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Mini Review

Possible mechanisms of *Pseudomonas aeruginosa*-associated lung disease

Cassiano Felippe Gonçalves-de-Albuquerque[a,*], Adriana Ribeiro Silva[a], Patrícia Burth[b], Patricia Rieken Macêdo Rocco[c], Mauro Velho Castro-Faria[d,1], Hugo Caire Castro-Faria-Neto[a,1]

[a] *Laboratório de Imunofarmacologia, Instituto Oswaldo Cruz, Fiocruz, Rio de Janeiro, Brazil*
[b] *Departamento de Biologia Celular e Molecular, Instituto de Biologia, Universidade Federal Fluminense, Niterói, Brazil*
[c] *Laboratório de Investigação Pulmonar, Instituto de Biofísica Carlos Chagas Filho, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil*
[d] *Laboratório Integrado de Nefrologia, Departamento de Medicina Interna, Faculdade de Ciências Médicas, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Brazil*

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ABSTRACT

Pseudomonas aeruginosa is an opportunistic bacterium causing lung injury in immunocompromised patients correlated with high morbidity and mortality. Many bacteria, including *P. aeruginosa*, use extracellular signals to synchronize group behaviors, a process known as quorum sensing (QS). In the *P. aeruginosa* complex QS system controls expression of over 300 genes, including many involved in host colonization and disease. *P. aeruginosa* infection elicits a complex immune response due to a large number of immunogenic factors present in the bacteria or released during infection. Here, we focused on the mechanisms by which *P. aeruginosa* triggers lung injury and inflammation, debating the possible ways that *P. aeruginosa* evades the host immune system, which leads to immune suppression and resistance.

1. *Pseudomonas aeruginosa*

Pseudomonas aeruginosa is an environmentally ubiquitous, flagellated, gram-negative bacterium that quickly adapts to new environments (Mathee et al., 2008). The bacteria are regarded as an opportunistic pathogen that causes pneumonia in immunocompromised patients (Williams et al., 2010) such as people with cystic fibrosis (CF) or chronic obstructive pulmonary disease (COPD). In addition, *P. aeruginosa* is a leading cause of hospital-acquired pneumonia in patients undergoing mechanical ventilation (Rello et al., 2009). The bacteria can also cause inflammation and tissue destruction in the urinary tract (Gupta et al., 2013). In ICUs, *P. aeruginosa* is among the top five organisms that cause pulmonary, urinary tract and bloodstream infections (Wolf and Elsasser-Beile, 2009), and its dissemination leads to high morbidity and mortality (Kang et al., 2003).

2. Virulence factors produced by *Pseudomonas aeruginosa*

Quorum sensing (QS) is a cell-to-cell communication system that controls the number of virulence factors (Lee et al., 2013) and biofilm maturation and may play a central role in establishing wound infection (Nakagami et al., 2015). The complex QS network regulate consist of three QS systems: las, rhl and PQS (Venturi, 2006; Williams and Camara, 2009). QS uses bacterial autoinducers to adjust behavior according to population density (Fig. 1A). *P. aeruginosa* uses acyl-homoserine lactones (acyl-HSLs) and pseudomonas quinolone signals (PQS) (Jimenez et al., 2012) as autoinducers for QS regulation, and the bacteria present signal-receptor systems for those signal molecules (Schuster and Greenberg, 2006). As the bacteria proliferate, autoinducer levels increase proportionally, inducing the gene transcription of virulence factors (de Kievit and Iglewski, 2000). The autoinducer N-3-oxo-dodecanoyl-L-homoserine lactone (C12) controls the production of exotoxin A, catalase, pilus and biofilm formation, flagella motility, and twitching motility (De Kievit et al., 2001). The quinolone system represents another layer of sophistication in the complex quorum sensing cascade (Bala et al., 2014). PQSE, induced by Pqs and activated by Pqs operon, from 4-alkyl-quinolone (4-AQ) system is very effective in controlling the production of several

* Corresponding author at: Laboratório de Imunofarmacologia, Instituto Oswaldo Cruz, Fiocruz, Rio de Janeiro, RJ, Brazil.
E-mail address: cassianofg@gmail.com (C.F. Gonçalves-de-Albuquerque).
[1] These authors contributed equally to this work.

