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Review article

Role of *Pseudomonas aeruginosa* in Stimulating Respiratory Pro-inflammatory Immune Response

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ABSTRACT

The current study sheds light on the innate immune response as well as the inflammation that occurs as a result of the host cells being exposed to *Pseudomonas aeruginosa*. It also showed the role of receptors on the surface of epithelial cells or other immune cells, especially those responsible for the primary immune response and the cells that cover the mucosal canal such as the respiratory tract. The study also showed how the response to *P. aeruginosa* occurs at the level of the inflammatory immune response as well as the cellular immune response represented by phagocytosis that occurs by phagocytic cells (macrophages) and polymorphonuclear cells (neutrophil). The possibility of finding a vaccine against infection with *P. aeruginosa* was also covered in this review, as this bacterium is responsible for a high rate of mortality, especially for patients who suffer from immunosuppression.

Keywords: Inflammation, Innate Immunity, *Pseudomonas aeruginosa*, Respiratory tract

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1. INTRODUCTION

Pseudomonas aeruginosa, a Gram-negative environmental bacterium, is responsible for the majority of morbidity and mortality in cystic fibrosis (CF) [1]. It is the type species of the genus *Pseudomonas*. It thrives not only in normal atmospheres, but also in hypoxic atmospheres, and has, thus, colonized many natural and artificial environments. Some strains were reported as plant-growth-promoting Rhizobacteria, and others can degrade environmental pollutants [2]. It is also an important opportunistic pathogen and a major cause of serious nosocomial infections, especially in immunocompromised patients or patients with a predisposing condition [3]. It also affects healthy individuals and is an etiological agent to consider in the differential diagnosis of rapidly progressing community-acquired pneumonia [3]. It isolates have been considered as potential biological control agents or inducers of systemic acquired resistance [4], and bioremediation processes [5]. No differences were found in selected pathogenicity determinants such as type-IV pilin and, flagellin in different isolates of *P. aeruginosa* [6]. Additionally, previous studies showed that the genomes of clinical and environmental strains are highly conserved [7]. *P. aeruginosa* isolates as determined in different animal model hosts such as fruit fly *Drosophila melanogaster* [8], and the plant model such as Lactuca sativa var. *P. aeruginosa* stimulates the innate immune response and mucosal response. *P. aeruginosa* in animal models plays a role in inflammatory regulation by adjusting cytokine levels such as Interleukin (IL)-1α, IL-1β, IL-5, IL-6, IL-8, and IL-18 [8].

2. CLINICAL MANIFESTATIONS

P. aeruginosa involved in infections are both invasive and toxigenic, as a result of the production of surface virulence factors(allowing bacterial attachment, colonization, and invasion) and secreted virulence factors (which damage tissues or trigger the production of cytokines), respectively [9]. These infections should be considered severe, and even life-threatening in specific situations, with the highest rates of mortality recorded for cases of bacteremia in neutropenic patients (30 – 50%) and cases of nosocomial pneumonia (45–70%). It is well-

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adapted to the respiratory tract environment, especially in patients with chronic obstructive bronchopulmonary disease, who are immunocompromised, or who are hospitalized in intensive care units [10]. It is also the third leading cause (12%) of hospital-acquired urinary tract infections [11]. These infections can occur via ascending or descending routes and are usually secondary to urinary tract catheterization, instrumentation, or surgery. It is the predominant causal agent of 'swimmer's ear', and of malignant otitis in diabetic patients [12]. Less frequent than other organisms, *P. aeruginosa* can also be the cause of devastating ophthalmic infections (e.g., bacterial keratitis in individuals with contact lenses, or neonatal ophthalmia, meningitis, and brain abscesses (spreading from contiguous structures such as the inner ear or paranasal sinus or after trauma, surgery or invasive diagnostic procedures, and endocarditis in intravenous drug users [13]. P. aeruginosa favors the development of invasive infections in patients at risk [11].

