].

3.1.EntB , Ybt-irp2 and kfugenes

Klebsiella pneumoniae (especially clinical isolates) has many genes capable of encoding many siderophores in order to be able to iron scavenge from thehost cell like: *entB* gene (enterobactin) , *Ybt-irp2*gene (yersiniabactin) and kfu gene (iron up take system), because iron is a very important factor in the development of bacteria in the host, and iron important for bacterial nutrient and growth and survive in the body, bacteria can get it from the host from carrier proteins such as transferrin, heme, or lactoferrin[56].

Klebsiella pneumoniae secreted molecules known as siderophores captures iron by binding with free iron or compete with host carrier proteins for iron , clinical isolates of *Klebsiella pneumoniae* encode the production of the siderophore like enterobactin and yersiniabactin for iron up take from the host, additional secretion of these siderophores enhances virulence of bacteria which are responsible for aggressive infections in healthy individuals[54,57].

The *kfu* gene is a putative pathogenic gene which codes for an iron uptake system, *kfu* gene associated with the purulent tissue infections ,capsule formation and virulent hypermucoviscosity phenotype therefor this gene consider is a very important gene in iron up take from host cell. (32).Enterobactin (*entb*) and Yersiniabactin (*Ybt*) are groups of siderophores and have strong affinity with iron, they are often found in *K. pneumoniae* ,*Escherichia coli* and *p.aeruginosa* and other gram negative bacteria and discovered for the first time in 1970 by Gibson and Neilands[58].

Enterobactin and Yersiniabactin have the same mode of action during binding to the ions of ferric (Fe^{3+}) with high affinity , this strong affinity is substantially more than even of many synthetic metal chelates , according to its strong affinity, enterobactin or yersiniabactin is capable of iron up take in spite of in circumstance where the concentration of ferric ion is very low, such as within living bacteria , enterobactin can uptake iron even from the air[59].

When iron become with a little level in bacterial cells, these cells secretion of enterobactin or yersiniabactin or both into the extracellular conditions such as human body , lead to formation of complex compound consist of enterobactin with ferric iron called ferrienterobactin (FeEnt) or called complex ferriyersiniabactin (*FeYbt*) in case of yersiniabactin production or formation both compounds this compounds is very important for iron up take from host system.

Ferrienterobactin esterase enzyme or ferriyersiniabactin esterase enzyme act to remove the iron from ferrienterobactin complex or from ferriyersiniabactin complex , respectively because of the extreme iron binding affinity of enterobactin, this degradation by enzyme lead to release three 2,3-dihydroxybenzoyl-L-serine units and thus leads to reduction of Fe^{3+} to Fe^{2+} which is important element for the life of bacteria[60,61,62].Pathogenic bacteria such as *K. pneumoniae* and *p.aeruginosa* can take iron from other living organisms by this mechanism, in spite of though the low concentration of iron[63,64,65].

Conclusions:

The study concluded that; *rmpA, wabG* and *uge* genes have an important role in capsule synthesis, resistanceof phagocytosis, liverabscess and blood infection in human.*Ycfm* and *fimh1*genes have an important role in urinary tract infection.*EntB* ,*Ybt-irp2* and *kfu* genes have an important role in classic pathogenicity of *K. pneumoniae.*

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