Microbial endocrinology: Target for new antimicrobial strategies to control infectious diseases

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Quorum sensing (QS) is a bacterial and fungal communication system that uses hormone-like molecules called autoinducers (AI) or quorum sensing molecules (QSM) to regulate virulence, bioluminescence, motility, biofilm formation, sporulation, antibiotic production and symbiosis. The interaction between microbial pathogens and their eukaryotic hosts is crucial in determining the outcome of infections. During colonization and invasion, both pathogen and host are exposed to molecules released by each other like bacterial QSM, or host's stress hormones and cytokines. Microbial endocrinology describes host molecular signals that improve pathogen cellular proliferation and virulence as well as bacterial molecules that promote host immune system evasion. The mechanisms and receptors involved in this new host-pathogen interplay are not well described to date. Here we describe the microbial QS systems, QSM, host signals and mechanisms that might be involved in crosstalk between microbial pathogens and their hosts, and we discuss which QS signals and receptors might be targets for the design of antimicrobial strategies to control infectious diseases.

Keywords: Quorum sensing; cytokines; virulence gene expression; host-pathogen crosstalk

1. Introduction

The human body is a biological niche to commensal, symbiotic and pathogenic microorganisms that include bacteria, viruses, protozoa, fungi and nematodes [1]. Breakdown of host-microbiome interaction might led to infection. The outcome of infection and establishment of disease depends on both the host defence and pathogen virulence determinants. During colonization and infection the expression of virulence factors is upregulated by environmental parameters such as pH, temperature and nutrient availability; extracellular accumulation of auto-inducing molecules and host signals [2-5]. Microbial endocrinology defines the research on molecules and mechanisms involved in the communication between pathogens and their host.

2. Quorum sensing and virulence regulation in pathogens

Quorum sensing (QS) is a type of cell-to-cell communication occurring in bacteria and some fungi. QS describes the mechanism in which as population density increases a small self-produced diffusible molecule, called autoinducer (AI) or quorum sensing molecule (QSM), accumulates in the extracellular matrix. When a threshold is reached, the QSM binds to its cognate receptor and then a response regulator modulates gene expression of motility, social behaviour, antibiotic resistance, plasmid conjugation, virulence, biofilms formation, bioluminescence and sporulation [6]. QS genes are not essential for the microorganism survival, but are important for its adaptation to the environment either to survive, colonize or persist.

2.1 Quorum sensing in Gram-negative bacteria

The first QS described was the LuxI/LuxR system of *Vibrio fischeri* that controls luminescence [7]. QSM in Gram negative include *N*-acylhomoserine lactones (AHLs) or AI-1, 2-alkyl-4-quinolones, γ-butyrolactones, furanones, long-chain fatty acid derivatives, fatty acid methyl esters, peptides, the 4,5-dihydroxy-2,3-pentandione (DPD) derivatives collectively referred to as autoinducer 2 (AI-2) and autoinducer 3 (AI-3, structure unknown) [8].

2.1.1 Autoinducer type 1 system

The Autoinducer type 1 system is represented for LuxI/LuxR-typed proteins (the AHL-synthase and the response regulator, respectively) and AHLs (autoinducer, AI-1). AHLs consist of a homoserine lactone ring and acyl side chains that may vary in the number of carbons (4 to 18). Oxo- or hydroxyl- substitutes have also been described [9]. AI-1 diffuses freely through the bacterial membrane and binds to the transcriptional activator LuxR. This system is distributed among Gram-negative bacteria, Enterobacteriaceae family and *Pseudomonas aeruginosa*. The latter has two LuxI/LuxR-type systems, the first LasI that produces 3O-C_{12}-HSL and the second, RhlI that synthesizes C_4-HSL, both AHLs regulate virulence and biofilm formation.