3. *P. aeruginosa* MODEL of PNEUMONIA

P. aeruginosa is a leading cause of such Gram-negative pneumonia and it is located on the 0 polysaccharide side chain of the outer membrane LPS, and the other is mucoid exopolysaccharide (MEP)/alginate, which is involved in the evasion of host defense [14]. They are frequently responsible for opportunistic infections, whereas mucoid strains are often recovered from CF patients [1]. The mucoid strains demonstrate properties such as 1) decreased motility by loss of pili and flagella which provides a better opportunity to adhere to the respiratory tract and resist phagocytosis by macrophages; 2) High intrinsic resistance to antimicrobial drugs, which could be associated with the low outer membrane permeability to antimicrobial agents and production of antibiotic modifying enzymes [15]; 3) Properties of mucoid MEP/alginate which are anti-phagocytic [15], immunosuppressive, and protective against reactive oxygen species [16]. In general, intratracheal installation of *P. aeruginosa* must be trapped in the lungs by using different immobilizing agents, such as seaweed alginate [17]. Moreover, a comparison of different strains of mice revealed that the susceptibility of mice was associated with predominant lung neutrophilic infiltration with lung damage [18].

4. VIRULANCE of CLINICAL and ENVIRONMENTAL *P. aeruginosa* isolates

Some strains have been reported as plant-growth-promoting Rhizobacteria, and others can degrade environmental pollutants [2]. It is also an important opportunistic pathogen and a major cause of serious nosocomial infections [3], especially in immunocompromised patients or patients with a predisposing condition [3, 10]. *P. aeruginosa* also affects healthy individuals and is an etiological agent to consider in the differential diagnosis of rapidly progressing community-acquired pneumonia [3, 14]. *P. aeruginosa* strain cross-infected non-CF parents [1], in bioremediation programs [5]. *P. aeruginosa* isolates were shown to be the same in a group of strains from the environment as in strains obtained from CF patients [1]. Virulence properties of pathogenic bacteria, as well as resistance to antibiotics, are thought to arise through a specialization process favored by the strong selection pressure imposed in clinical treatments. Clones of the opportunistic pathogen *P. aeruginosa* do not seem to be associated with a particular biovar or pathovar, which suggests that virulence characteristics in opportunistic pathogens may already be present in environmental (non-clinical) isolates explored this possibility, studying environmental isolates (mainly from oil-contaminated soils) and clinical isolates (from bacteremia and cystic fibrosis patients) of *P. aeruginosa* strains might be functionally equivalent in several traits relevant for their virulence or environmental properties such as antibiotic resistance or cellular invasiveness, in opportunistic pathogens present in soil ecosystems [1, 19]. Clinical *P. aeruginosa* isolates are typically more adapted to infecting humans. They have evolved mechanisms to adhere to and colonize human tissues, resist immune responses, and produce specific virulence factors that enhance their ability to cause disease. While the environmental isolates are generally less adapted to infecting humans. They may lack some of the specific virulence factors necessary for human infection and may not be as efficient at colonizing human tissues [20]. Clinical *P. aeruginosa* isolates often possess a wide array of virulence factors, including exotoxins, proteases, lipases, and a type III secretion system. These factors contribute to their ability to damage host tissues and evade the immune system. The environmental *P. aeruginosa* isolates may have a reduced set of virulence factors compared to clinical isolates. They might still produce some toxins and enzymes but to a lesser extent, as their primary role is not to cause disease in humans [21]. Clinical *P. aeruginosa* isolates are frequently exposed to antibiotics in healthcare settings. As a result, they tend to have a higher prevalence of antibiotic resistance mechanisms, which can make infections more challenging to treat. Environmental isolates are less likely to be exposed to antibiotics, and therefore, they may have a lower prevalence of antibiotic resistance. However, resistance can still be present, especially due to the natural genetic diversity of *P. aeruginosa* [22]. In terms of disease severity, Clinical *P. aeruginosa* isolates are more likely to cause severe and invasive infections, especially in individuals with compromised immune systems or underlying health conditions. Environmental isolates are less likely to cause severe disease in healthy individuals but can still be opportunistic pathogens in certain circumstances [23].

