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REVIEW

The Microbial Endocrinology of *Pseudomonas aeruginosa*: Inflammatory and Immune Perspectives

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Abstract

Pseudomonas aeruginosa is a major pathogen responsible for both acute and chronic infection. Known as a colonising pathogen of the cystic fibrosis (CF) lung, it is implicated in other settings such as bronchiectasis. It has the ability to cause acute disseminated or localised infection particularly in the immunocompromised. Human hormones have been highlighted as potential regulators of bacterial virulence through crosstalk between analogous "quorum sensing" (QS) systems present in the bacteria that respond to mammalian hormones. *Pseudomonas aeruginosa* is known to utilise interconnected QS systems to coordinate its virulence and evade various aspects of the host immune system activated in response to infection. Several human hormones demonstrate an influence on *P. aeruginosa* growth and virulence. This inter-kingdom signalling, termed "microbial endocrinology" has important implications for host–microbe interaction during infection and, potentially opens up novel avenues for therapeutic intervention. This phenomenon, supported by the existence of sexual dichotomies in both microbial infection and chronic lung diseases such as CF is potentially explained by sex hormones and their influence on the infective process. This review summarises our current understanding of the microbial endocrinology of *P. aeruginosa*, including its endogenous QS systems and their intersection with human endocrinology, pathogenesis of infection and the host immune system.

Keywords *Pseudomonas aeruginosa* · Endocrinology · Sex hormones · Immunology · Quorum sensing

Introduction

Pseudomonas aeruginosa is an opportunistic Gram-negative pathogen recently designated "critical" within the World Health Organisation list of global priority pathogens—the "dirty dozen"—for which novel therapeutics are urgently required (Vogel 2017). As a human pathogen, it is both invasive and toxigenic, producing a battery of virulence factors and colonising diverse host tissues where it may inflict localised tissue damage or disseminate, causing life-threatening systemic infections (Gellatly and Hancock 2013; Veesenmeyer et al. 2009).

Pseudomonas aeruginosa is the most prevalent non-fermentative opportunistic pathogen encountered clinically and has high associated mortality, particularly in ventilator-associated pneumonia and bloodstream infections (Jones 2010; Parkins et al. 2010; Tumbarello et al. 2011; Weiner et al. 2016; Wisplinghoff et al. 2004). Other patient cohorts at increased risk include burn wound victims and those suffering from cystic fibrosis (CF) or other chronic respiratory conditions such as bronchiectasis and chronic obstructive pulmonary disease (COPD) (Gellatly and Hancock 2013; Gibson et al. 2003; Leung et al. 2017; Tredget et al. 2004). *Pseudomonas aeruginosa* is an important plant pathogen that infects plants such as tobacco, tomato and lettuce (Djonovic et al. 2013) and is found ubiquitously in soil and aquatic environments. Its propensity to colonise diverse ecological niches is also reflected in the hospital environment where it can colonise common surfaces such as sinks and medical devices which act as reservoirs for outbreak strains (Quick et al. 2014). Figures reported to the National Healthcare Safety Network in the United States (2011–2014) show that *P. aeruginosa* is one of the "top ten" most common causes of hospital-acquired infections, surgical site infections, intra-abdominal infections and catheter-associated

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urinary tract infections (Crousilles et al. 2015; Weiner et al. 2016). As such it represents a key pathogen and major healthcare burden.

Pseudomonas aeruginosa Pathogenesis

Interaction between *P. aeruginosa* and the human host involves flagella and type IV pili—the main adhesins described in *P. aeruginosa*. Flagella bind to host epithelial gangliosides, asialo GM1 and GM2 bringing the host cell into contact with bacterial surface appendages such as lipopolysaccharide (LPS) which are highly inflammatory (Gellatly and Hancock 2013). Following host cell contact, *P. aeruginosa* secretes cytotoxins into the host cytoplasm through the activated-type three-secretion system (T3SS) (Crousilles et al. 2015; Gellatly and Hancock 2013). Production of proteases by *P. aeruginosa* also disrupts tight junctions and allows the dissemination of *P. aeruginosa* into the host (Gellatly and Hancock 2013). Pyocyanin, a redox-active toxin produced by *P. aeruginosa* interferes with host production of ATP and redox cycling further exacerbating infection (Gellatly and Hancock 2013; Hall et al. 2016). Another important virulence-associated molecule produced by *P. aeruginosa* is pyoverdine—a major siderophore that plays a role in biofilm formation. During iron-depleted conditions, such as that observed during infection, pyoverdine acts as an iron-chelator to aid *P. aeruginosa* survival by sequestering iron from the host (Gellatly and Hancock 2013; Peek et al. 2012; Visca et al. 2007).

Cell–Cell Signalling in *P. aeruginosa*—the Quorum Sensing Cascade

Pseudomonas aeruginosa coordinates infection via cell–cell communication termed quorum sensing (QS). Through production of QS signalling molecules, the expression of virulence-associated genes and the formation of biofilm are regulated in a cell density-dependent manner (Lee and Zhang 2015; O'Loughlin et al. 2013; Papenfort and Bassler 2016) (Fig. 1). The *P. aeruginosa* QS systems are deeply interconnected and represent one of the most complex and best-studied bacterial signalling systems described (Fig. 2). The major QS systems are the *las* (elastase) and *rhl* (rhamnolipid) systems which utilise acyl homoserine lactone (AHL), *N*-(3-oxododecanoyl)-L-homoserine lactone (3-oxo-C12-HSL) and *N*-butanoyl-L-homoserine lactone (C4-HSL), respectively, for signalling (Jimenez et al. 2012; Lee and Zhang 2015; Mund et al. 2017). When the concentration of