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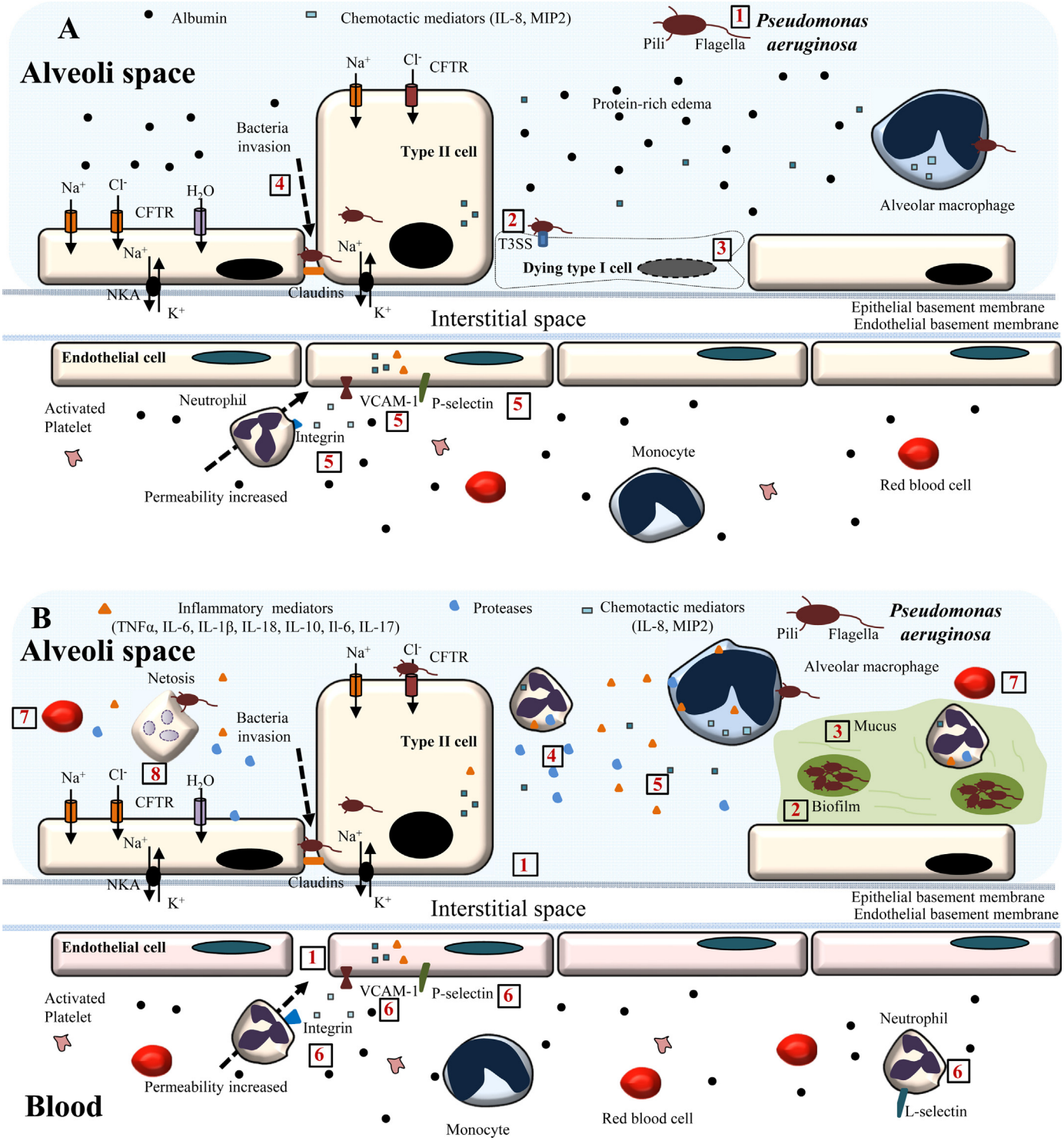

Fig. 1. Effects of *Pseudomonas aeruginosa* in lung disease. *P. aeruginosa* can induce damage in innate immune cells. *P. aeruginosa* possesses an arsenal of virulence traits including pili, flagella (A1), T3SS (A2) and also secretes virulence factors. Toxin release injures the surrounding host tissue, leading to cell death (A3). The bacteria invade the epithelial surface through a breach by an unclear mechanism that may involve claudins (A4). Epithelial injury results in the loss of the alveoli barrier (B1) and the establishment of a pseudomonal biofilm (B2) and a persistent infection (B). This infection occurs in the mucous layer rather than on the epithelial surface (B3). Pseudomonal groups are potent inflammatory stimuli but are resistant to the actions of neutrophils, which may injure surrounding tissue through the release of enzymes (B4). Flagella, pili and quorum sensing members are recognized by leukocyte receptors, triggering the production of inflammatory mediators and the release of proteases, potentiating lung damage (B5). *P. aeruginosa* also inject toxins directly into host cells through T3SS, inducing cell apoptosis or necrosis (A2). Chemoattractant mediators produced by neutrophil, alveolar macrophages, epithelial and endothelial cells induce increases in adhesion molecules such as VCAM-1, selectins and integrins, favoring inflammatory cell infiltration (A5 and B6). *P. aeruginosa* potentially induces lung hemorrhage (B7). The bacteria may induce NETosis (B8). CFTR, cystic fibrosis transmembrane conductance regulator; NKA, Na/K-ATPase; VCAM-1, vascular cell adhesion molecule 1; T3SS, type 3 secretion systems. Those lung alterations neither always occur or all patients present them. The numbering label was added just to better exemplify the phenomenon and it does not necessarily represent the sequence of the events.