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Review

Host cells response in *Pseudomonas aeruginosa* infections - role of quorum sensing molecules

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Cell-to-cell signaling is vital not only for communication among superior multicellular organisms, but also among bacteria and for host-pathogen interactions during infections. *Pseudomonas aeruginosa* is an opportunistic Gram-negative pathogen involved in a wide spectrum of acute and chronic infections, also causing severe nosocomial complications. Among its multiple virulence determinants, the quorum sensing (QS) signaling system is used to control and coordinate the production of other virulence factors required for colonizing and persistence in different environmental conditions, but also for interfering with the host core signaling pathways. Here we review the host response mechanisms in *P. aeruginosa* infections, focusing on the effect of QS molecules on immune response and host cell apoptosis modulation pathways. Deciphering the chemical language that this bacterium uses during the infectious process could open new perspectives for the development of intelligent anti-microbial strategies based on communication control of this highly versatile and resistant opportunistic pathogen.

Key words: Apoptosis, immune response, alkyl quinolone, acyl-homoserinlactone.

INTRODUCTION

Following different types of interactions between bacteria and superior hosts, both partners involved suffer ineluctable changes which are influenced not only by cell-to-cell contact, but also by a biochemical language which is poorly understood.

Being a versatile opportunistic pathogen, *P. aeruginosa* rarely causes symptomatic infections in a normal host, but is very efficient on triggering severe complications in immunocompromised individuals, ventilated patients, persons with different malignant diseases or HIV, and cystic fibrosis patients. The pathogenicity of *P. aeruginosa* is caused mainly by multiple virulence factors and by its genetic flexibility, traits allowing this bacterium to colonize, adapt and replicate in very different environmental conditions (Cotar et al., 2010; Ben Haj Khalifa et al., 2011). The virulence of this species depends mainly on two types of determinants: (i) factors that are involved in acute infections, usually membrane bound or secreted effectors. For example, pili allow the attachment of bacteria on host epithelium, while exoenzyme S (exoS) and other adhesins stabilize the adherence of bacterial cells. The role of exoS in *P. aeruginosa* pathogenesis is related to its capacity of inducing host cell cytoskeleton disruptions, by depolymerization the actin fibers (Rocha et al., 2003), inhibiting the macrophage engulfment and degrading immunoglobulin A and G (Ben Haj Khalifa et al., 2011). Exotoxin A (exoA) is involved in triggering host tissue necrosis (Pillar and Hobden, 2002), while phospholipase C acts as a thermo stable haemolysin (Hybenová and Majtán, 1995). *P. aeruginosa* also produces other proteases involved in host tissue distruction (Cotar et al., 2008); a recent mechanism refers to the modulation of certain ionic channels which are essential for local clearance

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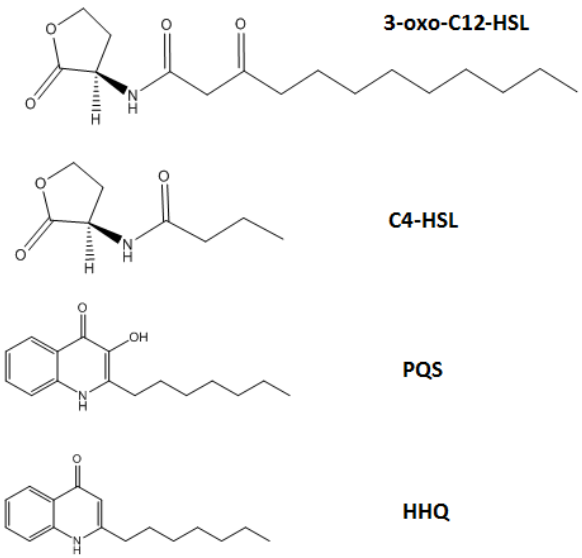

Figure 1. Chemical structure of the major QS signaling molecules (QSSMs) in *P. aeruginosa:* 3-oxo-C12-HSL (OdDHL), C4-HSL, PQS and HHQ.

