Pseudomonas aeruginosa and the multifactorial antibiotic resistance

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ABSTRACT

Pseudomonas aeruginosa is a gram negative bacterium ,causes many infections specially in immunocompromised individuals and causes critical infections in cystic fibrosis patients. It has remarkable ability to resist various kinds of antibiotics by intrinsic , acquired and adaptive resistance mechanisms , because of the diversity in resistance mechanisms this bacterium contributes in developing multidrug-resistant strains. *P.aeruginosa* infections' treatment is considered as a significant challenge which need to develop new therapies to treat these infections

Keywords: Pseudomonas aeruginosa, antibiotic resistance, multifactorial

Introduction

Pseudomonas aeruginosa is an opportunistic bacterium ,infects the immunocompromised individuals and causes critical infections in cystic fibrosis patients, this bacterium has a great ablility to survive in a broad range of environments[1].

P.aeruginosa infections' treatment is considered as significant challenge cause of the bacterium ability to resist various kinds of antibiotics[2-7]. Carbapenem-resistant *P. aeruginosa* is recently listed by the World Health Organization as a critical problem which need to develop new therapies to treat these infections[8]. Over use and/or misuse of antibiotics lead to develop multidrug-resistant strains of *P. aeruginosa*[2-7].

This study focused on the recent multifactorial antibiotic resistance mechanisms (intrinsic , acquired and adaptive) in *P. aeruginosa* .

1- Intrinsic antibiotic resistance

Define as the bacterial innate ability to minimize the antibiotic efficacy by inherent functional or structural characteristics[9] .

Pseudomonas aeruginosa has a great scale of this kind of antibiotic resistance by various mechanisms[10] as mentioned in (Fig. 1)[11] .