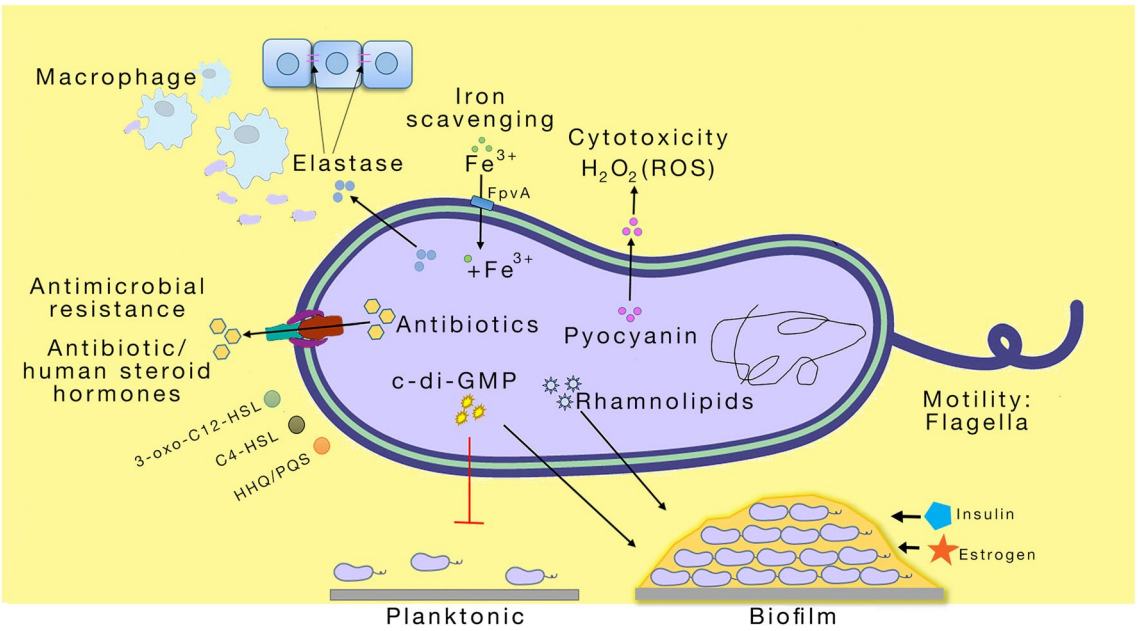

Fig. 1 *P. aeruginosa* virulence mechanisms. *P. aeruginosa* signalling molecules *N*-Acyl homoserine lactones coordinate several virulence mechanisms including motility, cytotoxicity, iron scavenging and elastase production based on cell density. Efflux pump systems regulate cellular concentrations of QS molecules and human hormones and the bacteria can exist either in planktonic or as biofilms. Insulin (pentagon) and estrogen (star) modulate biofilm formation. *QS* quorum sensing, Fe^{3+} iron (III), FpvA ferripyoverdine receptor, H_2O_2 hydrogen peroxide, *ROS* reactive oxygen species, *3-oxo-C12-HSL* *N*-(3-oxododecanoyl)-L-homoserine lactone, *C4-HSL* *N*-butanoyl-L-homoserine lactone, *HHQ* 2-heptyl-4-quinolone, *PQS* 2-heptyl-3-hydroxy-4-quinolone, *C-diGMP* Bis-(3′-5′)-cyclic dimeric guanosine monophosphate

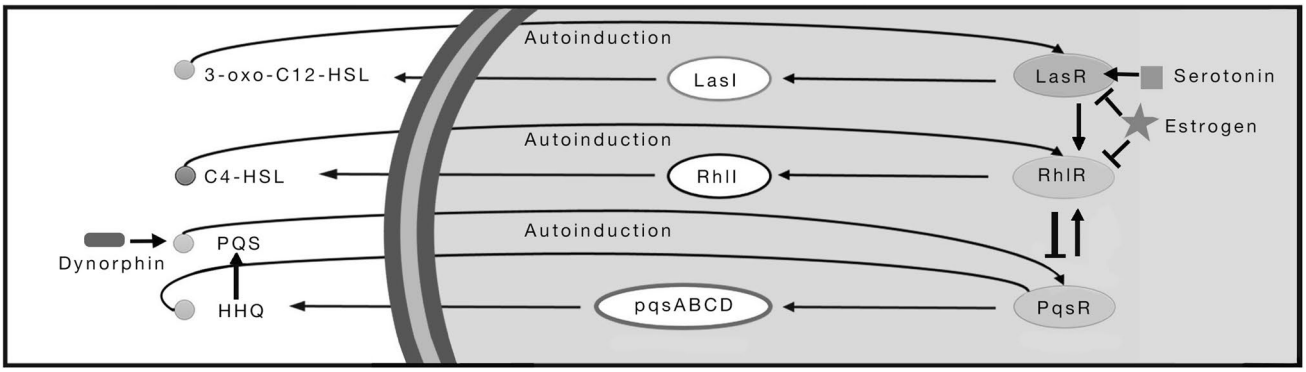

Fig. 2 *P. aeruginosa* quorum sensing system. Regulation of cell density-dependent virulence involves the different quorum sensing systems including *Las, Rhl* and *PQS*. Estrogen (star) inhibits quorum sensing systems and serotonin (square) and dynorphin (rectangle) exhibit crosstalk with quorum sensing molecules to regulate *P. aeruginosa* virulence. *3-oxo-C12-HSL N*-(3-oxododecanoyl)-L-homoserine lactone, *C4-HSL N*-butanoyl-L-homoserine lactone, *HHQ* 2-heptyl-4-quinolone

AHL reaches a threshold level, the *LasR* transcriptional regulator forms a complex with 3-oxo-C12-HSL that is synthesised by *LasI* (an autoinducer), which in turn binds to DNA, altering virulence gene expression (Jimenez et al. 2012). The *rhl* system, on the other hand, responds to C4-HSL produced by RhlI synthase. Similar to the *las* system, RhlR—a transcriptional regulator—induces virulence gene expression during times of high cell density. By regulating the production of rhamnolipids and T3SS assembly, this important QS pathway plays a key role in *P. aeruginosa* pathogenesis (Jimenez et al. 2012). Another important *Pseudomonas* signalling molecule is 2-heptyl-3-hydroxy-4-quinolone (PQS), possessing a differing chemical signal to that from the AHL system of *las* and *rhl* (Diggle et al. 2007). Studies show that the PQS system regulates biofilm formation and the production of virulence factors, namely pyocyanin, elastase, PA-IL lectin and rhamnolipids (Lee and Zhang 2015). Thus, a cascade of highly interconnected signalling molecules controls virulence in a synchronised and concentration-dependent fashion in *P. aeruginosa*.

The *P. aeruginosa* genome encodes several multidrug efflux pumps, which in addition to conferring antimicrobial resistance, can influence bacterial virulence and pathogenicity through extrusion of QS signalling intermediates (Sun et al. 2014). From a physiological perspective, efflux serves as a mechanism of metabolic rebalancing triggered in response to the accumulation of redox-active metabolites including those related to the QS signalling cascade (Fargier et al. 2012). This in turn, influences virulence and pathogenesis via dampening of QS virulence activation signals by reducing their intracellular concentration (Sakhtah et al. 2016). Conversely, the QS network also exerts influence over efflux pump expression suggesting the existence of interplay between these systems (Maseda et al. 2004). The co-ordinated regulation of efflux pumps and virulence gene expression by overarching global transcriptional regulators further infers the importance of efflux in pathogenesis of *P. aeruginosa* (Dietrich et al. 2008; Tian et al. 2009). Interestingly, bacterial efflux systems are also capable of extruding human steroid hormones and may thus play a role in inter-kingdom signal trafficking during human infection (Elkins and Mullis 2006).

The impact of efflux pump expression on antibiotic resistance is further compounded by the formation of multicellular biofilms—an important pathogenic feature of *P. aeruginosa* that in itself is regulated by the QS network (Vital-Lopez et al. 2015). This barrier provides protection against both antibiotic penetration and the host immune system leading to recalcitrant infection (Mulcahy et al. 2014). While the penetrability of mammalian hormones into structured bacterial biofilms remains unclear, mammalian hormones bear structural similarities to QS molecules that function in bacterial communication (Hughes and Sperandio 2008). As such, the ability of certain mammalian hormones to penetrate biofilm exists and in this context further studies are warranted to better understand this phenomenon. As bacterial QS molecules and human hormones affect the same essential functions—directing multicellular behaviour—it would be intriguing to consider both the penetration of QS molecules into host tissues and the dispersal of human hormones within the biofilm (Costerton et al. 2003).

