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# Inter-kingdom cross-talk: the example of prokaryotes - eukaryotes communication

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**ABSTRACT**

Some interactions between prokaryotes and between prokaryotes and eukaryotes are well known, but the intimate mechanisms of intercellular communication still remain fully unknown. Unicellular bacteria behave as multicellular organisms through intercellular communication. Microorganisms and their hosts communicate with each other by an array of chemical compounds (e.g. hormones and hormone-like molecules). Language and cross-talk between microorganisms and between them and their hosts determine specific behaviors. Inter-kingdom signalling has broad implications to evolution and human health, modulation of communication pathways being considered an effective future therapeutic approach.

**Keywords:** *quorum sensing, inter-kingdom signaling, autoinducers, host-pathogen relationship.*

## 1. Introduction

It is estimated that the human organism has approximately $10^3$ cells, but carries approximately $10^{14}$ microbial cells (comprising the endogenous microbiota). During the evolutionary process, a series of relationships and interactions have been established between host and its microbiota, as well as between different microbial species, either beneficial or detrimental. For example, mammals have established a symbiotic association with the intestinal microbiota, which is crucial to the nutrient assimilation process as well as to the development of the immune system. This kind of benefic mutual association is possible due to the fact that microorganisms and mammals are able to communicate through chemical signals. However, the same chemical signals can be used by many pathogenic bacteria, in order to activate their virulence genes.

Although the communication mechanisms between prokaryotes and eukaryotes are far from being fully understood, it is well known that eukaryotic cells communicate especially through *hormones*. On the other hand, one of the most significant inter-bacterial communication mechanisms relies on signals that coordinate the genes expression, as a response to a certain microbial density. This process was named *quorum sensing (QS)* [1], or *quorum sensing and response* [2]. It is considered that bacteria are able to communicate with the host organism through the *quorum sensing* molecules, which can be generically named *hormon-like* molecules [3, 4].

Currently, it is considered that *QS* molecules are involved not only in inter-bacterial but also in *inter-kingdom* communication networks. This type of communication may be a cross-adaptive

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strategy for survival, in case of both prokaryotes and eukaryotes, which allows a continuous monitoring of environmental changes and development of an appropriate response that fits to the new conditions.

In this review paper, we discuss several mechanisms that are involved in inter-bacterial and/or inter-kingdom communication, emphasizing the relationships between bacteria and host and the role of these interactions in the evolutionary process.

## 2. Inter-bacterial communication

The essential role that microbial consortia globally play is predetermined by their metabolic versatility and their ability to evolve quickly. Microorganisms have developed sophisticated mechanisms to receive, process and transduce information coming from the external environment. Keeping in mind the diversity of the niches they fill, the bacteria's ability to perceive and adapt to ambient conditions is a prerequisite for survival.

Communication between bacteria that belong to the same species or to different species is mediated by chemical signals which are synthesized and secreted by microbial cells. These signals may be influenced by cellular density, as they are secreted at certain densities (autoinducers), or they can be produced in various growth stages, to allow bacterial cells to monitor the outside medium, in order to gain a competitive advantage through the modification of gene expression [5]. Although microorganisms are able to detect signals at any concentration, the communication mediated by *autoinducers* generally occurs depending on concentration, unlike other types of signals [6].

*QS* signals have been discovered in the marine species *Photobacterium fischeri* (*Vibrio fischeri*), as they are involved in the control of bioluminescence process. These signals have later been identified in a large number of microorganisms (*Pseudomonas sp., Escherichia sp., Streptococcus sp.*, yeast, etc). The *QS* process is almost always used for the control of various microbial phenotypes, having a very high specificity. This extreme kind of specificity may first seem unexplainable, due to the fact that microorganisms are frequently present in multispecies communities (for example, hundreds of microbial species can exist in the oral cavity's biofilms), every species can produce multiple signals, and the response mechanisms to the received signals are frequently interconnected [6]. However, it is really not surprising that QS molecules have a very high specificity for the matching receptors (the signals are first recognized by the microorganisms which have produced them), this ensures efficiency for the communication process.

In order to include a molecule in the *QS* molecules category, it must meet certain conditions: a) it must be able to accumulate in the extracellular milieu during a specific growth phase, under certain physiological conditions, or as a specific response to modifications of the outside medium; b) it must be specifically recognized by surface or intracytoplasmatic bacterial receptors; c) it must determine a cellular response to a specific extent [7, 8].