(Butterworth et al., 2012). (ii) The second type of virulence determinants refers to factors involved in chronic infections, as siderophores (pioverdin, piochelin), that facilitate bacteria multiplication in low iron environments (Ben Haj Khalifa et al., 2011). Furthermore, during chronic infections bacteria are usually included in biofilms, which are protected by an alginate pseudocapsula that protects the biofilm against antibiotics, phagocytosis and deshydration (Høibya et al., 2010) and offers a better adherence to host epithelium. Since bacteria living in biofilms develop a great antibiotic resistance, alternative strategies aimed to inhibit bacteria adherence and biofilm formation (Saviuc et al., 2011a; Grumezescu et al., 2012). Recent studies aim to develop efficient target and drug control release systems (Grumezescu et al., 2011) to improve the activity of drugs or to use natural compounds exhibiting antimicrobial (Saviuc et al., 2011b) and antibiofilm activity (Anghel et al., 2012).

P. aeruginosa is a very well investigated opportunistic pathogen, the current medical focus including respiratory tract infections, especially ventilated patients and cystic fibrosis individuals. Pulmonary damage associated with *P. aeruginosa* infections occurs as a result of destruction imposed by some bacterial virulence determinants, but also because of the sustained immune response that escorts chronic infections (Ruxana et al., 2005). Among important virulence determinants involved in the evolution of infectious process the most studied are Quorum sensing (QS) signaling (Cotar et al., 2011), lipopolysaccharide production and type three secretion system (TSS) (Le Berre et al., 2011).

QS is a complex signaling mechanism used by many bacteria and its major effect is the coordination of target gene expression as a response of population density changes (Miller and Bassler, 2001). Nevertheless, bacteria cell-to-cell signaling may occur at any population density, the term QS being proposed to describe inter-bacteria communication using diffusible signaling molecules (Williams and Cámara, 2009). Key components of any QS module are: The synthase of QS signal, the receptor of the signal, and the signaling molecule (Williams, 2007), most of QS systems are being subjected to a positive feedback or auto induction.

P. aeruginosa utilizes QS to control and coordinate the production of virulence factors required for colonizing and persistence in different environmental conditions (Smith and Iglewski, 2003). By date, three QS systems have been described in *P. aeruginosa* - *Las, Rhl* and *Pqs*. Las and Rhl systems are responsible for N-acylhomoserine lactones (AHL) signaling, and the major autoinductors are N3-oxo dodecanoyl homoserine lactone (OdDHL, 3-oxo-C_{12}-HSL), which is produced by Las system, and N-butyryl-L-Homoserine lactone (C4-HSL), produced by Rhl QS signaling system. Las and Rhl systems are interconnected with a third signaling circuit that utilize 2-alkyl-4-quinolones for signaling, 2-heptyl-3-hydroxy-4(1H)-quinolone (PQS=Pseudomonas quinolone signal) and its precursor 2-heptyl-4 quinolone being the most relevant autoinducers of Pqs system [for a recent review (Williams and Cámara 2009)] (Figure 1).

Along with their essential role in microbial population fitness, bacteria auto inducers have a special impact on host cells, as well as some host signaling cell-to-cell molecules are recognized by many bacteria (Sperandio et al., 2003; Hughes and Sperandio, 2008; Holban and Lazar, 2011). *P. aeruginosa* AHLs are able to penetrate and be functional in host cells interfering with core signaling pathways (Simon et al., 2004) by unknown mechanisms. Functionally active AHLs has been found in host cell, even though shortly after penetrating into eukaryotic cell bacteria signaling molecules can be inactivated as a result of pH dependent hydrolysis or mammalian enzymatic activity (Carlene et al., 2004; Vladimir et al., 2011). The fact that the concentration of bacterial auto inducer molecules is rapidly reduced in host eukaryotic cell explains the necessity of using higher amounts of QSSMs when assessing their effect on host cell. Even though inside biofilms have been reported concentrations up to 600 µM, experimental evidence demonstrate that physiological amounts of QSSMs range from 1 to 5 µM in planktonic bacteria cultures (Vladimir et al., 2011). Therefore, authors proposed the use of concentrations ranging 10 to 50 µM (Tateda et al., 2003; Vladimir et al., 2011), or even 100 µM (Vikström et al., 2005) when the purpose of the study is to investigate the effect of bacteria autoinducers on host cells.

The aim of this paper was to review the host response in *P. aeruginosa* infections, focusing on the impact of QS molecules on immune response and host cell apoptosis

signaling pathways.