The Microbial Endocrinology of *P. aeruginosa*

Bacteria can influence host behaviour in a non-invasive manner, with the potential to perturb normal physiology and bypass the human immune system. This can be achieved both by the production and recognition of signalling molecules similar in structure to those of the host. Bidirectional inter-kingdom signalling, including crosstalk between

human hormones and their microbial counterparts, is termed "microbial endocrinology" (Freestone 2013; Lyte 2013). Studies supporting the existence of microbial endocrinology date back to the early 1990s and include the work of Lyte and Ernst, who demonstrated the recognition of stress hormones by Gram-negative bacteria, including *P. aeruginosa*, which exhibit greatly increased growth in the presence of noradrenaline (Lyte and Ernst 1992). Consistent with these observations, the studies by Li et al. (2009) have elucidated the mechanism by which catecholamines such as noradrenaline promote *P. aeruginosa* growth. It is shown that the increased growth induced by noradrenaline is promoted through the modulation of *P. aeruginosa* virulence genes. Consequently, it was later speculated that the upregulation of *P. aeruginosa* virulence, amplified by its increased ability to grow in the presence of catecholamine inotropes, might explain the development of *P. aeruginosa* ventilator-associated pneumonia in patients receiving inotropes in the intensive care unit (Freestone et al. 2012).

Another important signalling molecule implicated in host–microbe crosstalk is serotonin, an important human neurotransmitter. Serotonin is sensed by *P. aeruginosa* evidenced by Knecht and colleagues (2016) who have shown its ability to act in regulating *P. aeruginosa* virulence in a mouse model of infection. Here, an observed upregulation of biofilm formation and virulence factor production is described (Knecht et al. 2016). Interestingly, the endogenous opioid dynorphin—a κ-agonist and mediator of pain suppression—has been implicated in an enhancement of *P. aeruginosa*'s virulence through its interaction with one of the QS systems, PQS (Valentino and Van Bockstaele 2015). Histamine, another neurotransmitter which also plays an important role in allergic reactions is elevated in mice infected with *P. aeruginosa* through neutrophil-mediated histamine production, reflecting multiple potential crossovers between microbial endocrinology and host immune responses (Alcaniz et al. 2013; Xu et al. 2012; Zaborina et al. 2007). Additional evidence for microbial endocrinological crosstalk comes from diabetic mouse models that have shown the effect of insulin treatment on *P. aeruginosa* biofilm formation in vivo (Watters et al. 2014). From the many illustrated examples, it is clearly evident that host hormones have significant influences on *P. aeruginosa* and its virulence, which in turn influence the human host and their susceptibility to disease.

Sex hormones play diverse roles in mammalian hosts and are essential for their physiological wellbeing by influencing processes such as inflammation and cell proliferation (Garcia-Gomez et al. 2013). Similar to AHLs, they are lipids and communicate through intracellular receptors (Hughes and Sperandio 2008). Epidemiological data demonstrate that the susceptibility to microbial infections differs between genders suggesting that sex-influenced traits such as hormone levels may be implicated in disease (Chotirmall 2014; Leone et al. 2012). Sexual dichotomy in infection and disease is well-documented, with males being more susceptible than females in general, and mounting a weaker immune response to pathogens (Garcia-Gomez et al. 2013; Leone et al. 2012). However, in the case of CF, females have a worse survival outlook (Harness-Brumley et al. 2014). This has recently been dissected from a mechanistic perspective and contributing factors include the increase in mucus viscosity induced by the major female sex hormone, estrogen, through the regulation of epithelial airway ion channels (Garcia-Gomez et al. 2013; Harness-Brumley et al. 2014). Females with CF are also noted by epidemiological associations to have a higher likelihood of acquiring *P. aeruginosa* infection and subsequent colonisation (Silva Filho et al. 2013). In addition, alginate production plays an important role in *P. aeruginosa* biofilm formation and its synthesis has been shown to be induced in the estrogen-rich environment of CF women through acquired *mucA* mutations (Chotirmall et al. 2012; Ghafoor et al. 2011). Estrone, estriol and estradiol, at supra-physiological concentrations have each been shown to have inhibitory effects on QS as they downregulate *P. aeruginosa* QS-regulated gene expression (Beury-Cirou et al. 2013). Further work by Beury-Cirou et al. (2013) has reported on potential mechanisms based upon molecular modelling where the hormone competitively binds AHL-LuxR sensors, specifically LasR and TraR regulators.

Much of the specific mechanistic effects of hormones on *P. aeruginosa* (such as bacterial receptors, downstream signalling pathways and enzymes involved) still remains unclear and are the subject of ongoing work by our group and others. As such, pharmacological evidence for a receptor-mediated mechanism is lacking and ligand–receptor interaction vis-a-vis hormonal interactions with bacteria is not yet clearly defined. Despite our limited current understanding of the precise regulatory effects that sex hormones have in the modulation of *P. aeruginosa* gene expression, existing datasets by our group and others illustrate the strong support for the involvement of sex steroid hormones in *P. aeruginosa* inter-kingdom signalling which in turn influences virulence and potentially patient outcome and survival (Chotirmall et al. 2012; Garcia-Gomez et al. 2013; vom Steeg and Klein 2017). Here, it is, therefore, appropriate to mention that the cytotoxicity of *P. aeruginosa* can further be modulated by its sensitivity to natriuretic peptides, a family of eukaryotic hormones (Blier et al. 2011). These peptides are composed of three members: atrial natriuretic peptide, brain natriuretic peptide, and C-type natriuretic peptide (CNP) of which the latter is produced in significant amounts by the bronchial and alveolar epithelia (Nakanishi et al. 1999). It has also been described as a bacterial virulence enhancer by activating the regulatory proteins Vfr (Veron et al. 2007) and PtxR (Blier et al. 2011), leading to a rise of hydrogen cyanide and

exotoxin A production and reorganisation of LPS structure. One of the important effects of CNP is its modulation of biofilm formation. The bacterial protein AmiC, an ortholog of the human receptor NPR-C is identified as the sensor involved in CNP-driven effects (Rosay et al. 2015). Upon binding, AmiC triggers transcription of AmiE which further regulates *P. aeruginosa* virulence through modulation of pili synthesis and enhancing cell-to-cell communications (Clamens et al. 2017).

Immunology and *P. aeruginosa* Microbial Endocrinology

Several studies now confirm the ability of human hormones to modulate *P. aeruginosa* phenotypes. This occurs through exerting an influence on QS pathways that in turn affect bacterial virulence and infection. Hormones such as catecholamines (Freestone et al. 2012), serotonin (Knecht et al. 2016), dynorphin (Zaborina et al. 2007), insulin (Watters et al. 2014), and estrogen (Chotirmall et al. 2012) can encourage virulence factor production such as biofilm formation. This increases *P. aeruginosa* tolerance to host clearance mechanisms, helping *P. aeruginosa* evade both innate and adaptive immunity (Hartl et al. 2006; Jensen et al. 2010). Further, bacteria can hijack immune responses to favour their own survival and proliferation through numerous established mechanisms well-described by several published reviews (Guttenplan and Kearns 2013; Mulcahy et al. 2014; Rabin et al. 2015). Some immune responses against *P. aeruginosa* may also turn deleterious, such as that noted in states of chronic infection (Gellatly and Hancock 2013; Jensen et al. 2010).