5. INFLAMMATORY MEDIATORS

It is a part of the complex biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, or irritants. Chronic activation of the innate immune system could also induce systemic inflammation, which includes increased levels of inflammatory mediators in the blood, activation, and mobilization of inflammatory cells into the circulation, and production of acute phase proteins in the liver. Systemic inflammation, with an increased mobilization of monocytes from the bone marrow, has also been reported in humans exposed to PM [24]. In the inflammation phenomenon, a cascade of biochemical events propagates and matures the inflammatory response, involving the local vascular system, the immune system, and various cells within the injured tissue. Prolonged inflammation, known as chronic inflammation, leads to a progressive shift in the type of cells present at the site of inflammation and is characterized by simultaneous destruction and healing of the tissue from the inflammatory process [25]. The recruitment and accumulation of inflammatory cells are orchestrated by a large number of inflammatory mediators, defined as chemical messengers that act on blood vessels and/or cells to produce an inflammatory response. Pro-inflammatory cytokines such as tumor necrosis factor (TNF), interleukin (IL)-1, IL-6, and IL-8 may initiate and exacerbate inflammation, whereas anti-inflammatory cytokines like IL-4, IL-10, and IL-13 serve to reduce and regulate the inflammatory response and promote healing, especially during *P. aeruginosa*

infections [26]. Additional negative regulation of the inflammatory response is provided by soluble cytokine receptors that bind and inactivate pro-inflammatory cytokines, such as IL-1 and TNF-α. IL-1 and TNF-α are early pro-inflammatory cytokines that initiate expression and release of a cascade of pro-inflammatory cytokines, including IL-1 and TNF- themselves, but also other cytokines like IL-6, IL-8, and granulocyte-macrophage–colony-stimulating factor (GM-CSF), that contribute to the recruitment and activation of inflammatory cells [27, 28].

6. CELL SURFACE RECEPTORS

TLRs have recently emerged as key components of the innate immune system that recognize common molecular structures detected in certain groups of microorganisms and trigger the activation of adaptive immunity [29]. Previous studies have indicated that recognition of bacterial antigens is dependent on and mediated by members of the TLR superfamily, which are membrane-bound and expressed by various immune cells. Originally identified as the human homologs of the Drosophila transmembrane receptor, the TLRs are members of the IL-1R family [30]. The human TLR family is comprised of 10 highly conserved types I transmembrane receptors which are functionally expressed on antigen-presenting cells (APCs) [30]. Engagement of TLRs by microbial products is one of the most efficient ways to activate immune cells and induce productive T-cell responses. In addition, the role of *P. aeruginosa* flagellin in stimulating the cellular immune response is also well known [6]. TLR4 recognizes lipopolysaccharide (LPS) of *P. aeruginosa*, a component of the outer cell membrane of Gram-negative bacteria, while TLR2 is involved in the recognition of components from Gram-positive bacteria such as peptidoglycan and lipoteichoic acid [31].

7. PHAGOCYTIC CELLS

Phagocytic cells play a crucial role in the host defense against *P. aeruginosa* pulmonary infection. These cells, which include neutrophils and macrophages, engulf and kill bacteria through a process called phagocytosis. Neutrophils are the first phagocytic cells to arrive at the site of infection. They are recruited to the lungs by inflammatory signals, and they rapidly kill *P. aeruginosa* through a variety of mechanisms, including the production of reactive oxygen species and antimicrobial peptides [32]. Macrophages are also important in the defense against *P. aeruginosa*. They are more long-lived than neutrophils, and they can persist in the lungs for several weeks or months. Macrophages are also more effective at killing intracellular bacteria, which is important because *P. aeruginosa* can invade and replicate within lung epithelial cells [33]. *P. aeruginosa* has evolved several mechanisms to evade phagocytosis. For example, it can produce alginate, a slimy substance that coats the bacterial surface and makes it difficult for phagocytes to engulf. *P. aeruginosa* can also produce toxins that kill phagocytes or suppress their immune functions [33]. Despite these evasive mechanisms, phagocytic cells are essential for the control of *P. aeruginosa* pulmonary infection. In patients with impaired phagocytosis, such as those with chronic obstructive pulmonary disease (COPD) or cystic fibrosis, *P. aeruginosa* infections are more likely to become chronic and severe [34].