The most well known signaling molecules for Gram negative bacteria are *N-acyl homoserine lactones* (AHL), *2-alkyl-4-quinolone, γ-butyrolactones, furanones, long chain fatty acids* derivatives, *peptides, 4,5-dihydroxy-2,3-pentanediones* derivatives (DPD), known as *type 2* and/or *3 autoinducers* [8, 9, 10, 11].

In Gram positive bacteria, communication is based especially on the synthesis of specific peptides, which are post-translationally modified, whereas the universal chemical lexicon, found in

both Gram positive and Gram negative bacteria, is represented by the synthesis of the *autoinducer 2* (AI-2) [10, 12].

The reference model for Gram negative bacteria, concerning the pattern for *QS* signaling, is the one identified in *V. fischeri.* The basic circuit is determined by the presence of two specific proteins: *LuxI* and *LuxR,* whose activity is conditioned by the synthesis and recognition of the *autoinducers*, to control production of light. *LuxI* encodes the enzyme that leads to the synthesis of the *N-(3-oxohexanoyl)-L-homoserine lactone* (3-oxo-C6-HSL), a compound which can diffuse inside or outside the bacterial cell. At lower cellular densities, the *LuxI* protein will be present in small concentrations. This will generate low concentrations of *autoinducer* and the production of light due to gene expression for *luciferase* [13]. As the cellular density increases, the concentration of *autoinducer* will also increase, inside, and as well as outside the cell. When the concentration of the signal cells reaches a threshold level [14], the molecules of the *autoinducer* binds to the *LuxR* proteins, generating their activation, by exposing a *DNA* binding motif . The activated *LuxR* proteins, will bind to the promoter region of the *luxICDABE* operon, determining, among others, the supra-expression of genes for *luciferase*, stimulating the luminescence process. Keeping in mind that *luxI* is another target gene which is going to be over expressed, the production of *LuxI* protein will be greatly increased. This will result in a rapid growth of luminescence [5].

*QS* is mediated by an analogous regulator circuit, *LuxI/LuxR,* for the majority of Gram negative bacteria, i.e. *Pseudomonas aeruginosa* [15], *Burkoholderia cepacia* [16], *Yersinia enterocolitica* [17], *Agrobacterium tumefaciens* [18].

Many species use multiple *QS* systems. For example: *P. aeruginosa* uses at least two *luxI-luxR* homologous *QS* systems, *las* and *rhl* that control the expression of virulence factors: *elastase, alkalin protease*, *rhamnolipids*, *pyocyanin* and *cyanides* [19, 20].

Commonly, the *luxI* si *luxR* orthologs are encountered in the same genetic locus, even though, orphan *luxR* members have recently been described [21, 22]. Although many orphan sequences differ in length (due to deletions/insertions) from *luxR* orthologs which are part of a classic *luxI/luxR* pair, they generally maintain similar functions. However, orphan members with altered functions, due to the loss of key amino acids have also been highlighted [21].

It has been found that the *QS* system is responsible for a wide range of functions, like: production of siderophores [23], cellular division [24], polysaccharides synthesis [25], aggregation [26], and mobility [27].

Other types of molecules involved in the *QS* mechanisms of Gram negative bacteria are represented by small *diffusible signal molecules* (*DSF = diffusible signal factor*) [28], which can be chemically characterized as derivatives of *cis-11-methyl-2-dodecenoic acid* [29]. These molecules have initially been identified for *Xanthomonas campestris,* and subsequently for *Stenotrophomonas maltophilia* [30], *Xylella fastidiosa* [31] and *Burkholderia cenocepacia* [32]. *DSF* molecules have multiple roles, as they are involved in regulating the expression of extra cellular enzymes, dispersion of biofilms, toxins resistance and survival [33, 34].