As well as influencing the pathogen, hormones also directly influence immune cells and can play a role in immunosenescence (Murray and Chotirmall 2015) (Table 1). A

Table 1 The influence of hormones on the host and *P. aeruginosa*

Hormone	Effect	Effects on		References
		Host immune system	*P. aeruginosa*	
Catecholamines	Fight or flight response	Mediate cytokine production Antibody-mediated response > cell-mediated response Influence lymphocyte activity	Promote growth and biofilm formation	Jansen et al. (1995); Elenkov (2007); Freestone et al. (2012)
Serotonin	Neurotransmitter—regulates appetite, emotion Peripheral—hemostasis, gut contraction, cell growth, organ development	Complex immunomodulatory roles Influences immune cells such as neutrophils, macrophages and T cells Contrasting literature Concentration-dependent effects	Mimic quorum sensing signalling molecules (i.e. *las*) Enhance virulence phenotypes Promotes biofilm formation	Knecht et al. (2016) Herr et al. (2017)
Dynorphin	Learning and memory Stress response Emotional control Pain	Stimulates function of innate immune cells Inhibits function of adaptive immune cells	Interacts with PQS QS systems to enhance virulence	Zaborina et al. (2007); Schwarzer (2009) Gein (2014)
Histamine	Allergic inflammation Smooth muscle contraction Gastric acid secretion	Allergic reaction—smooth muscle contraction, stimulate cytokine production, cell adhesion molecules and type II antigens expression	Unknown	Mahdy and Webster (2011)
Insulin	Glucose absorption from blood	Anti-inflammatory	Regulates biofilm formation	Deng and Chai (2009); Watters et al. (2014)
Estrogen	Reproductive maintenance Development of female sexual characteristics	Complex immunomodulatory roles Known concentration-dependent effects Generally immuno-activating	Increase alginate production in CF patients Demonstrate QS inhibitor activity at supra- physiological level Promotes mucoidy	Chotirmall et al. (2012); Garcia-Gomez et al. (2013) Klein and Flanagan (2016)
Testosterone	Anabolism Development of male sexual characteristics	Immunosuppressive	Unknown	Leone et al. (2012) Garcia-Gomez et al. (2013) Klein and Flanagan (2016)

PQS 2-heptyl-3-hydroxy-4-quinolone, *CF* cystic fibrosis, *QS* quorum sensing

well-known example includes catecholamine hormones, classically associated with the adrenal medulla and its neurons, now known to be synthesised and released by phagocytic cells and lymphocytes (Flierl et al. 2008). Another key example is the sex steroid hormones. There are two described modes of action whereby sex hormones influence host physiology; classical and non-classical pathways. The classical pathway involves the binding of hormones to specific intracellular cytosolic receptors, whereas non-classical pathways acts through membrane-bound receptors such as G proteins (Garcia-Gomez et al. 2013). There is increasing evidence that immune cells carry sex hormone receptors and that hormones regulate immune cells such as lymphocytes, macrophages, granulocytes and mast cells. Hormones tend to play complex immunomodulatory roles that vary depending on several influencing factors including concentration, exposure time and cell state (Elenkov 2007; Herr et al. 2017; Klein and Flanagan 2016). It is worthwhile to note that contrasting results have been obtained for many hormones' and their impact on the host immune system, but data can still be interpreted by considering the different conditions assessed.

Innate Immunity

The innate immune system acts as a front-line barrier against *P. aeruginosa* infection. This includes the secretion of antimicrobial peptides and other immune and inflammatory signals such as cytokines, chemokines and neutrophil-mediated processes.

Antimicrobial peptides (AMPs), such as lactoferrin (Singh et al. 2002) and pulmonary surfactant protein A and D (Lecaille et al. 2016) are secreted by a range of host cells, participate in active killing of microorganisms and promote immune responses such as opsonin-mediated phagocytosis. However, *P. aeruginosa* is known to secrete factors such as alginate and proteases that counteract and inhibit the action of AMPs (Cole and Nizet 2016). Estrogen itself has also been shown to inhibit AMPs expression in CF mouse models of *P. aeruginosa* pneumonia highlighting its potential significance as an immune-regulatory molecule in the pathogenesis of this bacteria (Wang et al. 2010).

Pseudomonas aeruginosa pathogen-associated molecular patterns (PAMPs) are recognised by pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs) and Nod-like receptors. Triggering signalling pathways resulting in inflammatory responses against *P. aeruginosa*, such key mechanisms provide immune protection against bacterial infection. (Franchi et al. 2012; Lavoie et al. 2011; Mogensen 2009). The best-established PAMP–PRR interactions associated with *P. aeruginosa* involve TLRs such as TLR2, TLR4, TLR5 and TLR9. Well-known PAMP–TLR interactions include those between flagellin and TLR5 and LPS and TLR4 (Lavoie et al. 2011; Zhang et al. 2005). TLR2 has more potential agonists and is known to interact with a wide variety of *P. aeruginosa* PAMPs, such as tetra-/penta-acylated LPS, lipoprotein, alginate, the TTSS effector protein ExoS, flagellin and slime-GLP (Lagoumintzis et al. 2008; Xaplanteri et al. 2009). The MyD88 adaptor protein (Anas et al. 2016; Skerrett et al. 2004), NF-κB, AP-1 transcription factors (Lagoumintzis et al. 2003) and MAPK all play important roles in signalling pathways that result in the transcription of pro-inflammatory chemokines (such as interleukin (IL)-8, involved in neutrophil recruitment to the lung) and cytokines by immune cells including macrophages (Cosgrove et al. 2011).

Various mammalian hormones are known to have immunomodulatory roles such as influencing PRR-associated cytokine production. For example, catecholamines can mediate LPS-induced TLR-mediated pro-inflammatory cytokine release from monocytes and macrophages, which have adrenergic receptors capable of binding hormones (Grisanti et al. 2011). Steroid sex hormones can also influence host immunology and TLR-associated responses, such as 17β-estradiol (E_2), which has been found to inhibit TLR-mediated IL-8 release in cystic fibrosis bronchial epithelia (Chotirmall et al. 2010).