2.1.2 Autoinducer type 2 system

This QS pathway was discovered in *Vibrio harveyi* as a bioluminescence system mediated by the *luxS* gene locus. The observation that *luxS* is broadly distributed among bacterial genomes, initially suggested that AI-2 was also widespread and that it might facilitate interspecies interactions. LuxS synthetizes AI-2 which is exported to the extracellular matrix and then recognized by a receptor/sensor kinase complex. The best described AI-2 systems are those of *V. harveyi* and *Salmonella enterica*. In *Escherichia coli* LuxS controls the expression of the type III secretory system, encoded by the LEE genes [10].

2.1.3 Autoinducer type 3 system

The autoinducer AI-3 is an aromatic signalling molecule produced by bacteria of the human intestinal microflora as well as certain enteric pathogens. The molecular structure and the gene responsible for AI-3 production remain unknown [11]. The AI-3 in *E. coli* is detected by a two-component system (TCS), including the QseC sensor kinase and QseB response regulator. The TCS *qseBC* regulates the activation of flagella and motility genes. It's also demonstrated that AI-3 system is activated by catecholamine hormones, especially, epinephrine/norepinephrine produced by host [9, 12]. AI-3 controls the expression of LEE genes, virulence and colonization in the intestine.

2.1.4 Other non-traditional QS in Gram-negative bacteria

Pseudomonas uses the quinolone signal system (PQS) to control cooperative responses and gene expression of rhamnolipid, a critical biosurfactant during the late stage of biofilm formation. The QSMs of this system are bicyclic compounds like 2-alkyl-4(1H)-quinolones [13]. Other QS systems found in various *Vibrio* spp. as well as in *Legionella pneumophila* utilize α-hydroxyketones (AHKs) as signal molecules.

2.2 Quorum sensing in Gram positive bacteria

QS signalling in Gram positive bacteria operates through the activity of post-translationally modified oligopeptides, named autoinducing peptides (AIP) or pheromones, which can range from 5 to 34 amino acids in length and can adopt either linear or cyclical conformations [14]. Detection of AIP is mediated by a TCS which consists of a membrane-associated histidine kinase protein sensing the AIP, and a cytoplasmic response regulator protein enabling the cell response to the peptide through regulation of gene expression [15]. Recently production of AHLs has been identified in a marine Gram positive bacteria [16]. Competence, sporulation, conjugation, biofilms formation and virulence gene expression are mainly regulated by QS.

2.2.1 *Staphylococcus aureus*

The *agr* (accessory gene regulator) QS is the best described TCS in *S. aureus*. The *agr* locus is located in the *S. aureus* chromosome and is considered to be part of the core genome and not a pathogenicity island. The locus is known to contain two divergent transcripts called RNAII and RNAIII, driven by the P2 and P3 promoters, respectively. The RNAII transcript is an operon of four genes, *agrBDCA*, which encodes the core machinery of the system. AgrD is the peptide precursor and is processed and exported to the extracellular matrix through action of AgrB and SpsB at the cytoplasmic membrane. SpsB is the house-keeping type I signal peptidase. At the threshold concentration, AIP binds to its cognate AgrC receptor, a membrane-bound histidine kinase, this binding activates the AgrC kinase activity which results in the phosphorylation of the AgrA response regulator and then the P2 and P3 promoters activation. AgrA also activates the phenol-soluble modulins promoters PSMα and PSMβ [5]. RNAIII, the effector molecule of the system, post-transcriptionally activates virulence factor production and represses expression of the transcription factor *rot*.

Other QS systems have been describe in *S. aureus* like *sae* (*S. aureus* exoprotein expression), *srrAB* (Staphylococcal respiratory response), *ArlSR* (Autolysis related locus), and *LytRS* [17].

2.2.2 Group A Streptococcus (GAS)

Streptococcus pyogenes is a human-restricted pathogen capable of causing pharyngitis, impetigo, necrotizing fasciitis and toxic shock syndrome. QS in GAS can be classified in regulator gene of glucosyltransferase (Rgg), streptococcal invasion locus (Sil), lantibiotic systems, and LuxS/AI-2 [14].