HOST IMMUNE RESPONSE IN *P. AERUGINOSA* INFECTION

Researches aimed to elucidate the effects of bacteria autoinducers on host cells rely on the observation that many bacteria communicate each-other through small difusable molecules that possess the capacity to penetrate biological membranes. Consequently, there is a great possibility that these signaling molecules also modulate the outcome of infections by interfering with some key host signaling pathways, as immune response (Telford et al., 1998; Chifiriuc et al., 2007). One of the most important observations supporting this hypothesis is that pulmonary damage that appear during *P. aeruginosa* infection are mainly due to the high amount of cytokines and chemokines induced locally after infection (Christophersen et al., 2012). The fact that bacteria autoinducers may have also immunomodulatory effect has a great relevance for medical studies.

Early stages of *P. aeruginosa* pulmonary colonization is characterized by a high local level of neutrophils. The most important neutrophil chemo attractants are chemokines, including interleukine 8 (IL-8) (Hammond et al., 1995). It has been scientifically proved that individuals carrying *P. aeruginosa* lung infections exhibit impressive intrapulmonary amounts of IL-8, which may explain the increased presence of neutrophils next to infection site (Jorens et al., 1994; Terashima et al., 1996). This could also explain clinical consequences of persistent *P. aeruginosa* infections, characterized mainly by chronic pulmonary inflammation and local tissue damage. On the other hand, the considerable amount of neutrophils found locally could explain a trial of host to eradicate the infection. As a first line of defense neutrophils and monocyte-derived macrophages can perform nonopsonic phagocytosis of *P. aeruginosa* (Jahoor et al., 2008), but another novel efficient clearance mechanism has been proposed. Studies revealed that neutrophil extracellular traps (NETs) produced after bacteria infections are very efficient in neutralizing and killing invading bacteria without engulfment by a special incompletely elucidated cell death process. NETs are defined as extracellular structures comprising neutrophil chromatin complexed with granule proteins that bind and kill bacteria by juxtaposing them with neutrophil granule proteins and histones (Brinkmann et al., 2004). Even though NETs action mechanism is not fully elucidated is clear that these extracellular structures can be activated by certain cytokines and pathogens and their function depends on reactive oxygen species (ROS) generation and NADPH oxidase activity (Fuchs et al., 2007; Young et al., 2011). Along with their antibacterial effect NETs can be also involved in promoting pulmonary damage, since high amounts of DNA that are released during NETs formation may inhibit clearance.

It has been demonstrated that *P. aeruginosa* AHL autoinducers can stimulate in a dose dependent manner the host epithelial cells to produce increased levels of IL-8 independent by the presence of bacteria cells (DiMango et al., 1995). Telford and colleagues demonstrated that OdDHL stimulate immunoglobulin E (IgE) production by human B cells and it may inhibit IL-12 and tumor necrosis factor α (TNF-α) secretion by adherent peritoneal macrophages. Furthermore it has been demonstrated that OdDHL has also mitogenic properties, while C4-HSL, its molecular precursor is not able to significantly activate immune response *in vivo*, when used in the same experimental conditions (Telford et al., 1998). Smith and colleagues supports the idea of host immune response activation by using OdDHL, demonstrating that this molecule is a potent activator of functional IL-8 production *in vitro* and that the clinical consequences of this activation refers mainly to neutrophil chemotaxis. The same research group suggests that OdDHL induced IL-8 production is dependent on transcriptional nuclear factor NF-κB activity and this signaling is regulated by a mitogen activated protein kinase (MAPK) pathway (Smith et al., 2001).

Another immune related mechanism influenced by bacteria infection is inflammatory modulation affecting prostaglandin related-pathways. Studies have revealed that *P. aeruginosa* infections significantly induce prostaglandin E2 (PGE2) production, following cyclooxygenase Cox2 pathway (Smith et al., 2002). *In vitro* investigations using human pulmonary fibroblasts revealed that OdDHL induces *cox2,* but not *cox1* overexpression and this effect seems to be related to NF-κB activation. OdDHL enhances the production of membrane associated prostaglandin E (PGE) and PGE2, but not cytosolic PGE. PGE2 exhibits an important role in mucus secretion, vasodilatation and edema, acting as a lipidic mediator for immunomodulation (Smith et al., 2002). Therefore, these data indicate that OdDHL strongly influences local inflammatory processes, contributing to pulmonary pathology that occurs in *P. aeruginosa* lung infections. Furthermore, PGE2 and Cox2 can determine ROS suppression, diminishing the macrophage dependent bacterial clearance. For this aspect both PGE2 and Cox2 have been proposed as therapeutic targets for the treatment of severe *P. aeruginosa* related pneumonia (Sadikot et al., 2007).