*QS* systems found in Gram positive bacteria are different from the *QS* signaling mechanisms in Gram negative bacteria, regarding the structure of auto inducer molecules, as well as the signal recognition and processing mechanisms. Most Gram positive bacteria use oligopeptides as autoinducers (*AIP, or peptide pheromones*), similar to eukaryotes, functioning as specific communication signals. AIP signals are not able to diffuse freely inside and outside the cell. Instead, they are synthesized as precursor peptides, posttranslationally modified, and exported from the cell

with the help of the protein transport machine [35]. The detection and recognition occur not by direct binding to a suitable receptor, but by means of an intermediate transducer system, made up of two components, within which AIP binds to a *histidine-kinase* receptor attached to the membrane. The binding information will be transmitted by regulatory proteins phosphorylation, which will finally bind to the promoter region of target genes, in order to regulate their expression [27]. A classic example for *QS* regulatory mechanisms in Gram positive bacteria is offered by *Streptococcus pneumoniae.* In this case, the *comAB* genes are involved in the export of peptide signals, *comC* in AIP production, *comD* acts as a receptor for AIP and *comE* functions as an intracellular regulator of the response.

Another *QS* system prototype for many Gram positive bacteria is the *agr* (*accessory gene regulator*) of *Staphylococcus aureus*. This system has a central role in regulating genes responsible for virulence, intracellular survival, biofilm development and multiplication [36, 37]. Moreover, the *agr* system controls all three classes of exotoxins: *α-toxins, PVL* (*Panton-Valentine leukocidin*) and *PSM* (*Phenol-Soluble Modulin*). It plays a role in the invasion ability and controls the expression of genes involved in antibiotic resistance, including *methicillin* resistance (*mecA*) [37]. The *agr* sequence consists of two contiguous transcription units (*RNAII* and *RNAIII*), controlled by two promoters *agrP2* and *agrP3*. The *agrP2* operon consists of four genes *agrBDCA*. *AgrA* and *AgrC* compose a dual system together, within which *AgrA* represents a response regulator, and *AgrC* is a transmembrane *histidine-kinase* receptor that will be activated after the binding of proper autoinducer peptide. The activated *AgrC* will determine *AgrA* phosphorylation, thus leading to the transcription of *agrP2* and *agrP3,* promoters, and subsequently to the transcription of sequences from the *agr* region [8].

In *Bacillus* species, *QS* molecules are proteins that bind directly to the specific signaling peptides. The signaling peptides are represented by certain *aspartyl phosphate phosphatases* (*Rap phosphatases, Rap proteins*), by the regulator of *neutral phosphatase* (*NprR* and its orthologs) and by the regulator of *phospholipase C* (*PlcR*) [38]. Similarly, for *Enterococcus faecalis*, pheromone receptors are *QS* proteins that bind to the signal peptides. Although these proteins control different processes for different species of bacteria, it has been observed that they present similar structures. Phylogenetic analyses support the idea that these structures come from a common ancestor. Declerck and his collaborators [39] have proposed that these should be included in a family of proteins named *RNPP* (from Rap*, NprR, PlcR* and *PrgX* molecules). This family seems to include members involved in all *QS* systems from Gram positive bacteria, which act by directly binding to the signaling peptides in a receptor cell. It has been found that usually, the genes encoding for *RNPP* proteins family, and for the related signaling proteins, are placed in a cassette located on the bacterial chromosome or on plasmids. The receptor proteins remain intracellular, even if a fragment corresponding to the C-terminal of the signaling protein will be exported and processed by protease to the mature signaling peptide. The mature signaling peptide will be internalized by an oligopeptidic *permease* and will bind to the intracellular cognat receptor. [40].

Although there is a high specificity between a certain autoinducer and his receptor, many bacterial species produce several types of signals and possess multiple *QS* circuits (for example *P.aeruginosa* [41] and *S.aureus* [42]. Despite structural constraints and regulatory systems whose purpose is to ensure the specificity of *QS* mechanisms, there have been observed unspecific signaling mechanisms or cross communication for both Gram positive and Gram negative bacteria, that can occur at the recognition and autoinducer signals processing levels. So far, only one way of signaling,

about which it can surely be acknowledged to intervene in interspecies communication has been described. Initially indentified in *Vibrio harveyi* [43], the *luxS* gene, involved in the synthesis of *autoinducer-2* (AI-2), has been later identified in over 55 species of Gram positive and Gram negative bacteria [44]. Just like the universal signal molecule, AI-2 has a very important role for interspecies communication in certain micro-niches like the oral cavity and the gastrointestinal tract, where it can intercede in biofilm formation and in other stages of the infectious process [45].