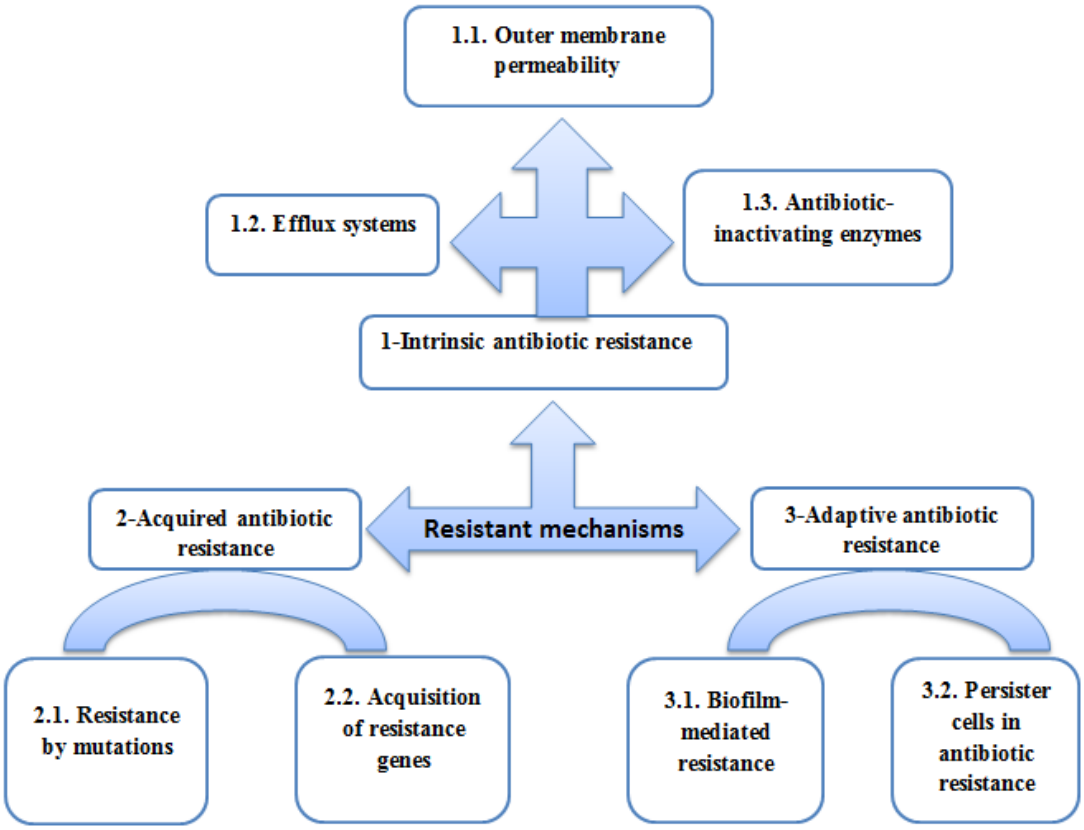

Figure 1- Antibiotic resistant mechanisms

1.1. Outer membrane permeability

P. aeruginosa has selective barrier outer membrane against penetration of antibiotics, contains porins, generally, the porins' family consist of four classes as mentioned in Fig.2. In *P. aeruginosa*, there are important and specific porins act as this kind of antibiotic resistance as mentioned in Fig.3[12].

The lower permeability of *P. aeruginosa* outer membrane compared with other bacteria is due to the closed OprF channels. While, the absence of OprF in this bacterium caused increasing in biofilm formation[13].

The absence of OprD in this bacterium increases the resistance against carbapenem antibiotics and the overexpression of the smallest porin (OprH) because of Mg2+ starvation is associated with the increasing of resistance against gentamicin and polymyxin B[14].