Testosterone and progesterone are generally anti-inflammatory, while the immune-activating effects of estradiol appear to be dependent on both concentration and the immune measures assessed (Brunelleschi 2016; Foo et al. 2017; Klein and Flanagan 2016). Biphasic effects of estrogen have also been observed where E_2 generally incites a pro-inflammatory response when observed in the follicular or reproductive phase of the menstrual cycle but anti-inflammatory responses with higher E_2 concentrations (Klein and Flanagan 2016; Ortona et al. 2015). Though our understanding remains incomplete, some of the established mechanisms of androgen-mediated immune modulation include an inhibition of Th1 differentiation and activation, coupled to cytokine production from conventional dendritic cells (Trigunaite et al. 2015). From the pathogens' perspective, QS signalling molecules and cognate effector proteins secreted by *P. aeruginosa* have established influences on the host inflammatory response. For example, 3-oxo-C12-HSL, a *P. aeruginosa* QS signal, has been shown to bind the nuclear hormone receptor isoforms PPARβ/δ and PPARγ in vitro leading to a pro-inflammatory state (Tateda et al. 2003). Consequently, both human and pathogen signalling molecules influence macromolecular components of host–pathogen interaction with direct relevance to pathogenesis.

Adaptive Immunity

Naïve $CD4^+$ T cells can differentiate into lineages including Th1, Th2, Th17 or regulatory T (Treg) cells (Zhu et al. 2010). Differentiation into Th1 cells is stimulated by IL-12, a major pro-inflammatory cytokine produced by antigen-presenting cells such as dendritic cells or monocytes/macrophages (Zhu et al. 2010). A common Th1 signature is interferon γ production whilst a common Th2 association is IL-4 (Franchi et al. 2012; Miao et al. 2010; Zhu et al. 2010). Th1 responses are associated with cellular immune responses such as macrophage activation, whilst Th2-driven processes include the stimulation of mast cells and the humoral immune system. Hormones can influence the Th1/Th2 axis. Insulin and catecholamines, for example, favour Th2 differentiation (Deng and Chai 2009), whilst the latter also enhances local inflammatory responses (Elenkov 2007).

The role of Th17 cells and Treg cells are an emerging area of research. Th17 responses have been proposed to synergise with Th2 pathways in *P. aeruginosa* chronic infection through the pro-inflammatory cytokine IL-17a. While Th2-mediated responses have traditionally been associated with CF, both Th2 and Th17 cytokine profiles are often enhanced in CF patients with *P. aeruginosa* infection (Tiringer et al. 2013) placing the potential role for Th17 into focus. In support, IL-17a is elevated in inflammatory lung diseases such as CF and COPD and a recent study identified IL-17a to negatively modulate the host immune response in *P. aeruginosa* chronic infection (Lore et al. 2016). It is reported that E_2 promotes pro-inflammatory effects in a male CF murine model through Th17-regulated pathways (Wang et al. 2010). In agreement, Tregs, which suppress T-cell activation, are shown to be impaired in the peripheral blood and airways of *P. aeruginosa*-colonised CF patients (Hector et al. 2015). Moreover, E_2 promotes Treg cell proliferation, while reduced testosterone levels are associated with reduced peripheral blood Treg counts (Klein and Flanagan 2016). An improved understanding of the adaptive defenses against *P. aeruginosa* clearly requires further and more detailed study with an improved integrated system-based model of infection encompassing both host and microbial endocrinology.

The *P. aeruginosa*-Associated Neutrophil Driven Immune Response

Neutrophil accumulation is one of the earliest responses in *P. aeruginosa* clearance, assisting in killing through phagocytosis and releasing proteases (e.g. elastase), enzymes (e.g. lysozyme), reactive oxygen and nitrogen species (Gellatly and Hancock 2013). While neutrophils play an important role in host defense against *P. aeruginosa*, neutrophil degranulation during the killing process can cause host tissue damage with prolonged stimulation, such as that observed during chronic infection (Williams and Parkos 2007). The loss of motility commonly accompanying transition to the mucoid phenotype in chronic infections also dampens the release of neutrophil extracellular traps (Rada 2017). Furthermore, chronic inflammation from persistent infection is linked to oxidative stress that promotes adaptive mutations favouring colonisation and persistence (Ciofu et al. 2005). Histamine, an important component of human neuronal and endocrine systems has major influences on the immune and inflammatory response to *P. aeruginosa* (Shajib and Khan 2015), and has been shown to be elevated in mice infected with laboratory PAO1 strains through neutrophil-mediated histamine production. An upregulation of neutrophil histamine production is associated with bronchoconstriction and persistent inflammation (Xu et al. 2012), which in turn impedes bacterial clearance from the lung, particularly in patients with obstructive airway disease where it contributes to lung damage (Gómez and Prince 2007). Histamine, therefore, contributes to over-zealous immune responses to *P. aeruginosa* and represents an important mediator of endocrinological dialogue between the host and pathogen.

Systemic Inflammation and Sepsis

Sepsis is characterised by systemic inflammatory responses while paradoxically also rendering the host immunocompromised. This can favour, in particular, secondary bacterial infections (Cinel and Dellinger 2007). One of the earliest signs of sepsis is macrophage dysfunction, mediated by IRAK-M inhibition of LPS/TLR4 activity (Deng et al. 2006). Recent work demonstrates interestingly that flagellin is a key activator of the inflammasome in a murine model of *P. aeruginosa* sepsis (Pu et al. 2017). In addition, the production of the TTSS effector protein ExoS has been linked to higher incidence of dissemination into the bloodstream in patients with hospital-acquired pneumonia (Kiseleva and Novik 2015). While much remains to be determined about the role of endocrine signalling in sepsis and its precise influence on *Pseudomonas* pathogenesis, insulin is known to have anti-inflammatory properties by reducing the production of pro-inflammatory cytokines (e.g. IL-1β and tumour necrosis factor α). In addition, it induces anti-inflammatory cytokines such as IL-4 and IL-10, which overall translates to a systemic anti-inflammatory response (Deng and Chai 2009) that potentially influences sepsis-related outcomes. How this specifically associates with *Pseudomonas* infection and its microbial endocrinology remains to be determined.

Conclusions and Future Directions

Studies explicitly linking the crosstalk between hormones, *P. aeruginosa* and the host immune response are limited. Most currently available studies either focus on the influence of hormones on the host, or on *P. aeruginosa*. It is worthwhile considering that both these hormonal influences occur concurrently in vivo and where studied together will better frame our understanding of the extent to which hormones modulate *Pseudomonas* pathogenesis and infection outcomes, especially clinically. Human hormones can directly modulate both the innate and adaptive arms of immunity while hormonal-rich environments account for phenotypic *P. aeruginosa* change, particularly in the context of its growth and virulence. This has clear influence on the host immune response, disease progression and infection outcome.

The study and understanding of the microbial endocrinology of *P. aeruginosa*, particularly its relationship to sex hormones, may help narrow observed gender gaps in infection and disease dichotomy. Manipulating hormones with antagonists or analogues could potentially be studied for their abilities to alter bacterial growth, quorum sensing and biofilm formation for therapeutic benefit. Understanding specific factors may provide possible avenues toward sex-specific therapeutic strategies that in turn result in better clinical outcomes for patients both acute and/or chronically infected with *P. aeruginosa*. The wider implications of current therapeutic uses of steroids, such as fluticasone or budesonide in COPD for instance, must also be considered in the context of microbial endocrinology and infection, and necessitates future work. Further developments in this fledgling field can serve to improve clinical strategies toward better patient outcomes especially in the current era of emerging antimicrobial resistance. Altering pathways associated with microbial endocrinology such as that described for *P. aeruginosa* may well represent an alternative to antibiotics in the treatment of such infection and reduce the pressure now conferred toward the development of new antibiotics to tackle emerging global resistance patterns.