The discovery of the QS processes involvement in regulation of microbial virulence, offers new opportunities to control infectious bacteria without interfering with bacterial growth. Recent studies have shown that different sub inhibitory concentrations of *phenyl lactic acid* (PLA), produced by probiotic strains of *Lactobacillus sp.,* may attenuate the virulence and pathogenicity of certain strains of *P.aeruginosa* and *S.aureus.* These studies indicate the potential of probiotic strains to produce anti infectious molecules, that can be successfully used in the biomedical domain, for both therapy and prevention, without affecting the environment's quality, as an alternative of conventional therapies [46].

## 3. Communication between bacteria and fungi – the impact on the plants

Prokaryotes often coexist and interact with different species of eukaryotes (animals, plants, fungi) by different means and for various reasons. Relationships between bacteria and fungi are well know, however it is often underestimated how intimate and decisive these interactions really are for the behavior and survival of each participant. Bacteria and fungi generally interrelate in a variety of niches: soil, animals, food. In the soil, they are involved in nutrient turnover in order to confer compounds in forms that can be assimilated by plants [47], and may play a decisive role in plant growth and development [48]. The balance between pathogenic and nonpathogenic microbial communities governs the frequency of soil born vegetal diseases. Certain nonpathogenic antagonistic microorganisms manage to inhibit the appearance of such disease by producing metabolic antagonists, which can be detected by pathogenic species [49].

Bacteria can facilitate fungi actions in mycorrhized symbioses (the most common type of symbiosis on earth), which is absolutely necessary for the processing of nutrients for many plant species [50]. It has been demonstrated that interactions between fungi and bacteria play a decisive role in several key processes: survival (environment change, protection against competitors), growth (through different antifungal and antibacterial components, *QS* inhibitors, growth promoters), health/disease (*Agaricales* disease), virulence factors expression, production of secondary metabolites (specific suppression, competitiveness increase due to mediators) [51, 52].

Microorganisms have managed to develop new antagonistic mechanisms, important for the protection of plant and animal (including human) hosts. The value of bacteria-fungi interactions is gradually being understood by the medical community. Due to the AIDS pandemic, fungal infections have exploded in recent years [53]. It has been proven that fungal infections can be effectively inhibited by bacteria, thus, the protection against fungal infections has great potential for the development of probiotics [52, 54]. Interestingly, bacteria generally produce a mixture of antagonists, instead of only one compound, in order to minimize the development of resistance mechanisms in pathogenic strains [55, 56]. Due to the different ways of gene transfer in bacteria (horizontal gene transfer, natural transformation), certain biosynthetic operons for antifungal

metabolites have been identified in taxonomically distinct and geographically distant bacterial strains. A good example is the production of the antifungal compound *2, 4-diacetylphloroglucinol* (DAPG) by different *Pseudomonas* isolates [57].

As a response to the antagonist actions exhibited by bacteria, fungi have developed different defense mechanisms. The presence of efflux pumps allows the target organisms to tolerate exogenous toxic compounds, by pumping them outside the cell. For example, the *BcAtrB* efflux pumps represent the first defense line of *Botrytis cinerea* against DAPG [58]. On the other hand, *Fusarium oxysporum,* has the capacity to attenuate DAPG by degradation of this antibiotic in less toxic ompounds such as *monoacetyl-phloroglucinol* and *phloroglucinol* [59]. Another protection mechanism is the inhibition of bacteria's antifungal action. For example, *Fusarium* species naturally produce *fusaric acid,* which is not only toxic for prokaryotes and eukaryotes, but also inhibits the production of antifungal metabolites by bacteria [60].

The impact and modulating effect of *QS* molecules over the two reigns has been intensely studied in recent years. In 2005, Rasmussen and his collaborators [20] have shown that certain compounds produced by *Penicillium,* species like *patulin* and *penicillic acid* have an inhibitory role on *QS* molecules, affecting the expression of 45-60% of the genes regulated by QS. It was found that the filamentation process in *Candida sp.* can be influenced by QS molecules. Hogan and his collaborators [61] (2004) have demonstrated that *P.aeruginosa* inhibits filamentation and promotes the reversion to yeast form of *C.albicans,* by producing *N-3-oxo-L-homoserine-dodecanoil-lactone* (3OC12, HSL; OdDHL). OdDHL structurally related compounds have been shown to affect the filamentation in *C.albicans*, used at comparable concentrations. Moreover, older studies of Hogan and Kolter [62] (2002), have shown that *P.aeruginosa* can invade the filamentous form of *C.albicans,* with a subsequent killing effect (taken like this, we could conclude that *C. albicans* is preventing the killing effect of *P. aeruginosa* by reverting to the yeast form). It has been demonstrated that the virulence factors of *P.aeruginosa* which are involved in the development of different infectious disease are also being incriminated for the killing of the yeast's filamentous form [62].