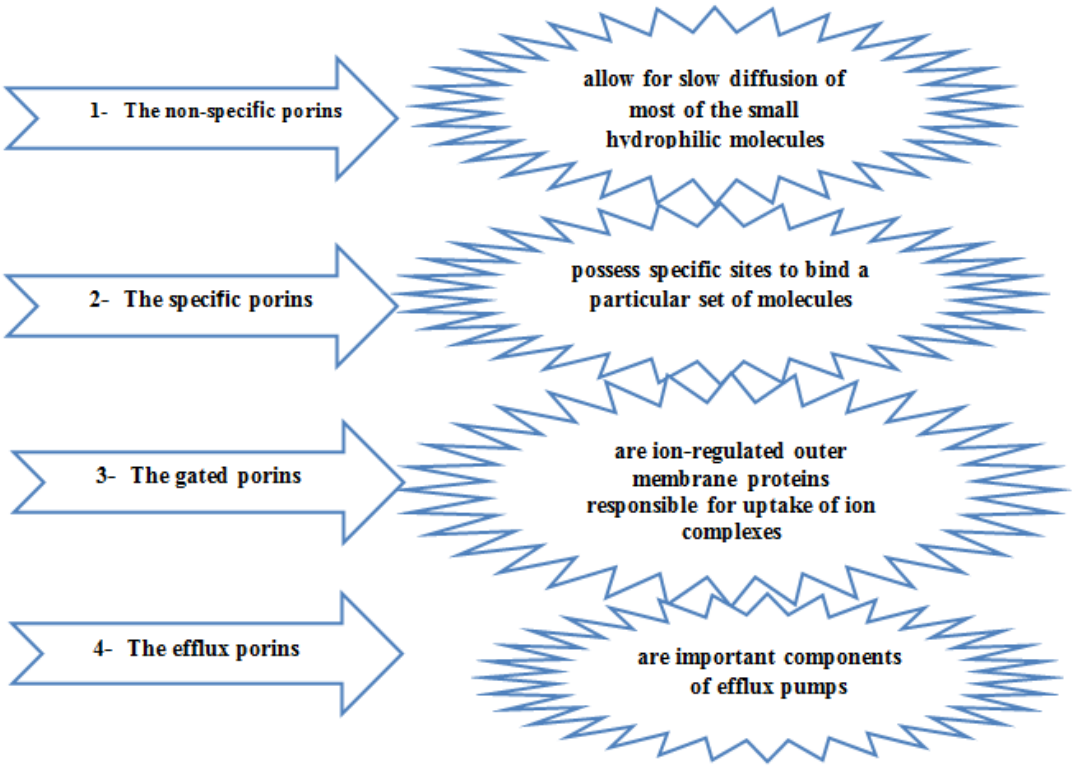

Figure 2- The four classes of porins family

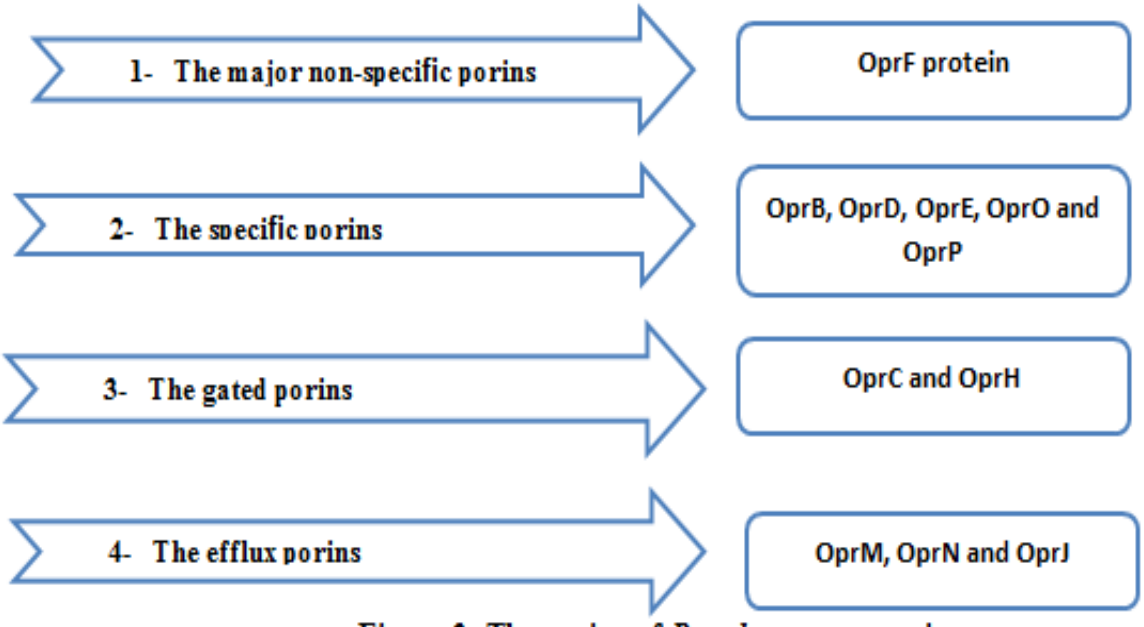

Figure 3- The porins of *Pseudomonas aeruginosa*

1.2. Efflux systems

Expelling toxic compounds out of the bacterial cells, consist of five families[15] as mentioned in Fig.4. In *P. aeruginosa* ,the proteins of RND efflux pumps family play a significant role in their antimicrobial resistance[16].

This bacterium has twelve RND family efflux pumps, four of them contribute in antimicrobial resistance[17] as mentioned in Fig.5 .