Even though it has been proved that NF-κB is a central modulator for bacteria derived immune response, complete signaling pathway that leads to inflammation in *P. aeruginosa* infections is incompletely elucidated. As a central innate immunity regulator, NF-κB can be quickly translocated into nuclei of infected cells. Because signalling through Toll-like receptors (TLRs) is responsible for host response in many bacterial, fungal and viral infections, TLR-dependent signaling pathways have been proposed to be involved also in *P. aeruginosa*-host interac-

tion. TLRs as TLR2, TLR4 and TLR5 are incriminated for NF-κB activation in *P. aeruginosa* infection considering that *P. aeruginosa* flagellin determines IL-8 production by an NF-κB dependent pathway after activating TLRs (Adamo et al., 2004).

Studies demonstrated that TLRs do not differentiate among pathogens and commensal microbiota components, but is enhanced by effector molecules of pathogens especially in innate immunity compromised patients (McIsaac et al., 2012). There have been described two major TLR-dependent signaling pathways involved in bacteria signaling: MyD88 (myeloid differentiation factor 88) pathway, that leads to NF-kB activation and TRIF (Toll/IL-1R domain-containing adaptor inducing IFN-1β), which involves Toll/IL-1R pathway that controls the activation of transcription factors dependent by IFN - IRF3/7 using IFN-1β (Takeda and Akira 2004). Both TRIF and MyD88 signalling pathways are involved in host defence against *P. aeruginosa* infections (Skerrett et al., 2004), studies revealing that their synergic action significantly enhance immune response (Power et al., 2007). Along with its role in activating IRF3 and 7 transcriptional factors, TRIF signaling is also involved in NF-kB activation following RIP1 (receptor-interacting protein 1) pathway (Meylan et al., 2004). Recent evidence revealed that *P. aeruginosa* infections stimulates IRF3-ISRE-IFN (IFN regulatory factor 3 - IFN-stimulated response element-IFN) pathway activation and that IRF3 represent a key determinant for host defence against *P. aeruginosa* infections (Carrigan et al., 2010).

Reiniger and colleagues demonstrate that IL-1 receptor is another important factor involved in NF-κB, its function being essential for the rapid nuclear translocation of NF-κB, highlighting the impact of innate immunity in *P. aeruginosa* infections (Reiniger et al., 2007). Furthermore, it has been demonstrate that NF-κB can be rapidly translocated into nucleus only in cells expressing functional CFTR (cystic fibrosis (CF) transmembrane conductance regulator). If CFTR is mutant or nonfunctional, example cystic fibrosis patients, both pulmonary clearance and NF-κB nuclear translocation are defective (Schroeder et al., 2002). This observation supports the conclusion that inflammation obtained after NF-κB activation possess a dual role for the host, being beneficial since it helps clearance as well as detrimental due to the fact that pulmonary damage is enhanced.

Even though host response to chronic infections seems to be completely different comparing with acute infections, many common aspects have been identified in *P. aeruginosa* infections. The similarities refer to pathogens associated molecular patterns PAMPs, as membrane associated patterns CFTR and TLR (TLR4, 2, 9, MD2, CD14), and cytoplasmic patterns - Nod-like receptors (NLR) as NOD (Nucleotide-binding oligomerization domain), NLR (Nod-like receptor) and IPAF (ICE-protease activating factor). In both chronic and acute *P. aeruginosa* response, MyD88 - Nf-kB signaling pathway seems to be activated preferentially and the result is cytokine and chemokine production that attract effector cells next to infection site (Figure 2). Furthermore, another important host cell effect in *P. aeruginosa* infections is the activation of cell programmed death, usually by caspase activation following IPAF (ICE-protease activating factor) pathway (Cigana et al., 2011).

Even though it has not been clearly identified a mammalian receptor for bacteria QSSMs, studies have revealed that OdDHL may use mammalian intracellular receptors as PPAR (nuclear peroxisome proliferator-activated receptors) in order to activate NF-kB dependent signaling pathways (Jahoor et al., 2008; Cooley et al., 2010). Very recent studies demonstrate that *P. aeruginosa* AHLs are recognized by mammalian IQGAP1 (IQ-motif containing GTPase-activating protein 1) *in vitro* and this interaction has a decisive impact on epithelial cell migration in a dose dependent manner. Excepting their co-localization with IQGAP1, OdDHL can also trigger remodeling actin effectors RAC1 and Cdc42 phophorylation, supporting the idea of controlling cellular migration (Karlsson et al., 2012).

