

Review Article **Overview of Mink Immunity and Resistance to** *Pseudomonas aeruginosa*

Jiangsong Bai,¹ Xiao Wang¹,^{2,3} Zihui Zhang,¹ Pengjing Lian,¹ and Jian Qiao¹

¹College of Veterinary Medicine, China Agricultural University, Beijing 100193, China ²Institute of Animal Science and Veterinary Medicine, Shandong Academy of Agricultural Sciences, Jinan 250100, China ³Konge Larsen ApS, Kongens Lyngby 2800, Denmark

Correspondence should be addressed to Xiao Wang; xiaowangzntc@163.com and Jian Qiao; qiaojian@cau.edu.cn

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Pseudomonas aeruginosa is one of the most host-susceptible pathogenic bacteria to cause acute and chronic infections in humans and animals. Notably, its infection can especially cause fatal pathogenic infectious pneumonia in minks. Many previous mink studies have investigated the pathology, pathogenesis, serology, antimicrobial resistance, virulence gene, vaccination, and related diseases of *P. aeruginosa*. However, the relationship of *P. aeruginosa* infections with mink immunity and resistance is relatively less studied that needs more elaborations. Therefore, we here provide a comprehensive review about mink immunity and resistance to *P. aeruginosa* infections and the pathogenesis of mink hemorrhagic pneumonia in four major aspects. They include characterization, infection, immunity, and resistance of *P. aeruginosa*, and their implication and perspective, which aim to contribute the useful and valuable information to further related research and clinical treatment of *P. aeruginosa* and to avoid the potential fatal hemorrhagic pneumonia spreading.

1. Introduction

Pseudomonas aeruginosa (*P. aeruginosa*) is one of the most host-susceptible pathogenic bacteria that causes a wide range of acute and chronic infections in humans and animals [1, 2]. In minks, *P. aeruginosa* induces serious pulmonary diseases to deaths and subsequent economic losses, as an environmentally ubiquitous, extracellular, and opportunistic pathogen [3–5]. For example, it can cause fatal pathogenic infectious hemorrhagic pneumonia with cystic fibrosis, chronic bronchitis, and bronchiectasis, when the host resistances decrease [6–9]. In the real farming environment, the interactions of *P. aeruginosa* and host immunity and resistance determine the pathogenic mechanism, so it can survive in the varied environments based on the multiple bacterial virulence factors and genetic flexibility [6, 7].

Many previous mink studies have worked on the pathology, pathogenesis, serology, antimicrobial resistance, virulence gene, and related diseases of *P. aeruginosa* to understand its molecular infectious mechanism, to find the clinically suitable antibiotics, and to provide the best strategic treatment solutions [10–15]. In the meantime, mink vaccinations against *P. aeruginosa* were developed for clinical treatments, such as bacterin, multicomponent (common protective antigen of *P. aeruginosa* mixed with toxoids of protease and elastase of the bacillus), and other technological vaccines to protect minks with effective immunity from hemorrhagic pneumonia [5, 16, 17].

However, the relationship study of *P. aeruginosa* infections with mink immunity and resistance is relatively less so far and it is still required to be further studied and deeply elaborated. Here, we summarized the characterizations and infectious mechanisms of *P. aeruginosa* and the mink immunity and resistance to *P. aeruginosa* from the previous studies to understand the relationships of *P. aeruginosa* infections with the host immunity that could provide the valuable understandings of pathogenesis of mink hemorrhagic pneumonia for further related research and to contribute to the potential clinical treatments of *P. aeruginosa*

infections and to avoid the fatal hemorrhagic pneumonia spreading in the future.

2. Characterization of Pseudomonas aeruginosa

Several previous P. aeruginosa studies have characterized the isolates for strain type, prevalence, occurrence rate, antibiogram, and molecular pattern [18, 19], where they found the following: (1) the respiratory tract was the most common place for P. aeruginosa multiplication; (2) the significant declines of β -lactam and aminoglycoside susceptibility rates were only found in Europe regions; (3) β -lactamase production and multiple drug resistance efflux pumps contributed to the presence of antibiotic-resistant P. aeruginosa isolates [18, 19]. Those characterization studies of P. aeruginosa aim to know the resistance rates of tested antibiotics among different strains, to understand a variety of resistance mechanisms through different phenotypes, to characterize the transcriptional regulator of catabolic genes (phhA, HPD, hmgA, dhcA) that were induced during P. aeruginosa growth in cystic fibrosis (CF) sputum, to demonstrate the virulence factors involved in adherence and secretion systems, and to reveal the potential phage therapy candidate for the infection treatment [20-24].