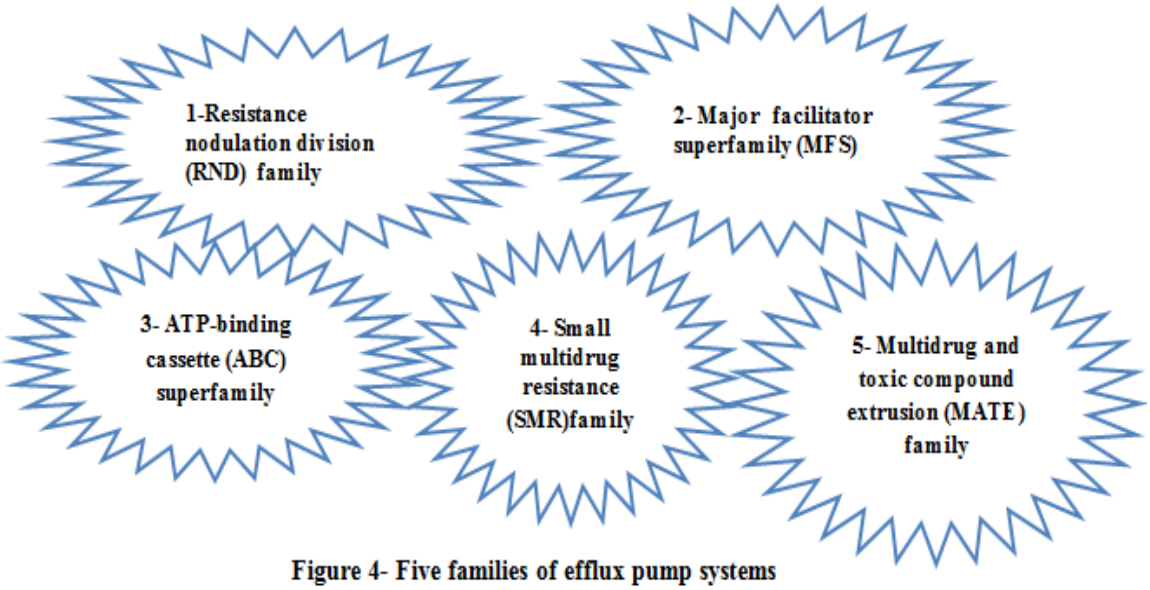

Figure 4- Five families of efflux pump systems

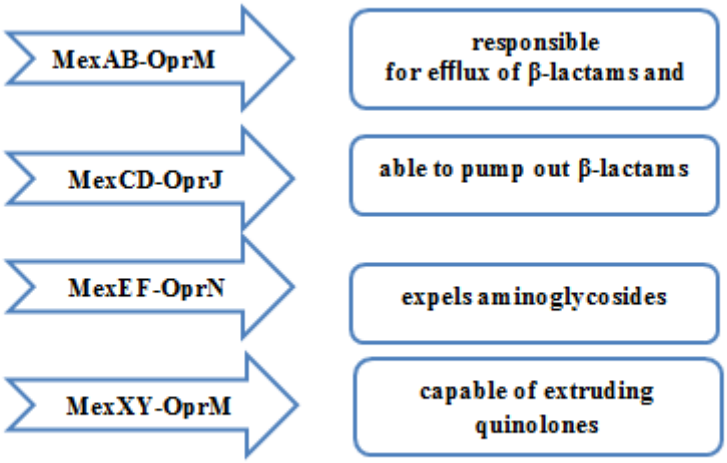

Figure 5- Four RND family efflux pumps in *Pseudomonas aeruginosa*

1-3 Antibiotic-inactivating enzymes

These enzymes can modify or break down antibiotics. Esters and amides chemical bonds in many antibiotics are broken down by these enzymes such as aminoglycoside-modifying enzymes and β-lactamases which commonly produced by *P.aeruginosa*[18,19].

This bacterium has an inducible ampC gene, like other Gram-negative bacteria, this gene encoding for production of β-lactamase which can hydrolysis the amide bond of β-lactam ring [18].

There are four classes of β- lactamases: A, B, C and D, classified by depending on the sequences of amino acids[20].

Some stains *P. aeruginosa* can produce extended-spectrum-β-lactamases (ESBLs) which give a high level of resistance against various classes of β-lactam antimicrobials. Clavulanate, tazobactam and sulbactam considered as β-lactamase inhibitors used to overcome β-lactamase enzymes and useful in combination therapies[21].

2. Acquired antibiotic resistance

This kind of resistance consists of two ways, detailed below.

2.1. Resistance by mutations

Mutations cause decreasing of antibiotic uptaking, overexpression of efflux systems, inactivating enzymes and modifications of antibiotic targets, thus the bacteria can survive against antibiotics attack[22].

Such as, a deficiency in OprD cause a high degree of resistance in *P. aeruginosa* against carbapenem antibiotics, specifically imipenem[23].

2.2. Acquisition of resistance genes

Acquisition of plasmids, prophages, integrons and transposons via horizontal gene transfer causes this kind of resistance[10] as mentioned in Fig.6&7. In *P. aeruginosa* acquisition of resistance genes against aminoglycosides and β-lactams has been conducted[24].