The family of Rgg peptide-binding transcription factors possesses helix-turn-helix (HTC) motifs for DNA binding and direct regulation of gene expression including virulence, capsule formation, biofilms formation and colonization. The putative Rgg pheromones are short hydrophobic peptides (SHPs) and peptides involved in competence pathways, termed XIPs [18, 19]. Homologous *loci* encoding *rgg2-shp2* are present in *S. canis*, *S. agalactiae*, *S. dysgalactiae* and *S. iniae*. The Rgg2 homolog, called RovS, has been involved in regulating expression of genes required for epithelial cell attachment and haemolysis activity [20].

The *sil* QS system consists of the genes *silABCDE* and *silCR*; *silAB*, a putative TCS, *silDE*, a putative ABC transporter, and *silCR*, the pheromone pro-peptide gene [21]. The *silAB* promoter is more responsive to host environment and secreted molecules than to the QSM itself, and activation of the promoter occurs at early time of infection increasing streptolysin toxins and downregulation of cellular proliferation [22, 23]. Approximately 16% of GAS strains are positive for *sil* locus, and only 9% of them have a functional *sil-loci*, independently of the clinical origin [24].

Lantibiotics, class I bacteriocins, are sensed by TCS, they exhibit a cell-density dependent pattern regulated by QS like circuits. These molecules are synthesized as inactive propeptides and then modified through amino acid dehydration and/or thioether bridge formation to generate unusual amino acid residues, and are cleaved during the secretion process to generate a mature active lantibiotic. Bacteriocins can act as an interspecies and intraspecies signalling molecule [14].

3. Signals, receptors and mechanisms involved in microbial endocrinology

It's well stablish that bacterial species sense and respond to environmental conditions like temperature, pH and nutrients, [17, 25, 26] but they also may interact with host molecules. Prokaryotes and eukaryotes have coexisted for many years, during this time they have been exposed to signals produced and released by the other [27]. These two organisms have also assimilated their various molecules including QS signals to influence gene expression and behaviour (Table 1). The interaction between bacteria and their host through QSM, hormones, peptides and cytokines is the main concern of microbial endocrinology, the new way to understand host-pathogen relationship. Such new relationship is what determines health and disease.

3.1 Bacterial signals that modulate host cell response

The first report describing host response to QSM from pathogenic *P. aeruginosa* was described by Telford *et al.,* [28], they demonstrated that N-(3-oxododecanoyl)-L-homoserine lactone downregulates the production of tumor necrosis factor alpha (TNFα) and interleukin-12 (IL-12) as well as it promotes IgE production by interleukin-4-stimulated human peripheral blood mononuclear cells. AHLs have effects on epithelial cells like cytoskeleton remodeling, migration, wound healing, barrier integrity, and paracellular permeability and they also change the behaviour and function of human innate immune cells and the signalling machinery responsible for their recognition [13]. N-(3-Oxo-dodecanoyl)-L-homoserine lactone modulates innate immunity in macrophages, it downregulates production of the canonical pro-inflammatory cytokine TNFα, in contrast it upregulates the production of the major anti-inflammatory cytokine IL-10 (interleukin 10) in a murine model of chronic infections [29]. The immunomodulation of N-(3-oxododecanoyl)-L-homoserine lactone in epithelial cells from lungs of cystic fibrosis patients is through induction of the transcription factors NF-κB (nuclear factor κB) and AP-2 (activator protein-2) [30]. Recently, Wynendaele *et al.,* [31] demonstrated that the QSM Phr0662 produced by *Bacillus halodurans* promotes angiogenesis in HCT-8/E11 colon cancer cells.

3.2 Host signals sensed by pathogens

Pathogenic bacteria have also been found to respond to molecules produced by the host during their interaction. In this regard Wu *et al.,* [32] identified OprF ,an outer membrane protein, as the receptor involved in the response to interferon-γ (IFN-γ) in *P. aeruginosa*. The stimulation of OprF with INF-γ resulted in the expression of a QS dependent virulence determinant, the PA-I lectin. OprF is conserved among many bacteria, suggesting a role in the recognition of host signals by bacteria [33].