2.1. Pseudomonas aeruginosa. P. aeruginosa is a heterotrophic, motile, Gram-negative rod-shaped bacterium belonging to the class of gamma-Proteobacteria in the family Pseudomonadaceae with around $1-5\,\mu m$ long and around $0.5-1 \,\mu\text{m}$ wide [25]. Based on differences in the O-antigen of lipopolysaccharide, Liu and Wang identified 20 different serotypes of P. aeruginosa [26]. P. aeruginosa owns a large size of genome that is estimated to 6.4 Mb on average reflecting the extreme versatility [27]. P. aeruginosa strains are normally subdivided into two major groups that are group I including strain PAO1 and group II including strain PA14 [25, 28]. In the clinical applications, the acquisition of resistance genes via horizontal gene transfer and the mutations in genes can cause antimicrobial resistance of *P. aeruginosa* to up-regulation of efflux pumps, β -lactamase or changes in porins [25]. P. aeruginosa can be easily found in almost any human and animal environments, even if it can be hardly isolated from a number of environments including soil and water. Due to the tendentious formation of multicellular biofilms with a wide variety of antibiotic resistance mechanisms, it majorly caused humans illness and death under immunosuppressive and chronic conditions, so such infections are difficult to treat in these patients [25].

2.2. Virulence Factors of Pseudomonas aeruginosa. Lipopolysaccharide (LPS) normally contains a tripartite structure that are lipid A, core oligosaccharide, and O antigen polysaccharide, where lipid A is the hydrophobic moiety that anchors LPS to outer leaflet together with core oligosaccharide to maintain the integrity of the outer membrane. O antigen polysaccharide is connected to the core with a polymer made of repeating oligosaccharide units

in direct contact with the external milieu [29]. The complete LPS with tripartite structure is normally called "smooth," but LPS molecules referred to lipooligosaccharides are normally called "rough" only with the lipid A and core [30].

Particularly, the low outer membrane permeability of P. aeruginosa contributes its high intrinsic resistance to antiseptics and antibiotics because the general outer membrane porin (OprF) displays structural, adhesion, and signaling functions [31]. Fito-Boncompte et al. revealed the involvement of OprF in P. aeruginosa virulence through modulation of the quorum-sensing network, so OprF is required for P. aeruginosa virulence. In addition, the absence of OprF results in secretion of ExoT and ExoS toxins through the type III secretion system (T3SS), impaired adhesion to animal cells, and production of the quorum-sensingdependent virulence factors pyocyanin, elastase, lectin PA-1L, and exotoxin [32]. Recently, Remans et al. [33] indicated that the number of lipoproteins in P. aeruginosa was 175 reduced from 185 compared with the previous studies; lipoproteins are translocated from the cytoplasm, and their Nterminal signal peptide is cleaved by the signal peptidase II [33, 34].

As a biofilm research model that enables drug resistance with biofilm formations to cause chronic infections, *P. aeruginosa* can produce such robust biofilms in immunocompromised patients with severe problems; furthermore, the unique biofilm properties complicate eradication of biofilm infection that resulted in the chronic infection developments [35, 36]. Pseudomonads produce several biofilm matrix molecules (polysaccharide, nucleic acid, and protein) and accessory matrix components to aid biofilm formation and adaptability under varying conditions [37]. Tielen et al. found the influences of secreted enzymes EstA, LasB, and LipC on formation and architecture of mucoid *P. aeruginosa* biofilms because of changes in EPS composition and properties and their cell motilities [38].

3. Pseudomonas aeruginosa Infections

P. aeruginosa can cause various host infections under immunocompetent and immunocompromised conditions such as folliculitis, osteomyelitis, otitis externa, and pneumonia. Meanwhile, its extreme versatility together with a wide array of antibiotic resistances and dynamic defenses make it extremely challenging to be treated [39–41]. The pathogenicity and infection symptoms of *P. aeruginosa* in human, mink, and other species are listed in Table 1.