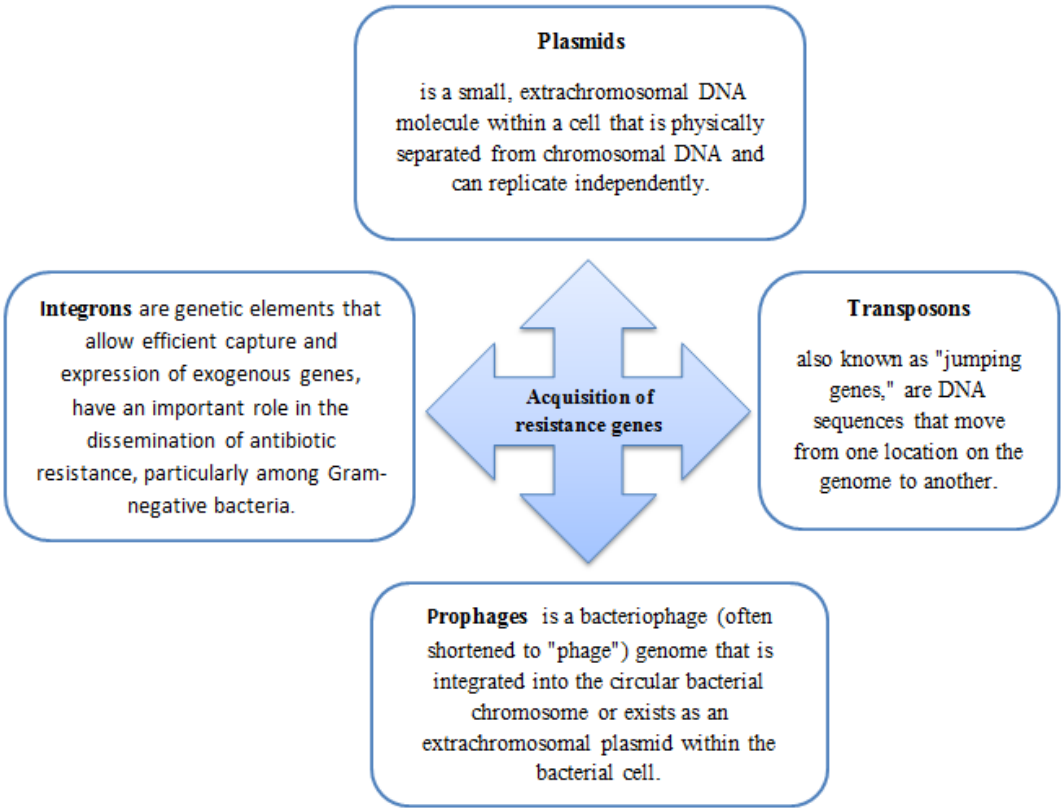

Figure 6- Acquisition of resistance genes

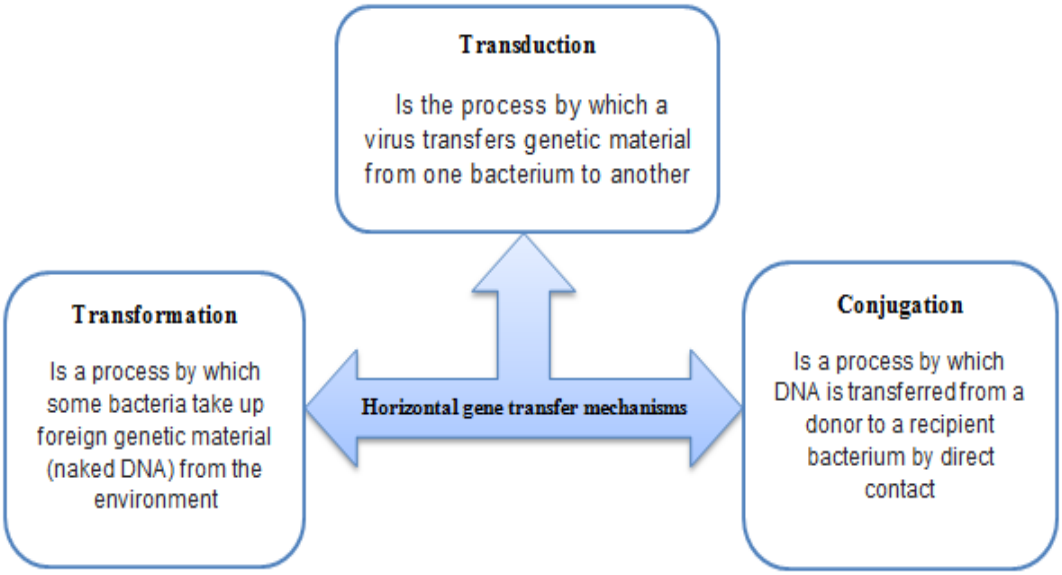

Figure 7- Horizontal gene transfer mechanisms

3- Adaptive antibiotic resistance

Another mechanism to increase the bacterial ability to survive from antibiotic concentrations[25,26].

3-1 Biofilm-mediated resistance

This kind of mechanism makes the bacterial cells less sensitive to antibiotics and immune response of the host[27], mentioned in Fig 8[28].

Two-component regulatory systems regulate the formation of biofilms; called by GacS/GacA & RetS/LadS, exopolysaccharides & cdi- GMP in *P. aeruginosa* [29]. This bacterium has three main quorum sensing as mentioned in Fig 9 contribute in the formation of biofilms[11,30].