During the process of host-pathogen interaction, tissue gets damaged and induces an inflammatory reaction as the first general response of innate immunity, and is characterized by production of pro-inflammatory cytokines like TNFα and interleukin 1β (IL-1β). Activation of endothelial cells by these cytokines results in recruitment of leukocytes and lymphocytes to focus on inflammation to restore homeostasis [34]. There are circumstances when the response of the host defence, in terms of inflammation, is exacerbated and might cause enhanced tissue damage and organ dysfunction. On the other hand, there is evidence that bacteria sense cytokines including IL-1β, interleukin 2 (IL-2), granulocyte macrophage colony stimulating factor (GM-CSF), interleukin 6 (IL-6), INF-γ, interleukin 3 (IL-3), interleukin 10 (IL-10) and interleukin 4 (IL-4) to promote cellular proliferation and virulence gene expression [35-42]. *P. aeruginosa* upregulates virulence gene expression and aminoglycosides resistance in response to the antimicrobial peptide cathelicidin (LL-37) [43]. Other host signals that promote cellular proliferation in *Salmonella* Typhimurium and *Burkholderia pseudomallei* are cortisol and insulin, hormones associated with stress and glucose metabolism [44, 45]. The opportunistic pathogen *S. aureus* upregulates virulence gene expression like haemolysins and leucotoxins, and induction of the expression of protein A (Spa) after the priming with α-defensin (HNP-1) and chemokines 9 and 10 (CXCL9, CXCL10) [46, 47]. The response to HNP-1 is associated to the QS SaeRS.

The AI-3 QS communicates prokaryotes and eukaryotes within the intestine. Several works have described the response of bacteria to the presence of epinephrine (EPI), norepinephrine (NE) and dopamine (DO). In

enterohemorrhagic *E. coli* (EHEC) EPI and NE modulates motility, biofilm formation, gene expression and colonization of host cells [3, 48], this crosstalk is mediated by a sensor histidine kinase named QseC, the receptor of the QS QseCB. The latter is not restricted to EHEC, it is also found in *Sallmonella* sp., *Shigella flexneri*, *Francisella tularensis*, *Haemophilus influenzae*, *Erwinia carotovora*, *Pasteurella multocida*, *Ralstonia eutropha*, *Chromobacterium violaceum* and others [49]. According to bioinformatics there are no significant amino acid sequence similarities between mammalian adrenergic receptors and bacterial histidine kinase sensors [50]. *In* vivo microbiota is capable of producing neuroendocrine hormones that are commonly associated with host production [51].

Table 1 The bidirectional effects of prokaryotic and eukaryotic signals.

SIGNAL	PRODUCING ORGANISM	SENSING ORGANISM	ATYPICAL RECEPTOR	FUNCTION	REFERENCE
Prokaryotic					
AHLs (*N*-acyl-homoserine lactones)	Gram negative bacteria and *Exiguobacterium* sp. MPO from Gram positive	*Staphylococcus aureus*	AgrC	Inhibition of *agr* locus	[16, 52]
		Human intestinal epithelial cells, neutrophils, macrophages, monocytes	IP3R*, PPAR*, IQGAP1*	Alteration of barrier epithelial integrity, chemoattractant for neutrophils, increase phagocytic in macrophages, downregulation of IL-12 production, inhibition of monocyte proliferation	[29, 53, 54]
AI-2 (Autoinducer-2, furanosyl borate diester)	Gram negative and Gram positive bacteria	Intestinal epithelial cells	NF-κB*, NOD*	Activation of IL-8 expression	[55]
Phr0662	*Bacillus halodurans*	Human ileocecal colorectal adenocarcinoma cells	EGFR*, ErbB2*	Upregulates cell invasion, promotes angiogenesis and metastasis	[31]
Eukaryotic					
FOH (Farnesol)	*Candida albicans*	Gingival cells, oral carcinoma cells, spermatozoids	Unknown	Inhibition of immune response, apoptosis and necrosis	[56-58]
Catecholamines (epinephrine, norepinephrine, dopamine)	Adrenal medulla, postganglionic fibers	Gram negative bacteria, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus pneumoniae*, *Mycoplasma hyopneumoniae*, *Listeria monocytogenes*, *Borrelia burgdorferi*, *Enterococcus faecalis*, *Enterococcus cloacae*	QseC^, QseE^, OmpA^, BasS^, CpxA^	Activation of motility, T3SS, Shiga toxin, toxin haemolysin E, promotes cellular proliferation, induction of biofilms formation	[2, 3, 48, 49, 59-71]
Estrogens	Ovary, placenta	*Candida albicans*	Unknown	Invasiveness improvement	[72]