3.1. Mink Infections of Pseudomonas aeruginosa. Due to *P. aeruginosa* infections, minks develop acute, contagious, and fatal hemorrhagic pneumonia as the only known animal species in healthy individuals (Table 1). In Denmark, hemorrhagic pneumonia in minks was firstly reported in 1953 that caused variable mortalities ranging from 1% to 75% [4, 5, 10, 11]. In China, *P. aeruginosa* pneumonia in minks was firstly reported in 1985 with percentages of mortality ranging from 6% to 54%. The outbreaks appear

Species	Infection disease	Symptom	Reference
Human	Chronic obstructive pulmonary disease (COPD)	Breathing difficulty, coughing, wheezing persistently, and producing sputum	[8, 43]
Human	Cystic fibrosis (CF)	Cough persistently, produce thick sputum, wheeze, exercise intolerance, repeated lung infection, inflamed nasal passages, and recurrent sinusitis	[7, 48]
Mink	Hemorrhagic pneumonia	Lung inflammatory consolidation and lung bleeding	[4, 5]
Chicken	Pericarditis	Cough, fever, and heart palpitations	[44]
Horse	Endometritis	Purulent vaginal discharge and an excess of echogenic fluid within the uterine lumen	[45]
Pet	Otitis externa	Head shaking, ear pain and swelling, and ceruminous gland inflammation	[46, 47]

TABLE 1: Pathogenicity and infection symptoms of Pseudomonas aeruginosa in different species.

every year in different farms, particularly from August to early December, when all-age minks are affected with typical symptoms, such as nose bleeding, mouth bleeding, pulmonary hemorrhage, and pleural effusions [3, 42]. Qi et al. revealed the genetic similarities and antimicrobial susceptibility profiles of *P. aeruginosa* from clinical cases of mink hemorrhagic pneumonia that facilitated prevention and control of such disease in China [3]. Bai et al. [42] proved the genetic diversity of mink *P. aeruginosa* isolates from different farms and indicated the potential risk to human health, especially for patients with CF as a result of the unique *P. aeruginosa* strains that was acquired in the environment of the patient.

3.2. Human and Other Species Infections of Pseudomonas aeruginosa. In humans and other species, P. aeruginosa is known as an opportunistic pathogen that enables establishment of an infection when the host is immune compromised or susceptible in other ways [1], so it can cause pulmonary disease, pericarditis, endometritis, otitis externa, etc. (Table 1). P. aeruginosa isolated from adult sputum cultures with chronic obstructive pulmonary disease (COPD) displayed two distinct patterns of carriage: short-term colonization followed by clearance and long-term persistence. Different manifestations of P. aeruginosa were observed in COPD that causes acute exacerbations and probably chronic infection in a subset of adults [43]. Generally, airways of patients with CF can be infected by different bacterial species, but P. aeruginosa infection causes the greatest burden of morbidity and mortality, which begins with a period of recurrent, intermittent colonization from the environment or from a protected niche within the patient. Such chronic infections of the CF airway provide a valuable opportunity to study bacterial evolution in a complex natural environment [7].

Hassan et al. [44] performed a study to probe the antimicrobial resistance and virulence gene profiling of P. aeruginosa in broiler chickens with pericarditis. They found that P. aeruginosa was highly virulent and resisted most of the therapeutic agents that bore hazards for poultry industry and represented a public health concern [44]. Kidd et al. studied the relatedness among P. aeruginosa isolates to suggest that most equine genital P. aeruginosa infections were probably acquired from mechanisms other than direct horse to horse [45]. Haenni et al. found the drug resistance to P. aeruginosa with a low proportion of diseased cows and horses, but resistance phenotypes were more frequently observed in dogs. Therefore, the monitorization is important as a result of the animal-to-human transfer between pets and humans, especially for patients with CF [46]. Multidrug efflux pumps are essential for inhibitor development to P. aeruginosa treatment, so Poonsuk and Chuanchuen concluded that the MexXY multidrug efflux pump could act aminoglycoside resistance to P. aeruginosa infection in dogs and cats, which indicates the existence of uncharacterized aminoglycoside-resistance mechanisms [47].

4. Immunity and Resistance to *Pseudomonas aeruginosa*

Sindeldecker and Stoodley [49] summarized the various antibiotic resistance and tolerance mechanisms of *P. aeruginosa* including classic mutation driven resistance, adaptive resistance, persister cells, small colony variants, phoenix colonies, and biofilms. They evaluated the antibiotic surviving isolates to combat the rising number of recurrent and recalcitrant infections by characterizing these phenotypes after distinguishing various phenotypes [49].

4.1. Immunity and Resistance to Pseudomonas aeruginosa with Hormones. Clearly, various hormones can affect immune defense, such as prolactin and melatonin, because immune and endocrine systems communicate each other to influence each other [50–52]. At the onset of fall, hormones fluctuations could possibly cause the hemorrhagic pneumonia in minks because the hormones involved in change of fur and adaptation to altered photoperiod exhibit fluctuations, such as a slow rise in testosterone, a rise in melatonin, and a fall in circulating prolactin [53, 54].