The impact of HSL autoinducers on host immune response is well investigated, but recent evidence provides valuable information regarding alkyl quinolone (AQ) effect on host immune modulation. In bacteria populations PQS has a dual role, being called “little poison” since it modulates survival rate of *P. aeruginosa* populations supporting the survival of the most adapted bacteria (Ha¨ussler and Becker, 2008). The same research group demonstrates that both beneficial and detrimental PQS activities are closely related with the oxidative activity of this molecule, which can act as a pro-oxidant factor sensitizing un-adapted bacteria to oxidative stress, but on the other hand may determine an efficient anti-oxidant protective effect.

P. aeruginosa AQs can also interact with some oxygen-dependent signaling pathways in host cells, as the one controlled by Hipoxia- Inducible Factor-1 (HIF-1) (Legendre et al., 2012). HIFs are transcriptional factors very sensitive to free oxygen levels, being required mainly for hypoxia cell response. Hif-1 can be stabilized only in hypoxia, while is rapidly degraded in normal oxygenation, oxygen being a cosubstrate involved in its degradation as well as succinate (Benizri et al., 2008). HIF mediated signaling is controlled by NF-kB, which is a direct modulator of HIF-1α expression in normal oxygen conditions (van Uden et al., 2008). Signalling pathways that are dependent on HIFs are involved in certain diseases, as anemia, because HIF-2 controls erithropoietin production (Haase, 2010). Furthermore, HIFs are involved in immune response regulation and in malignization, being involved in tumors angiogenesis (Semenza, 2007; Melillo, 2006). HIF-1 activation may occur as a response in certain bacterial infections, as *Escherichia coli* (Cane et al. 2010), *Chlamydia* sp. (Sharma et al.,