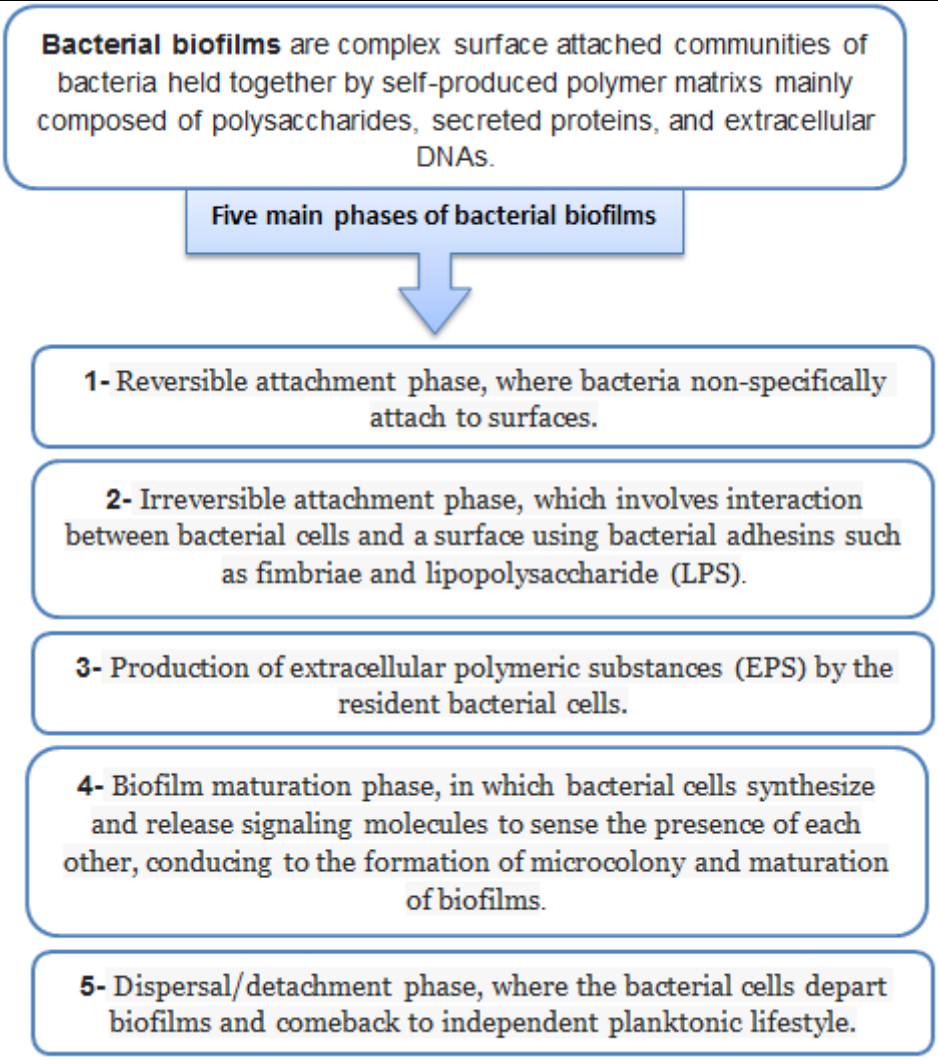

Figure 8- The phases of biofilms

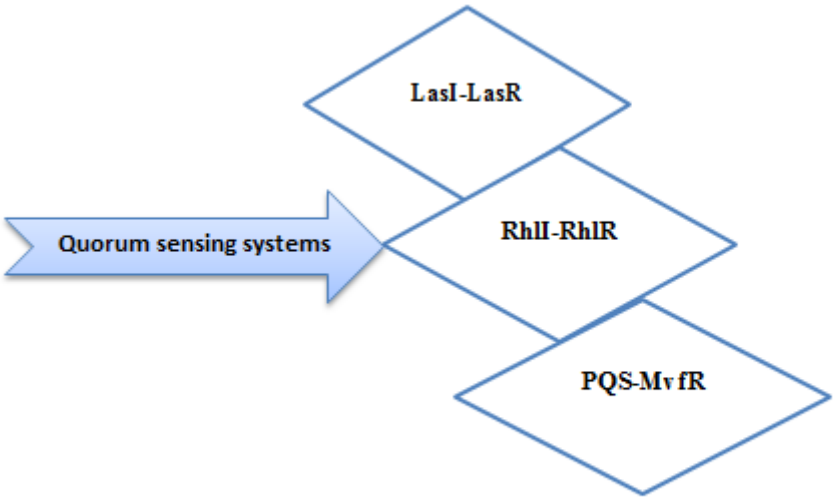

Figure 9- **Quorum sensing systems in *Pseudomonas aeruginosa***

3.2.Bacterial persister cells

Another resistant mechanism against antibiotics with many significant properties as mentioned in Fig.10 [11].