Besides the fungi's capacity to perceive bacterial *QS* molecules, it has been demonstrated that they are also able to degrade them. In 2008, Uroz and Heinonsalo, have shown that mycorrhized and non-mycorrhized fungal species, belonging to the both *Ascomycota* and *Basidiomycota* phylum, have the capacity to hydrolyze *3-oxo-C6-HSL* through a lactonase activity.

It has recently been shown that some bacteria species can induce a programmed cellular death to fungi they are competing with. Wichmann and his collaborators [63], have demonstrated that the ectopic expression of a gene from *Pseudomonas syringae,* functionally homologous to a fungal gene involved in the control of apoptosis, can induce a programmed cell death in the filamentous *Neurospora crassa* fungal species. The ectopic expression of the pseudomonadal gene in *N. crassa* can be explained through the horizontal gene transfer between the two species. A very important aspect of the interaction between fungi and bacteria is the influence on different human diseases. The fungi-bacteria co-infections are frequently involved in the stimulation of host colonization and virulence [64]. Researchers have lately focused on the relationship between *Candida sp.* and different species of bacteria. For example, *Escherichia coli* and *C. albicans,* manifest a cooperative relationship, where, *E. coli* stimulates the adherence of *C. albicans* to the urinary mucosa, thus increasing the rate of fungal urinary infections [65]. It has been observed that the risk of developing *P. aeruginosa* lung infections, in association with ventilation, is higher for

patients who have initially been colonized by *Candida sp.* [66]. Moreover, it has been observed that the association between *C. albicans* and bacteria from the oral microbiota (*Streptococcus sp., Actinomyces sp., Fusobacterium sp.*) contributes to a more efficient colonization of dental surfaces and the development of oral fungal infection, as well as to the development of inflammatory processes like stomatitis [67]. In contrast, lactic bacteria, which normally colonize the intestinal tract and the female reproductive tract, are in competition with *C. albicans* for the adherence sites and secrete compounds that inhibit fungal adherence, thus controlling the invasion of *C. albicans* and the development of disease [64, 68].

It has been found that certain fungal signaling *QS* molecules can intervene in controlling the virulence of some bacterial strains. *Farnesol,* a factor involved in inducing the transition from hyphal to the yeast state in *C.albicans,* can alter the production of *toxic phenazines,* like *pyocyanin,* in *P.aeruginosa* [69]. Moreover, *farnesol* may generate oxygen reactive species in a great number of microbial species. This process plays an important role in the competition between bacteria and fungi [64].

It is known that bacteria and fungi, taken together or as separate entities can form well structured communities associated to surfaces that are generically called *biofilms*. A significant number of human infections is associated with biofilm production, micro niches within which microorganisms are better protected, and intermicrobial communication is facilitated [5, 70, 71]. The currently approach is focused on mixed, multispecific biofilms. The well known relationship between *Candida sp*. and the oral streptococci, illustrates different means by which bacteria and fungi can attach in an aggregate through certain cellular factors of specific surface, leading to the mixed biofilms [67]. The study of these structures supports the idea according to which, interreign communication occurs frequently and natural, and the *QS* signals play an important role in interspecific communication between prokaryotes and eukaryotes.

## 4. Bacteria and animal host cross-talk

The intimate association between nonpathogenic bacteria and eukaryotes, as well as the identification of certain intermicrobial signaling mechanisms, has lead to the idea that intercellular communication exist between microorganisms and their hosts.

In the context of the interactions between host and pathogens, it has been revealed that pathogens can respond to the host's signals and, in turn, the host organisms are able to recognize and respond to the messages sent by pathogenic bacteria. [3, 5]. In order to solve the mechanisms that represent the base for communication between microorganisms and host, studies have been intensely focused on the bacteria-mammals relationship. Studies have shown that bacteria are able to communicate with the eukaryotic host through certain chemical compounds such as *hormones* or *hormone-like* molecules [3, 4].