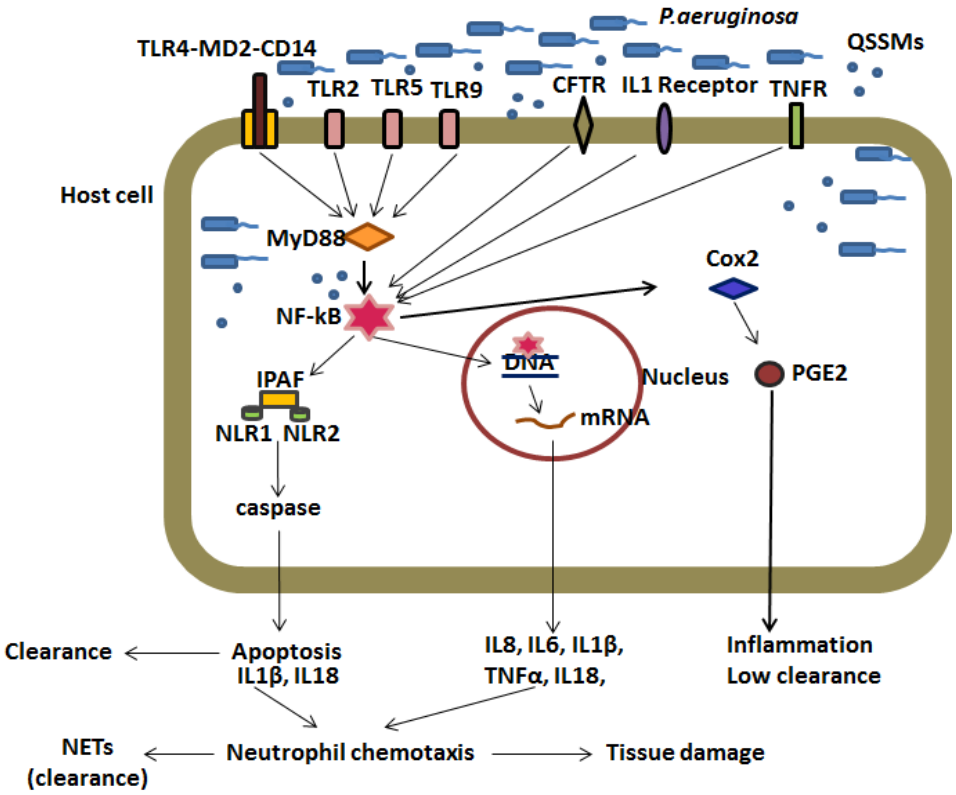

Figure 2. *P. aeruginosa* recognition by PRR (pattern recognition receptors) and host molecular response during infection. Even though *P. aeruginosa* can invade and disseminate into host tissue, causing massive damage during infection, imunocompetent hosts manage often to develop an efficient immune response. After membrane associated TLRs (TLR2, TLR4-MD2-CD14, TLR5 si TLR9), CFTR and IL-1R or cytosolic NLR (NOD1, NOD2 si IPAF) and PPAR (nuclear peroxisome proliferator-activated receptors) PAMPs recognition in both epithelial and immune infected host cells downstream activation pathways are rapidly activated. NF-κB is the central mediator in all *P. aeruginosa* induced responses and its activation leads to transcriptional activation of pro-inflammatory mediators and mucins. They recruit immune cells in a trial to neutralize and clear the infection, but this effect could also lead to massive tissue damage.

2011), *P. aeruginosa* (Legendre et al., 2011; Shao et al., 2010) and *Streptococcus* sp. (Peyssonnaux et al., 2005; Peyssonnaux et al., 2008), which has the ability to stabilize HIF-1α in both epithelial and immune cells. Even if the role of HIF-1 in infections is well investigated, molecular pathways involved in their control governed by bacteria are completely unknown. Intriguingly, while other bacteria species determines HIF-1α stabilization and accumulation, *P. aeruginosa* PQS suppress HIF-1α accumulation, by degrading HIF-1α protein using 26S-proteasome proteolytic pathway (Legendre et al., 2012).

Recent studies demonstrate that OdDHL and PQS exhibit different effects on IL-2 production by activated human T cells, using T receptors and CD28. PQS suppress T cell proliferation and IL-2 production, and stimulates TNFα release at concentrations lower than 10 μM, while OdDHL inhibits TNFα secretion by LPS (lipopolysaccharide) stimulate human monocites (Hooi et al., 2004). Same research group suggests that PQS and AHLs function as distinct immunomodulatory active molecules, possessing a synergic role. PQS also produces IL-12 suppression *in vitro* and prevents maturation T naïve cells to type I T-helper cells, suppressing cell-mediated immunity (Skindersoe et al., 2009). Both PQS and HHQ are able to suppress immune response *in vivo* and *in vitro*, using a NF-kB dependent signaling pathway. Thus, PQS and HHQ suppress NF-kB binding to specific sites blocking target gene expression (Kim et al., 2010), demonstrating that AQs are able to actively modulate host immune response during infection.

HOST APOPTOSIS MODULATION DURING *P. AERUGINOSA* INFECTION

Along with immune response modulation another key aspect in bacteria-host interaction is the ability of pathogens

to interact with host cell viability. Bacteria can induce host cells apoptosis using a wide battery of mechanisms, that can be clustered in two main strategies: i) directly by producing host protein synthesis inhibitors, pore forming molecules, superantigens and effectors that activate host endogenous cell death program (Weinrauch and Zychlinski, 1999; Kubori et al., 2000; Iordache et al., 2011) and ii) indirectly by stimulation of cytokine production (Hausmann, 2010). Host cell apoptosis modulation has been investigated mainly during bacterial infection, but recently has been demonstrated that certain *P. aeruginosa* QSSMs can stimulate host apoptosis (Worgall et al., 2002; Zhang et al., 2008; Allen et al., 2005). Considering their relation with host cells, *P. aeruginosa* strains can be divided in invasive and non-invasive strains (Fleiszig et al. 1997), this characteristic being essential in host apoptosis modulation (Kaufman et al., 2000). Invasive *P. aeruginosa* strains produce cell contact dependent factors, as ExoS, that induce specific apoptotic morphology into host cell (Kaufman et al., 2000; Chifiriuc et al., 2008).

During *in vivo* and *in vitro* epithelial cells infection the expression of surface bound CD95 receptor is induced. CD95/CD95 system is one of the most important endogenous receptor/ligand endogenous couple involved in cell apoptosis. Overexpression of CD95 leads to JNK (Jun N-terminal kinase) activation and determine mitochondrial changes, releasing of cytochrome c (Jendrossek et al. 2001), and rapid caspase 8 and 3, followed by caspase 9, 7 and 1 activation (Grassm´ et al., 2001; Jendrossek et al., 2003). Once initiated the apoptotic cascade will propagate rapidly. Chai and colleagues demonstrate that *P. aeruginosa* initiate host apoptosis by overexpressing pro-apoptotic mediator Bax and down-regulation anti-apoptotic molecule Bcl-2 expression, concomitant with cytochrome c releasing and activation of caspase 3 and 9 (Chai et al., 2008).