		Pseudomonas aeruginosa	Unknown	Inhibition of virulence gene expression	[73]
INF-γ (Interferon gamma)	Lymphocyte T and Natural killer	*Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*	OprF	Promotes cellular proliferation, induction of virulence genes expression	[32, 74, 75]

*Induction occurs through the receptor but not ligand binding has been demonstrated. ^Only in Gram-negatives

Response to NE by *S. aureus* might be also through QS, this to the fact that it only shows enhancement of *in vitro* growth only during long incubation times (18-48 h) [67].
Perié *et al.,* [76] proposed that QS might be a mechanism used by immune system to induce proliferation and changes in gene expression that lead to the differentiation of T-helper lymphocytes into various T-helper subtypes. This might explain the crosstalk between host signals and pathogen signals.

4. Strategies to mediate infectious diseases through QS

Bidirectional communication between pathogens and host cells have been demonstrated to occur through QS, using QSM or the complete system. Since pathogens show resistance to most antibiotics used routinely to control infectious diseases there is a need for new strategies of control. This could be achieved by blocking QS pathways or by modification of QSM to attenuate virulence, such strategies are termed quorum quenching (QQ).

4.1 Inhibition of *agr* QS in *S. aureus*

S. aureus is a major human and animal opportunistic pathogen. It causes hospital-acquired infections (meningitis, osteomyelitis, septicaemia), community-acquired infections (diarrhoea, acne, toxic shock syndrome) and animal infections (mastitis, bumblefoot). There are four subgroups of *agr* in *S. aureus*, each producing a specific AIP with a different amino acid sequence, but a conserved thiolactone ring structure. The AIP produced by one group inhibit the others, and an association of the *agr* group and the type of infection has been described [5, 77]. Based on this, natural and modified AIPs have been intensively studied as potential *agr* inhibitors [77, 78]. The half-life of AIPs *in vitro* is relative short (~4 h) [79]. Next a description of modification in AIP sequences and its potential use as infection inhibitors is presented.

AIP-I, substitution of the aspartate residue at position 5 with alanine leads to a loss of the full cognate activation activity which makes it a potent inhibitor for all *agr* groups [80, 81]. The inhibitor tr-AIP-I-D2A has the best inhibitory activity [81]. Some modified AIP-I still have the ability to induce biofilm formation. AIP-II, a truncated analogue (tr-AIP-II) results in inhibition all *agr* groups [81]. AIP-III, an alanine substitution for the aspartate residue at position 4 (AIP-III-D4A) display greater AgrC inhibition towards all *agr* groups [82]. AIP-IV, removing of its exocyclic tail creates a universal inhibitor [81]. Cross-inhibition between *S. epidermidis* and *S. aureus* has also been evaluated [83].

Inhibition of *agr* is also achieved by N-(3-oxododecanoyl)-L-homoserine lactone in sub-inhibitory concentrations resulting in downregulation of exotoxins [52]. Li *et al.,* [84] identified cyclic dipeptides (or diketopiperazines), cyclo (L-Tyr-L-Pro) and cyclo (L-Phe-L-Pro) in *Lactobacillus reuteri* that repressed the toxic shock syndrome toxin (TSST-1) in all *agr* groups.