The catecholamines promoted in vitro P. aeruginosa growth, while corticosteroids and catecholamines were also believed to be important as suppressors and modulators in the immune system [55-60]. Corticosteroids were commonly used combined with antimicrobials to treat infectious diseases for inflammatory process control and potential toxicity minimum of antimicrobials to avoid sequelae [61, 62]. Rodrigues et al. provided in vitro and in vivo effects of antimicrobials and glucocorticoids combinations that were the interference evidences of dexamethasone on the pharmacological activity of clinically antimicrobial drugs against biofilms and planktonic cells of *P. aeruginosa* [61]. In addition, Satoh et al. [62] established fatal pneumonia with bacteraemia in mice after dexamethasone treatment using intratracheal infection of P. aeruginosa to elucidate in vivo mechanisms in the pulmonary defense impairment. They found the suppressed production of tumour necrosis factor alpha (TNF- α) during the early phase of pneumonia under dexamethasone treatment, so such TNF- α producing inhibition in the lung could be responsible for the progression of the fatal pneumonia [62].

Melatonin could play an important role as well in regulation of immune defense by stimulating acute inflammation and attenuating chronic inflammation [50], where females were considered to show a stronger immune response compared to males that was probably caused by the onset of production of testosterone for the apparent increased susceptibility of male minks that were infected with *P. aeruginosa* [63–65]. Melatonin has also showed antibacterial effects by reducing intracellular substrates, especially for Gram-negative microorganism with more potent antimicrobial effects, such as *Acinetobacter baumannii*, *Staphylococcus aureus*, and *P. aeruginosa* [66]. The melatonin mechanisms of the removal of free radicals, the induction of antioxidant enzymes, or the modulation of immunity might protect minks against diseases [67].



FIGURE 1: Mink lung lesions of HG, IG, IGM, and IGP groups after (a) 20-hour and (b) 48-hour infections. Note: HG indicates the healthy mink group. IG indicates the infected mink group including minks infected with *P. aeruginosa*. IGM indicates the infected mink group with melatonin including minks treated with melatonin and infected with *P. aeruginosa*. IGD indicates the infected mink group with dexamethasone including minks treated with dexamethasone and infected with *P. aeruginosa*.

4.2. Mink Immunity and Resistance to Pseudomonas aeruginosa. In our previous study [68], we used melatonin and dexamethasone with the dosages of 10 mg and 5 mg, respectively, per body weight (kg) to treat minks at the ages of 5~6 months before the infections of 1×10^9 colony forming units (CFUs) P. aeruginosa. After 20-hour infections, the immunity and resistance results of the minks' infected group (IG) showed more swelling in lungs (Figure 1(a)) with more histopathological changes (Figure 2). The swelling and histopathological changes reduced with melatonin pretreatment (IGM), but the severity of them increased with less resistance to P. aeruginosa if dexamethasone (IGD) was used for the pretreatment (Figures 1(a) and 2). Similarly, lung lesion and histopathology after 48 h infections (Figure 1(b)) were kept consistent with the results after 24 h infections but were more serious (Figure 1(a)). Long et al. [12] found the dispersion of P. aeruginosa antigen within pulmonary cells and its drift in the lung parenchyma using the immunofluorescence method. After 60-hour infections, survived minks showed the macrophage infiltration into limited pulmonary lesions [12].

We also found that bacterial loads of minks after 20-hour infection were higher than those after 8-hour and 48-hour infections (Figures 3(a) and 3(b)). The bacterial loads of minks in IGM groups were significantly lower (P < 0.05) than those in IG groups at the infected time points of 8, 20,

and 48 hours (Figure 3(a)); however, the opposite results of bacterial load were found in IGD groups that were significantly higher than IG groups (Figure 3(b)).

4.3. Experimental Animal Model for P. aeruginosa Study. Otani et al. established an experimental model of nonbacteremic pneumonia with a virulent strain of P. aeruginosa in guinea pigs; the lesions were characterized by dissemination of multiple purulogranulomatous changes. In the early and later stages of infections, infiltration of polymorphonuclear neutrophils (PMNs) in the bronchiolar and alveolar spaces was diffused, where multifocal accumulation with the formation of central spherical grains enclosed bacterial colonies, granulation tissues consisting of large mononuclear cells, fibroblasts, and collagen fibers were developed around the PMN accumulation [69]. P. aeruginosa possessed different receptors such as two PA-IL lectins (α -d-galactose (PA-IL) and l-fucose (PA-IIL)) with best characteristics that bound to carbohydrates; such lectin-carbohydrate interactions may create bacterial adherence to epithelial and endothelial cells to cause microbial pathogenicity [70, 71]. Kirkeby et al. suggested that minks should be considered as a suitable model to study P. aeruginosa adherence based on the following results: (1) both PA-IL lectins adhered to seromucinous glands were located in the submucosa of the larger bronchi in the lungs; (2)



FIGURE 2: Mink lung histopathologies of HG, IG, IGM, and IGP groups under 50× microscope after 20-hour infection. Note: HG indicates the healthy mink group. IG indicates the infected mink group including minks infected with *P. aeruginosa*. IGM indicates the infected mink group with melatonin including minks treated with melatonin and infected with *P. aeruginosa*. IGD indicates the infected mink group with dexamethasone including minks treated with dexamethasone and infected with *P. aeruginosa*.