P. aeruginosa can invade both epithelial and immune cells (Chifiriuc et al., 2008), and it can initiate lymphocyte apoptosis after phagocytosis. *P. aeruginosa* invade natural killer (NK) cells by activating phosphoinositide 3-kinase (PI3K) during phagocytosis and this activation triggers apoptosis cascade following a caspase 9-MAPK (mitogen-activated protein kinases) pathway, along with ROS (Chung et al., 2009). Studies using mast cells demonstrated that *P. aeruginosa* triggers apoptotic death suppressing the action of endogenous anti-apoptotic molecules as FLIP (Fas-associated death domain protein-like IL-1β-converting enzyme-inhibitory proteins) and activating caspase 8. Along with FLIP-Caspase 8 modulation, mitochondrial activated proteins Bcl cluster are also involved in *P. aeruginosa* induced mast cells apoptosis, by overexpressing Bcl-xS and down-regulating Bcl-xL (Christopher et al., 2006).

It is well known that cell response can be triggered not only during infection and cell-to-cell direct contact, but also by using signaling molecules. First scientific proof regarding the role of AHLs in host cell apoptosis can be found in Tateda and colleagues research (Tateda et al., 2003). Their studies revealed that OdDHL are able to specifically activate apoptosis in certain cell types, as cultured macrophages or neutrophils, but no epithelial cells. OdDHL significantly affect cell viability in a dose dependent (among 10-100 µM) and time dependent (1-24h) manner. Even though a signaling pathway leading to OdDHL induced apoptosis is still unknown, is well accepted that AHLs induce apoptotic features in mammalian cells, as membrane blebbing, chromatin fragmentation, fosfatidilserine expression and caspase 3 and 8 activation. Interestingly, the apoptotic effect can be quantified only when using OdDHL, but no C4-HSL or other short chain synthetic AHLs derivatives (Tateda et al., 2003).

Miyairi and colleagues demonstrated that mice immunization using OdDHL conjugated with a protein carrier (BSA, ovalbumine) protects animals against lethal *P. aeruginosa* infection and the apoptotic rate of OdDHL stimulate macrophage seems to be also lower if serum of immunized mice is. The authors explain this effect by the fact that OdDHL immunization block host inflammatory response, reducing additional effects as apoptotic death. This idea is based on the observation that immunized mice express significantly lower TNF-α concentrations in the lungs after *P. aeruginosa* infection that leads to an attenuated immune response (Miyairi et al., 2006). Figure 3 represents a molecular network containing the main effectors known to be involved in *P. aeruginosa* induced host cell apoptosis.

Recent evidence demonstrates that high concentrations of OdDHL, above 100 µM, inhibits cell proliferation and induce mast cells apoptosis, along with repression of IL-6 and increasing of intracellular calcium content (Li et al., 2009).

Regarding the role of quinolone autoinducers on host cells apoptosis the data available is few. Studies revealed that PQS is able to induce apoptosis *in vitro* using a murine cell line in a dose and time dependent manner and the effect seems to be influenced by the presence of rhamnolipidic biosurfactants that along with increasing PQS solubility also stimulates its biological activity (Calfee et al., 2005). To date, there are no reports demonstrating host apoptosis-related signaling pathways which are regulated by AQs in *P.aeruginosa*.

Knowing that both AHLs and quinolones are able to modulate host immune response and that some immune effectors are involved in control of cellular programmed death lead to the conclusion that bacteria QSSMs can modulate indirectly host cell viability. One of the most commune indirect apoptotic mechanisms is the one depending on cytokines, which are induced during immune activation. TNF is a major immune element responsible also for tissue damage, its production being massively influenced by bacteria infections (Hausmann, 2010). It has been demonstrated that TNF is able to initiate