In mammals, there are three major categories of hormones: proteins (or peptides), steroids (a subclass of lipid hormones) and aminoacid derivates (or amines). The amines and peptide hormones (examples: *epidermal growth factor* (EGF), *insulin*, *glucagon*) cannot cross the cellular membrane and they will bind to membrane receptors (kinase receptors and receptors coupled with G proteins), while steroid hormones (*adrenaline, noradrenaline*) are able to pass through the plasmatic membrane, and will especially bind to intracellular receptors. It has been shown that all of these

hormones are involved in the inter-kingdom signaling between microorganisms and their mammalian host [4].

Although bacterial cells do not express adrenergic receptors, some studies indicated that bacteria can respond to *adrenaline* and/or *noradrenaline* [4, 72, 73, 74].

It was demonstrated that *noradrenaline* (NA) are able to increase bacterial growth and gene expression for fimbriae and toxins in pathogenic *E.coli* strains [72, 75, 76]. The existing data claimed that NA may work as a siderophore [77, 78]. It is believed that NA is involved in overexpression of *enterobactin* and in the iron chelating mechanism in *E.coli*, subsequently increasing the bacterial growth rate [76]. However, the role of NA in bacterial pathogenesis seems to be more complex; for example the *pyoverdine* siderophore from *P.aeruginosa* can act also as a signaling molecule [79]. Moreover, it has been reported that during the surgical wounds, NA released in the intestines can induce the expression of virulence features in *P.aeruginosa,* leading to sepsis with gastrointestinal origin [80].

The role of *adrenaline* and NA signaling molecules in bacterial pathogenesis is supported by studies,confirming that these hormones are involved in *flagella* and the *type III secretion system* (T3SS) production in enterohemorrhagic *E.coli* (EHEC) O157:H7 [3]. EHEC has the capacity to detect the presence of NA and aromatic *QS* signaling bacterial molecules, like the *autoinducer 3* (AI-3), in order to activate its virulence mechanisms, suggesting that bacterial and host signals are interchangeable [3]. The intestine colonization with EHEC leads to the development of epithelial cells lesions, characterized by the destruction of microvilli and the formation of pedestal shape structures, named *attaching/effacing* lesions (AE). The genes involved in the formation of AE lesions are located at the level of a pathogenicity island (*LEE* or *locus of enterocyte effacement*), that contains a region involved in the "erasing" of the enterocytes microvilli [81]. The *LEE* region encodes a T3SS [82], an adhesin and its receptor [83, 84], and as well as effector proteins [85].

The recognition of the three signals (AI-3, produced by different bacterial species in the intestinal microbiota, adrenaline and NA produced by the host) is essential for the expression of EHEC virulence *in vivo*. AI-3, NA and adrenaline are antagonistic signals and all three can be blocked by adrenergic antagonists [3, 86]. These signals are received by a *histidine kinase* receptor placed in the EHEC membrane, and will determine the activation of a complex regulatory cascade, that will culminate with the activation of motility genes, the expression of LEE sequences and *Shiga-like* toxin [3, 87]. One kind of such kinase receptor is *QseC,* a functional bacterial analogous of adrenergic receptors, essential for the complete virulence of EHEC [87]. *QseC* specifically detects AI-3, adrenaline and NA (in order to be phosphorylated) by the direct binding of these signals [4]. Typical kinase receptors are composed by a system with two components that activate through autophosphorylation of a preserved histidine rest, as a response to an outside signal. Subsequently, the phosphate group will bind at a histidine residue from the receptor; next will be transferred to an aspartate rest from a proper response regulator, which, once activated, will determine direct regulation of target genes. In bacteria, this system of two components represents the major transducer system of the signal [88]. After the binding of one of the three signaling molecules (AI3, adrenaline, NA), *QseC* will determine the phosphorylation of the response regulator *Qseb*, which will auto activate, and will determine activation of motility genes expression [73]. Moreover, *QsebC* plays an important role in regulating LEE genes, in performance of iron chelating systems, in expression of certain adhesion molecules, and as well as in the expression of Shiga-like toxins [4].

These observations suggest the importance of *QseC*, in the pathogenesis of EHEC, as well as in inter-kingdom signaling.