Other strategies to inhibit *agr* activation are inactivation of AIP through its oxidation by NADPH [85] and its sequestration by apolipoprotein B, inhibiting the activation of AgrC [86]. An *in vivo* mouse model of abscess formation was used to demonstrate the efficacy of an anti-autoinducer monoclonal antibody, AP4-24H11 that sequesters the AIP-IV and complete protection against a lethal *S. aureus* strain was observed [87].

4.2 Inhibition of QS in *P. aeruginosa*

P. aeruginosa is an opportunistic pathogen that causes acute and chronic infections in humans depending of the state of the host immune system. Most prevalent *P. aeruginosa* infections occur in the lungs of people with cystic fibrosis (CF) [88]. *P. aeruginosa* persists as a facultative anaerobic bacterium with biofilm formation under the hypoxic conditions found in CF mucus plugs, suggesting that the environmental milieu may be favourable for anaerobes [89]. *P. aeruginosa* QS-activated virulence factors include elastase, proteases, pyocyanin, lectin, swarming motility, rhamnolipids, and toxins [90].

Inhibitors of LasR have been reported that contain modifications to the native N-(3-oxododecanoyl)-L-homoserine lactone ligand [91], such modifications include substitution of the lactone ring for a thiolactone ring to increase stability under biological conditions [92]. Other inhibitors include furanones and patulin [93].

Degradation and inactivation of AHLs constitutes another way to attenuate virulence in *P. aeruginosa*. Enzymatic degradation of AHLs has been found in mammals, plants, fungi, archaea and bacteria [11, 94, 95]. AHLs-degrading enzymes may be classified into 1) AHL lactonases (lactone hydrolysis), 2) AHL acylase (amidohydrolysis) and, 3) AHL oxidoreductases (oxidoreduction) [11, 96, 97].

Lactonases belong to the metallo-β-lactamase superfamily, they hydrolyse the ester bond of the homoserine lactone ring to yield the corresponding acyl homoserine molecule, hydrolysis of this ester bond can also occur spontaneously at alkaline pH, so acidic conditions can restore the bond [98]. The first described AHL lactonase was encoded in the *aiiA* gene of a *Bacillus* sp. [99]. Lactonases have broad substrates and activity of AiiA and SsoPox reduce AHL accumulation decreasing virulence gene expression [99, 100]. The mammalian enzymes paraoxonases 1,2,3 (PON 1-3) have lactonase activity, PON1 purified from serum reduces *in vitro* biofilm formation [101].

Acylases hydrolyse the acil-amide bond between the acyl tail and lactone ring of AHLs in an irreversible manner, resulting in the release of a fatty acid chain and a homoserine lactone moiety [97]. The PvdQ and QuiP acylases are the ones described to have activity in *P. aeruginosa* [102, 103].

Oxidoreductases target the acyl side chain by oxidative or reducing activity and thus catalyses a modification of the chemical structure of the signal but not its degradation, affecting both the specificity and recognition of the AHL. BpiB09, a NADH-dependent enzyme, inactivates N-(3-oxododecanoyl)-L-homoserine lactone, reducing pyocyanin production, motility and biofilm formation [95, 104].

5. Concluding remarks

As approaches have been designed to inhibit bacterial virulence traits through the manipulation of QS systems or QSM-analogues, microbial endocrinology opens a new pathway for the control of host-pathogen interactions and offers a series of molecules and its receptors that can be blocked or degraded to inhibit the interaction. For example, innate immune signals seem to promote both inflammatory responses and changes in virulence gene expression, so blocking the effect of cytokines may help to control both inflammation and pathogenesis. This cross communication is still an emerging issue in host-pathogen research, since only individual cross-talking molecules and their receptors have been described, but certainly, they may be involved in complex networks of bidirectional communication constructed along millions of years of coevolution. To date and to the best of our knowledge, no expression profiling studies have been performed for this cross-talking phenomenon. So microbial endocrinology raises as a potential area of research for the understanding and control of bacterial pathogenesis and host responses.

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