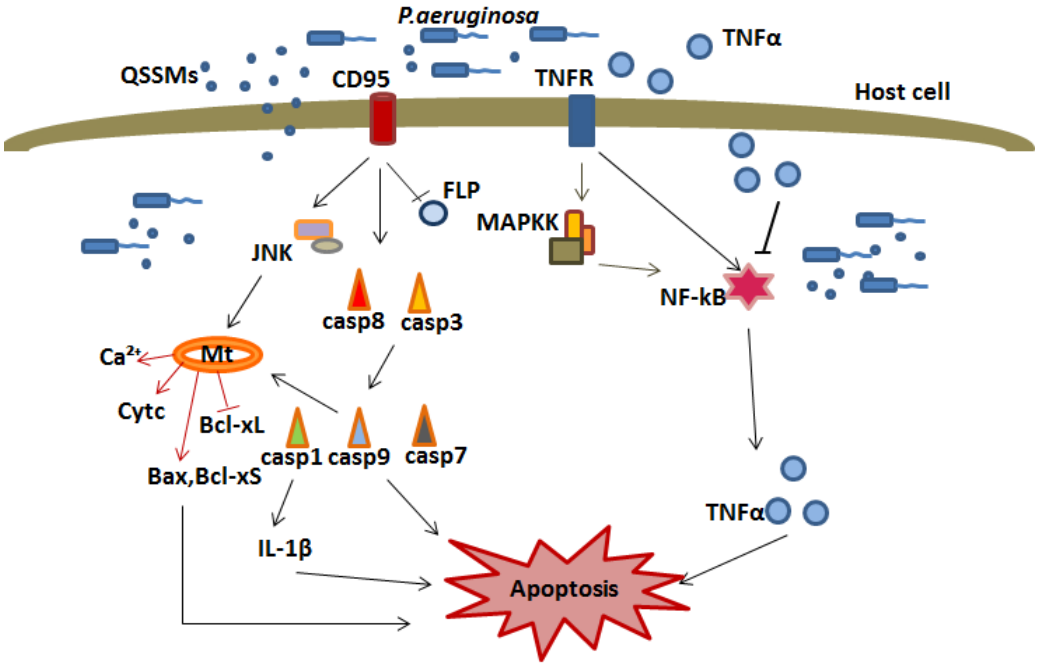

Figure 3. Host apoptosis pathways modulation during *P. aeruginosa* infection. During infection CD95 receptors are rapidly activated, triggering an activation cascade dependent on JNK signalling, leading to releasing of mitochondrial pro-apoptotic effectors and increasing intracitoplasmatic Ca^{2+} content. Apoptosis following *P. aeruginosa* infection can be enhanced also by direct caspase activation. Both cell-to cell bacteria-host contact and QSSMs are able to initiate apoptotic signaling by cytokine production and NF-kB signaling modulation.

pro-apoptotic pathways, but also anti-apoptotic pathways using different receptors, as TNFR1 and 2 in a dose and concentration dependent manner (Seidelin et al. 2004). Modulation of NF-kB pathway using TLRs may also influence programmed cell death, since the blockage of NF-kB signaling is leading rapidly to activation of apoptosis cascade (Sen et al., 2005). Nevertheless, the results regarding the role of NF-kB in different apoptotic pathways are controversial because this pleiotropic core signaling effector has both pro and anti-apoptotic function, depending on multiple signaling conditions, most of them unknown. Furthermore, it has been demonstrated recently that OdDHL induces rapid activation of some molecular markers involved in stress response, as eIF2α (eukaryotic translation initiation factor 2 α) and MAPK p38 (mitogen activated protein kinase p38) (Vladimir et al., 2011; Vikström et al., 2005) and these effectors have the potential of triggering apoptosis directly or during phagocytosis.

Even though the theoretical correlations seem reliable they need to be scientifically supported and proved.

Conclusions

Since interkingdom signaling have proved to be possible, new perspectives considering cell-to-cell communication highly impacts on development and species evolution have arisen. Revealing the intimate molecular mechanisms of inter-species communication has, besides its evolutionary importance, a practical one, providing new perspectives in the management of microbial infections. Despite their tiny structure QSSMs are able to produce a very specific response not only within the producing species but also in host eukaryotic cells, demonstrating the great adaptability of bacteria to environmental conditions, including hosts.

This review gives an insight of the way by which *P. aeruginosa*, a universal pathogen with both environmental and clinical implications, interacts with the eukaryotic host cell. Decrypting the chemical language that this bacterium uses in order to control its own activity and some host key signaling pathways may lead to novel intelligent anti-microbial strategies based on inter-species communication control.

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