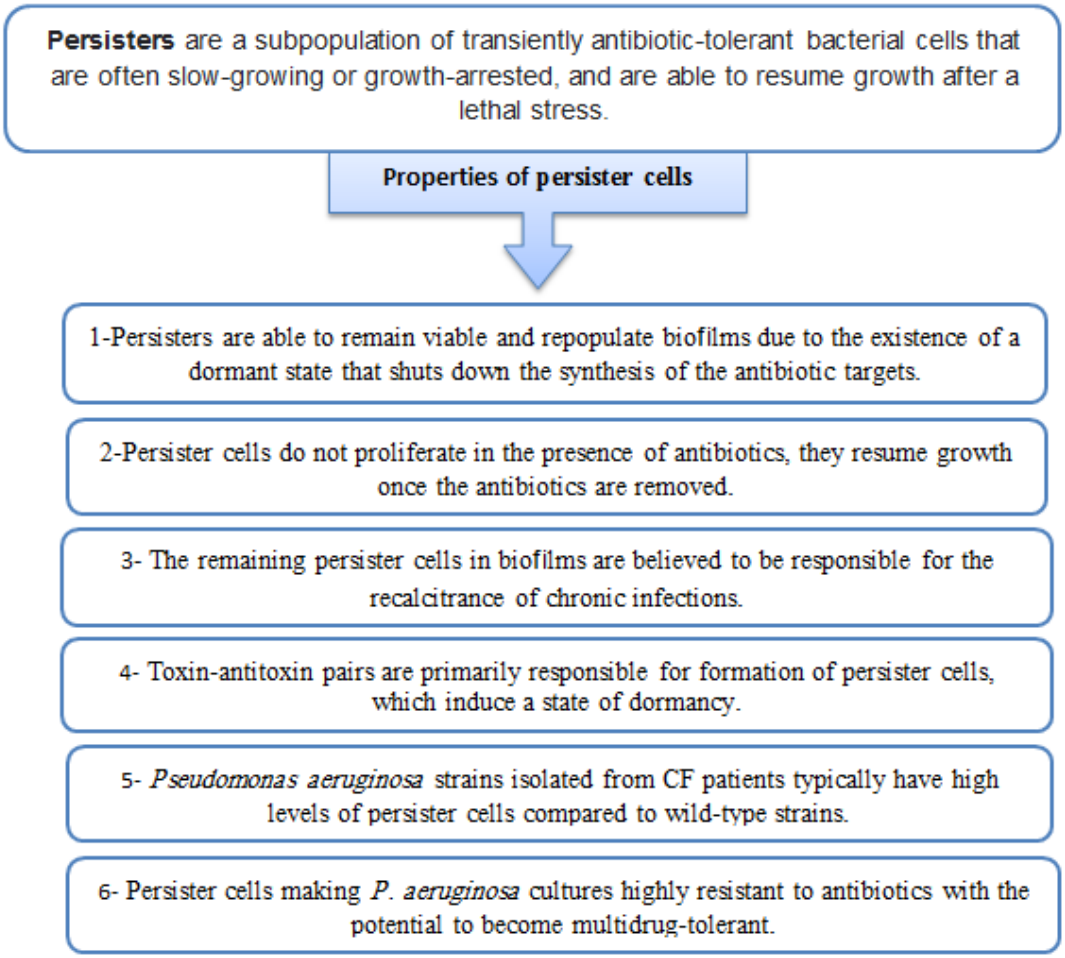

Figure 10- Properties of persister cells in *Pseudomonas aeruginosa*

Conclusion

The treatment of infections that caused by *P. aeruginosa* considered as a serious challenge. *P. aeruginosa* has multifactorial antibiotic resistance because of the diversity in resistance mechanisms (intrinsic , acquired and adaptive) this bacterium contributes in developing multidrug-resistant strains.

In addition to that *P. aeruginosa* able to form biofilms and persister cells which are the causative of continuous and difficult infections in Cystic fibrosis patients.

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