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Compliance with Ethical Standards

Conflict of interest All authors have no conflicts of interest to disclose.

References

Alcaniz L, Vega A, Chacón P et al (2013) Histamine production by human neutrophils. FASEB J 27:2902–2910

Anas AA, van Lieshout MH, Claushuis TA et al (2016) Lung epithelial MyD88 drives early pulmonary clearance of *Pseudomonas aeruginosa* by a flagellin dependent mechanism. Am J Physiol Lung Cell Mol Physiol 311:L219–L228

Beury-Cirou A, Tannières M, Minard C et al (2013) At a supra-physiological concentration, human sexual hormones act as quorum-sensing inhibitors. PLoS One 8:e83564

Blier AS, Veron W, Bazire A et al (2011) C-type natriuretic peptide modulates quorum sensing molecule and toxin production in *Pseudomonas aeruginosa*. Microbiology 157(Pt 7):1929–1944

Brunelleschi S (2016) Immune response and auto-immune diseases: gender does matter and makes the difference. Italian J Gender Specific Med 2:5–14

Chotirmall SH (2014) The microbiological gender gap in cystic fibrosis. J Womens Health 23:995–996

Chotirmall SH, Greene CM, Oglesby IK et al (2010) 17Beta-estradiol inhibits IL-8 in cystic fibrosis by up-regulating secretory leucoprotease inhibitor. Am J Respir Crit Care Med 182:62–72

Chotirmall SH, Smith SG, Gunaratnam C et al (2012) Effect of estrogen on pseudomonas mucoidy and exacerbations in cystic fibrosis. N Engl J Med 366:1978–1986

Cinel I, Dellinger RP (2007) Advances in pathogenesis and management of sepsis. Curr Opin Infect Dis 20:345–352

Ciofu O, Riis B, Pressler T et al (2005) Occurrence of hypermutable *Pseudomonas aeruginosa* in cystic fibrosis patients is associated with the oxidative stress caused by chronic lung inflammation. Antimicrob Agents Chemother 49:2276–2282

Clamens T, Rosay T, Crépin A et al (2017) The aliphatic amidase AmiE is involved in regulation of *Pseudomonas aeruginosa* virulence. Sci Rep 7:41178

Cole JN, Nizet V (2016) Bacterial evasion of host antimicrobial peptide defenses. Microbiol Spectr 4:413–443

Cosgrove S, Chotirmall SH, Greene CM et al (2011) Pulmonary proteases in the cystic fibrosis lung induce interleukin 8 expression from bronchial epithelial cells via a heme/meprin/epidermal growth factor receptor/Toll-like receptor pathway. J Biol Chem 286:7692–7704

Costerton W, Veeh R, Shirtliff M et al (2003) The application of biofilm science to the study and control of chronic bacterial infections. J Clin Invest 112:1466–1477

Crousilles A, Maunders E, Bartlett S et al (2015) Which microbial factors really are important in *Pseudomonas aeruginosa* infections? Future Microbiol 10:1825–1836

Deng HP, Chai JK (2009) The effects and mechanisms of insulin on systemic inflammatory response and immune cells in severe trauma, burn injury, and sepsis. Int Immunopharmacol 9:1251–1259

Deng JC, Cheng G, Newstead MW et al (2006) Sepsis-induced suppression of lung innate immunity is mediated by IRAK-M. J Clin Invest 116:2532–2542

Dietrich LE, Teal TK, Price-Whelan A et al (2008) Redox-active antibiotics control gene expression and community behavior in divergent bacteria. Science 321:1203–1206

Diggle SP, Matthijs S, Wright VJ et al (2007) The *Pseudomonas aeruginosa* 4-quinolone signal molecules HHQ and PQS play multifunctional roles in quorum sensing and iron entrapment. Chem Biol 14:87–96

Djonovic S, Urbach JM, Drenkard E et al (2013) Trehalose biosynthesis promotes *Pseudomonas aeruginosa* pathogenicity in plants. PLoS Pathog 9:e1003217

Elenkov IJ (2007) Effects of catecholamines on the immune response. NeuroImmune Biol 7:189–206

Elkins CA, Mullis LB (2006) Mammalian steroid hormones are substrates for the major RND- and MFS-type tripartite multidrug efflux pumps of Escherichia coli. J Bacteriol 188:1191–1195

Fargier E, Mac Aogáin M, Mooij MJ et al (2012) MexT functions as a redox-responsive regulator modulating disulfide stress resistance in *Pseudomonas aeruginosa*. J Bacteriol 194:3502–3511

Flierl MA, Rittirsch D, Huber-Lang M et al (2008) Catecholamines-crafty weapons in the inflammatory arsenal of immune/inflammatory cells or opening pandora's box? Mol Med 14:195–204

Foo YZ, Nakagawa S, Rhodes G et al (2017) The effects of sex hormones on immune function: a meta-analysis. Biol Rev Camb Philos Soc 92:551–571

Franchi L, Munoz-Planillo R, Nunez G (2012) Sensing and reacting to microbes through the inflammasomes. Nat Immunol 13:325–332

Freestone P (2013) Communication between bacteria and their hosts. Scientifica 2013:361073

Freestone PP, Hirst RA, Sandrini SM et al (2012) *Pseudomonas aeruginosa*-catecholamine inotrope interactions: a contributory factor in the development of ventilator-associated pneumonia? Chest 142:1200–1210

Garcia-Gomez E, Gonzalez-Pedrajo B, Camacho-Arroyo I (2013) Role of sex steroid hormones in bacterial-host interactions. Biomed Res Int 2013:928290

Gein SV (2014) Dynorphins in regulation of immune system functions. Biochemistry 79:397–405

Gellatly SL, Hancock RE (2013) *Pseudomonas aeruginosa*: new insights into pathogenesis and host defenses. Pathog Dis 67:159–173

Ghafoor A, Hay ID, Rehm BH (2011) Role of exopolysaccharides in *Pseudomonas aeruginosa* biofilm formation and architecture. Appl Environ Microbiol 77:5238–5246

Gibson RL, Burns JL, Ramsey BW (2003) Pathophysiology and management of pulmonary infections in cystic fibrosis. Am J Respir Crit Care Med 168:918–951

Gómez MI, Prince A (2007) Opportunistic infections in lung disease: *Pseudomonas* infections in cystic fibrosis. Curr Opin Pharmacol 7:244–251

Grisanti LA, Woster AP, Dahlman J et al (2011) Alpha1-adrenergic receptors positively regulate Toll-like receptor cytokine production from human monocytes and macrophages. J Pharmacol Exp Ther 338:648–657

Guttenplan SB, Kearns DB (2013) Regulation of flagellar motility during biofilm formation. FEMS Microbiol Rev 37:849–871