FIGURE 3: Mink lung bacterial loads of the (a) IGM group and (b) IGD group compared with IG groups at the infected time points of 8, 20, and 48 hours. Note: IG indicates the infected mink group including minks infected with *P. aeruginosa*. IGM indicates the infected mink group with melatonin including minks treated with melatonin and infected with *P. aeruginosa*. IGD indicates the infected mink group with dexamethasone including minks treated with dexamethasone and infected with *P. aeruginosa*.

PA-IL reacted with the capillaries in the alveolar walls to form the vasa vasorum around the larger vessels with the small blood vessels, but PA-IIL marked the goblet cells in the bronchial surface epithelium; (3) both PA-IL lectins bound to the epithelium in the excretory ducts in the pancreas; (4) PA-IL strongly stained the pancreatic capillaries, but PA-IIL staining was found in the apical part of acinar cells in the exocrine part of the gland, while no lectin reaction was found in the endocrine cells [71]. In addition, Kirkeby et al. suggested that mink is also suitable for the study of *P. aeruginosa* mediated rhino-sinusitis [13].

5. Implications and Perspectives

Due to *P. aeruginosa* infections, high mortality and morbidity and the increased resource utilization and cost appear to influence the life quality of patients [72–74]. Mink is the only known animal that is susceptible to acute, contagious, and fatal lung infections, i.e., hemorrhagic pneumonia as an acute and fatal disease caused by *P. aeruginosa*, but its pathogenesis has not yet been issued. Salomonsen et al. [4] clarified the carriers of *P. aeruginosa* on the nasal mucosa in Danish minks during the season for hemorrhagic pneumonia and illustrated that predisposing factors in the mink itself probably played the key role in disease developments [4].

P. aeruginosa characteristics could affect the innate and adaptive immunizations of lung epithelial cells differentially in the mediator production and the recruitment of additional immune cell subsets [75]. Curran et al. [75] discussed the quick adaptation of P. aeruginosa to the host microenvironment through the modulation of expressions of cell surface molecules and virulence factors that influenced the innate and adaptive immune responding efficiencies of hosts directly. Such P. aeruginosa interactions with host cells assisted in effective eradication of P. aeruginosa from the most vulnerable mink populations using innovative approaches, such as bacteriophage, immunomodulatory agent, pyocin, QS inhibitor, neutralizing antibody, and aptamer with conventional antibiotic therapy, to reveal the targeted pathways in the combined therapies for clinical cure and survival improvements. To avoid cross-resistance against current therapeutic agents, Wagner et al. suggested the novel mode action antibiotics. Importantly, antivirulence drugs are expected to yield a significantly reduced rate of resistance developments. However, the combined therapy containing antivirulence agents could pave the way toward novel treatment against *P. aeruginosa* [76].

6. Conclusions

In summary, this review concludes the useful and valuable information of mink, infection, immunity, and resistance to *P. aeruginosa* from the previous studies that are crucial for understanding fatal pathogenic infectious pneumonia including the characterization of *P. aeruginosa*, *P. aeruginosa* infections, immunity and resistance to *P. aeruginosa*, and the further implication and perspective in minks, which may contribute to further related research and clinical treatment of *P. aeruginosa* for mink fatal pathogenic infectious pneumonia and to avoid fatal hemorrhagic pneumonia spreading based on further collaborative international multidisciplinary efforts using current knowledge and strategies.

Abbreviations

CF:	Cystic fibrosis
CFU:	Colony forming unit
COPD:	Chronic obstructive pulmonary disease
IFN-γ:	Interferon-y
LecA:	Galactophilic lectin
LPS:	Lipopolysaccharide
OprF:	Outer membrane porin
PMN:	Polymorphonuclear neutrophil
P. aeruginosa:	Pseudomonas aeruginosa
QS:	Quorum sensing
T3SS:	Type III secretion system
TNF- α :	Tumour necrosis factor alpha.

Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Jiangsong Bai and Xiao Wang contributed equally to this manuscript.

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