8. EPITHELIAL CELLS in INNATE IMMUNITY

Certain studies suggest that invertebrate epithelial cells can recognize microorganisms and mount a fast defense response as a result of the production of various inducible antibiotic peptides. This leads to a characteristic broad spectrum of antimicrobial activity against bacteria and fungi. There are related airway epithelia-derived antibiotic peptides, which are collectively called tracheal antimicrobial peptide (TAP) and lingual antimicrobial peptide (LAP). This discovery gave rise to the speculation that these vertebrate peptide antibiotics, which are induced by contact with bacteria, are important compounds of the respiratory innate immune system that help to keep airways sterile. The main anti-microbial products of epithelial cells include defensins and cathelicidin [35]. Several studies focused on the role of epithelial cells in pro-inflammatory immune response. The main role of epithelial cells is producing of pro-inflammatory mediators such as pro-inflammatory cytokines and phagocytosis [36]. That is why; this kind of cell occupies a central role in inflammatory immune response and represents the first line of defense against external infectious elements.

9. VACCINATION AGAINST RESPIRATORY *P. aeruginosa*

Respiratory infections caused by *P. aeruginosa* are a major clinical problem globally, particularly for patients with chronic pulmonary disorders, such as those with cystic fibrosis (CF), non-CF bronchiectasis (nCFB), and severe chronic obstructive pulmonary disease (COPD) [37]. In addition, critically ill and immunocompromised patients are also at significant risk of *P. aeruginosa* infection. For almost half a century, research efforts have focused on the development of a vaccine against infections caused by *P. aeruginosa,* but a licensed vaccine is not yet available [38]. Significant advances in identifying potential vaccine antigens have been made. Immunizations via both the mucosal and systemic routes have been trialed in animal models and their effectiveness in clearing acute infections demonstrated. The challenge for translation of this research to human applications remains since *P. aeruginosa* infections in the human respiratory tract can present both as an acute or chronic infection. In addition, immunization before infection may not be possible for many patients with CF, nCFB, or COPD. Therefore, the development of a therapeutic vaccine provides an alternative approach for the treatment of chronic infection. Preliminary animal and human studies suggest that mucosal immunization may be effective as a therapeutic vaccine against *P. aeruginosa* respiratory infections. Nevertheless, more research is needed to improve the understanding of the basic biology of *P. aeruginosa* and the mechanisms needed to up-regulate the induction of host immune pathways to prevent infection. Recognition of variability in the host immune responses for a range of patient health conditions at risk from *P. aeruginosa* infection is also required to support the development of a successful vaccine delivery strategy and vaccine [39]. Activation of mucosal immune responses may provide improved efficacy of vaccination for *P. aeruginosa* during both acute exacerbations and chronic infection.

10. CONCLUSION

It is clear that the *P. aeruginosa* cells, as a whole cell or one of its parts, have an important role in stimulating the innate immune response by regulating the inflammatory immune response, which occurs through the binding of bacterial surface proteins to special receptors present on the surface of immune cells. Stimulating the immune system by developing an inflammation immune response could open the door to working on developing vaccines specifically for *P. aeruginosa*, which infection with this bacterium is considered one of the biggest challenges that doctors face at present.

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Conflict of interest
The authors declare that they have no conflict of interests.

Ethical Approval

This review was approved by the Scientific Committee of the Ministry of Higher Education, Baghdad, Iraq (No 1014, 2020).

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