Hall S, McDermott C, Anoopkumar-Dukie S et al (2016) Cellular effects of pyocyanin, a secreted virulence factor of *Pseudomonas aeruginosa*. Toxins 8(8):236. https://doi.org/10.3390/toxins8080236

Harness-Brumley CL, Elliott AC, Rosenbluth DB et al (2014) Gender differences in outcomes of patients with cystic fibrosis. J Womens Health 23:1012–1020

Hartl D, Griese M, Kappler M et al (2006) Pulmonary T(H)2 response in *Pseudomonas aeruginosa*-infected patients with cystic fibrosis. J Allergy Clin Immunol 117:204–211

Hector A, Schäfer H, Pöschel S et al (2015) Regulatory T-cell impairment in cystic fibrosis patients with chronic pseudomonas infection. Am J Respir Crit Care Med 191:914–923

Herr N, Bode C, Duerschmied D (2017) The effects of serotonin in immune cells. Front Cardiovasc Med 4:48

Hughes DT, Sperandio V (2008) Inter-kingdom signalling: communication between bacteria and their hosts. Nat Rev Microbiol 6:111–120

Jansen ASP, Van Nguyen X, Karpitskiy V et al (1995) Central command neurons of the sympathetic nervous system: basis of the fight-or-flight response. Science 270:644–646

Jensen PO, Givskov M, Bjarnsholt T et al (2010) The immune system vs. *Pseudomonas aeruginosa* biofilms. FEMS Immunol Med Microbiol 59:292–305

Jimenez PN, Koch G, Thompson JA et al (2012) The multiple signaling systems regulating virulence in *Pseudomonas aeruginosa*. Microbiol Mol Biol Rev 76:46–65

Jones RN (2010) Microbial etiologies of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia. Clin Infect Dis 51(Suppl 1):S81–S87

Kiseleva E, Novik G (2015) Role of type III secretory system and related exotoxins in infections induced by an opportunistic pathogen *Pseudomonas aeruginosa*. In: Méndez-Vilas A (ed) The battle against microbial pathogens: basic science, technological advances and educational programs. FORMATEX microbiology series N 5, vol 2. pp 733–744

Klein SL, Flanagan KL (2016) Sex differences in immune responses. Nat Rev Immunol 16:626–638

Knecht LD, O'Connor G, Mittal R et al (2016) Serotonin activates bacterial quorum sensing and enhances the virulence of *Pseudomonas aeruginosa* in the host. EBioMedicine 9:161–169

Lagoumintzis G, Christofidou M, Dimitracopoulos G et al (2003) *Pseudomonas aeruginosa* slime glycolipoprotein is a potent stimulant of tumor necrosis factor alpha gene expression and activation of transcription activators nuclear factor κB and activator protein 1 in human monocytes. Infect Immun 71:4614–4622

Lagoumintzis G, Xaplanteri P, Dimitracopoulos G et al (2008) TNF-alpha induction by *Pseudomonas aeruginosa* lipopolysaccharide or slime-glycolipoprotein in human monocytes is regulated at the level of Mitogen-activated Protein Kinase activity: a distinct role of Toll-like receptor 2 and 4. Scand J Immunol 67:193–203

Lavoie EG, Wangdi T, Kazmierczak BI (2011) Innate immune responses to *Pseudomonas aeruginosa* infection. Microbes Infect 13:1133–1145

Lecaille F, Lalmanach G, Andrault PM (2016) Antimicrobial proteins and peptides in human lung diseases: a friend and foe partnership with host proteases. Biochimie 122:151–168

Lee J, Zhang L (2015) The hierarchy quorum sensing network in *Pseudomonas aeruginosa*. Protein Cell 6:26–41

Leone M, Textoris J, Capo C and Mege J-L (2012) Sex hormones and bacterial infections. In: Dubey R (ed) Sex hormones. InTech. https://doi.org/10.5772/26871. https://pdfs.semanticscholar.org/a7cc/19ed33b3596e9536f7951a399ad58cc22194.pdf. Accessed 8 July 2017

Leung JM, Tiew PY, Mac Aogáin M et al (2017) The role of acute and chronic respiratory colonization and infections in the pathogenesis of COPD. Respirology 22:634–650

Li W, Lyte M, Freestone PP et al (2009) Norepinephrine represses the expression of toxA and the siderophore genes in *Pseudomonas aeruginosa*. FEMS Microbiol Lett 299:100–109

Lore NI, Cigana C, Riva C et al (2016) IL-17A impairs host tolerance during airway chronic infection by *Pseudomonas aeruginosa*. Sci Rep 6:25937

Lyte M (2013) Microbial endocrinology in the microbiome-gut-brain axis: how bacterial production and utilization of neurochemicals influence behavior. PLoS Pathog 9:e1003726

Lyte M, Ernst S (1992) Catecholamine induced growth of gram negative bacteria. Life Sci 50:203–212

Mahdy AM, Webster NR (2011) Histamine and antihistamines. Anaesth Intensive Care Med 12:324–329

Maseda H, Sawada I, Saito K et al (2004) Enhancement of the mexAB-oprM efflux pump expression by a quorum-sensing autoinducer and its cancellation by a regulator, MexT, of the mexEF-oprN efflux pump operon in *Pseudomonas aeruginosa*. Antimicrob Agents Chemother 48:1320–1328

Miao EA, Mao DP, Yudkovsky N et al (2010) Innate immune detection of the type III secretion apparatus through the NLRC4 inflammasome. Proc Natl Acad Sci USA 107:3076–3080

Mogensen TH (2009) Pathogen recognition and inflammatory signaling in innate immune defenses. Clin Microbiol Rev 22:240–273

Mulcahy LR, Isabella VM, Lewis K (2014) *Pseudomonas aeruginosa* biofilms in disease. Microb Ecol 68:1–12

Mund A, Diggle SP, Harrison F (2017) The fitness of *Pseudomonas aeruginosa* quorum sensing signal cheats is influenced by the diffusivity of the environment. MBio 8(3):e00353-17. https://doi.org/10.1128/mBio.00353-17

Murray MA, Chotirmall SH (2015) The impact of immunosenescence on pulmonary disease. Mediators Inflamm 2015:692546

Nakanishi K, Tajima F, Itoh H et al (1999) Expression of C-type natriuretic peptide during development of rat lung. Am J Physiol 277(5 Pt 1):L996–L1002

O'Loughlin CT, Miller LC, Siryaporn A et al (2013) A quorum-sensing inhibitor blocks *Pseudomonas aeruginosa* virulence and biofilm formation. Proc Natl Acad Sci USA 110:17981–17986

Ortona E, Delunardo F, Maselli A et al (2015) Sex hormones and gender disparity in immunity and autoimmunity. Italian J Gender Specific Med 1:45–50

Papenfort K, Bassler BL (2016) Quorum sensing signal-response systems in Gram-negative bacteria. Nat Rev Microbiol 14:576–588

Parkins MD, Gregson DB, Pitout JD et al (2010) Population-based study of the epidemiology and the risk factors for *Pseudomonas aeruginosa* bloodstream infection. Infection 38:25–32

Peek ME, Bhatnagar A, McCarty NA et al (2012) Pyoverdine, the major siderophore in Pseudomonas aeruginosa, evades NGAL recognition. Interdiscip Perspect Infect Dis 2012:843509

Pu Q, Gan C, Li R et al (2017) Atg7 Deficiency intensifies inflammasome activation and pyroptosis in *Pseudomonas sepsis*. J Immunol 198:3205–3213

Quick J, Cumley N, Wearn CM et al (2014) Seeking the source of *Pseudomonas aeruginosa* infections in a recently opened hospital: an observational study using whole-genome sequencing. BMJ Open 4:e006278

Rabin N, Zheng Y, Opoku-Temeng C et al (2015) Biofilm formation mechanisms and targets for developing antibiofilm agents. Future Med Chem 7:493–512

Rada B (2017) Interactions between neutrophils and *Pseudomonas aeruginosa* in cystic fibrosis. Pathogens 6(1):E10. https://doi.org/10.3390/pathogens6010010

Rosay T, Bazire A, Diaz S et al. (2015) *Pseudomonas aeruginosa* expresses a functional human natriuretic peptide receptor ortholog: involvement in biofilm formation. MBio 6(4):e01033-15. https://doi.org/10.1128/mBio.01033-15

Sakhtah H, Koyama L, Zhang Y et al (2016) The *Pseudomonas aeruginosa* efflux pump MexGHI-OpmD transports a natural phenazine that controls gene expression and biofilm development. Proc Natl Acad Sci USA 113:E3538–E3547

Schwarzer C (2009) 30 years of dynorphins—new insights on their functions in neuropsychiatric diseases. Pharmacol Ther 123:353–370

Shajib MS, Khan WI (2015) The role of serotonin and its receptors in activation of immune responses and inflammation. Acta Physiol 213:561–574

Silva Filho LV, Ferreira Fde A, Reis FJ et al (2013) *Pseudomonas aeruginosa* infection in patients with cystic fibrosis: scientific evidence regarding clinical impact, diagnosis, and treatment. J Bras Pneumol 39:495–512

Singh PK, Parsek MR, Greenberg EP et al (2002) A component of innate immunity prevents bacterial biofilm development. Nature 417:552–555

Skerrett SJ, Liggitt HD, Hajjar AM et al (2004) Cutting Edge: Myeloid differentiation factor 88 is essential for pulmonary host defense against *Pseudomonas aeruginosa* but not *Staphylococcus aureus*. J Immunol 172:3377–3381

Sun J, Deng Z, Yan A (2014) Bacterial multidrug efflux pumps: mechanisms, physiology and pharmacological exploitations. Biochem Biophys Res Commun 453:254–267

Tateda K, Ishii Y, Horikawa M et al (2003) The *Pseudomonas aeruginosa* autoinducer *N*-3-Oxododecanoyl homoserine lactone accelerates apoptosis in macrophages and neutrophils. Infect Immun 71:5785–5793

Tian ZX, Fargier E, Mac Aogain M et al (2009) Transcriptome profiling defines a novel regulon modulated by the LysR-type transcriptional regulator MexT in *Pseudomonas aeruginosa*. Nucleic Acids Res 37:7546–7559

Tiringer K, Treis A, Fucik P et al (2013) A Th17- and Th2-skewed cytokine profile in cystic fibrosis lungs represents a potential risk factor for *Pseudomonas aeruginosa* infection. Am J Respir Crit Care Med 187:621–629

Tredget EE, Shankowsky HA, Rennie R et al (2004) Pseudomonas infections in the thermally injured patient. Burns 30:3–26

Trigunaite A, Dimo J, Jørgensen TN (2015) Suppressive effects of androgens on the immune system. Cell Immunol 294:87–94

Tumbarello M, Repetto E, Trecarichi EM et al (2011) Multidrug-resistant *Pseudomonas aeruginosa* bloodstream infections: risk factors and mortality. Epidemiol Infect 139:1740–1749

Valentino RJ, Van Bockstaele E (2015) Endogenous opioids: the downside of opposing stress. Neurobiol Stress 1:23–32

Veesenmeyer JL, Hauser AR, Lisboa T et al (2009) *Pseudomonas aeruginosa* virulence and therapy: evolving translational strategies. Crit Care Med 37:1777–1786

Veron W, Lesouhaitier O, Pennanec X et al (2007) Natriuretic peptides affect *Pseudomonas aeruginosa* and specifically modify lipopolysaccharide biosynthesis. FEBS J 274:5852–5864

Visca P, Imperi F, Lamont IL (2007) Pyoverdine siderophores: from biogenesis to biosignificance. Trends Microbiol 15:22–30

Vital-Lopez FG, Reifman J, Wallqvist A (2015) Biofilm formation mechanisms of *Pseudomonas aeruginosa* predicted via genome-scale kinetic models of bacterial metabolism. PLoS Comput Biol 11:e1004452

Vogel G (2017) Meet WHO's dirty dozen: the 12 bacteria for which new drugs are most urgently needed. Science Magazine, 27 Feb 2017. https://doi.org/10.1126/science.aal0829

vom Steeg LG, Klein SL (2017) Sex steroids mediate bidirectional interactions between hosts and microbes. Horm Behav 88:45–51

Wang Y, Cela E, Gagnon S et al (2010) Estrogen aggravates inflammation in *Pseudomonas aeruginosa* pneumonia in cystic fibrosis mice. Respir Res 11:166

Watters C, Everett JA, Haley C et al (2014) Insulin treatment modulates the host immune system to enhance *Pseudomonas aeruginosa* wound biofilms. Infect Immun 82:92–100

Weiner LM, Webb AK, Limbago B et al (2016) Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2011–2014. Infect Control Hosp Epidemiol 37:1288–1301

Williams IR, Parkos CA (2007) Colonic neutrophils in inflammatory bowel disease: double-edged swords of the innate immune system with protective and destructive capacity. Gastroenterology 133:2049–2052

Wisplinghoff H, Bischoff T, Tallent SM et al (2004) Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis 39:309–317

Xaplanteri P, Lagoumintzis G, Dimitracopoulos G et al (2009) Synergistic regulation of *Pseudomonas aeruginosa*-induced cytokine production in human monocytes by mannose receptor and TLR2. Eur J Immunol 39:730–740

Xu X, Zhang H, Song Y et al (2012) Strain-dependent induction of neutrophil histamine production and cell death by *Pseudomonas aeruginosa*. J Leukoc Biol 91:275–284

Zaborina O, Lepine F, Xiao G et al (2007) Dynorphin activates quorum sensing quinolone signaling in *Pseudomonas aeruginosa*. PLoS Pathog 3:e35

Zhang Z, Louboutin JP, Weiner DJ et al (2005) Human airway epithelial cells sense *Pseudomonas aeruginosa* infection via recognition of flagellin by Toll-like receptor 5. Infect Immun 73:7151–7160

Zhu J, Yamane H, Paul WE (2010) Differentiation of effector CD4 T cell populations. Annu Rev Immunol 28:445–489