*QseC* homologues have been identified in other pathogenic bacteria like: *Salmonella enterica* serovar *Typhi* (*S. typhi*), *Salmonella enterica* serovar *Typhimurium* (*S.typhimurium), Vibrio parahaemolyticus* si *Francisella tularensis*. Although their role is not fully elucidated, it has been shown that they are involved in regulating the expression of virulence factors, in survival and colonization [89]. Callaway and his collaborators [90] (2006) stressed the importance of signal receiving device due to adrenaline and NA, issued by the host during infection and colonization with *Salmonella sp*. Their studies on swine have shown that any kind of stress (social stress, stress due to transportation) that the swine have been exposed to, resulted in the reactivation of subacute infections with *Salmonella sp.,* and the stimulation of feces elimination of these bacteria.

Although adrenaline and NA are considered typical stress hormones, having a major role in stress response, it has been observed that mammal organisms produce *endogenous opioids*, like *dynorphin,* during stress. Recent studies have demonstrated that the opportunistic pathogen *P.aeruginosa* can use *dynorphin*, in order to stimulate its own virulence factors expression, at the same time showing that this mammalian stress hormone cross-interact with the signaling *QS* system in *P.aeruginosa* [91].

These studies demonstrate the existence of a clear connection among host signaling systems, bacterial QS and pathogenesis. This suggests that the stress response mechanism is one of the fundamental physiological mechanisms, both in prokaryotes and eukaryotes, having a central role in inter-kingdom communication [4].

The fact that *AHL* can determine different responses in eukaryotes is known for more than 10 years. The recognition of bacterial signaling molecules by mammalian receptors such as *Toll-like* or *Nod-like*, leads to the rapid synthesis and secretion of different *cytokines* and *chemokines* with an active role in immunity modulation. It has been observed that AHL can stimulate the production of *interleukin 8* (IL-8) in epithelial respiratory tract cells, in a manner depending on concentration [92]. The studies of Telford and his collaborators [93] (1998) have shown that OdDHL inhibits lymphocyte proliferation, as well as *TNFα* (*tumor necrosis factor α*) and *IL-12* production in macrophages stimulated with *lipopolysaccharides (LPS).* Lately, more researchers agree that AHL have a biphasic role in immunomodulation, specifically, lower concentrations of AHL stimulate the immune response, while at higher concentrations the immune function of the host is exaggerated.

Besides the classic effects produced by microorganisms in the host cell (internalizing or phagocytosis of bacteria, cytokines release, secretion of *defensines or* the production of *free oxygen radicals*), studies have shown that many bacteria can induce apoptosis of the host cell. Apoptosis after bacterial infection occur subsequent to a complex interaction between the host cell and the bacterial cells. It has been found that bacterial cells are able to activate certain proapoptotic proteins, like *caspases* , to inactivate *antiapoptotic* proteins (for example *NFkB* or *MAP kinases*), or to stimulate the formation of ligand/receptor systems, specific for the apoptosis induction, on the surface of infected cells [94]. Different bacterial products like *OdDHL* can initiate apoptosis in many mammalian cell types: neutrophils, macrophages, fibroblasts, endothelial cells, tumoral cells [95, 96]. Tateda and his collaborators [95] (2003) have observed for the first time that *OdDHL* can promote apoptosis. Their studies indicate a stimulation of the apoptotic process in neutrophils and macrophages, in a manner depending on concentration and incubation period, after adding *OdDHL*. It is more interesting that this effect has not been observed after treatment with *N-butanoyl-*

*homoserine lactone* (*C 4 -HSL*), another *QS* molecule similar with *OdDHL* [95]. Studies have shown that these discrepancies may occur due to differences in hydrophobicity of the molecules' side chain. It has been demonstrated that synthetic analogs of AHL with the addition of polar groups cancel the apoptotic activity of the molecule [97].

Besides the *AHL* molecules, other compounds involved in pathogen-host communication and playing an important role in apoptosis have been identified. *Porphyromonas gingivalis*, the agent that causes chronic periodontitis in adults, a widely spread disease among the population, presently represents a subject of great interest. It has been found that *P. gingivalis* adheres to the host cells and invades them through *adhesins* and certain cysteine proteases (similar to trypsin), named *gingipain adhesins*, which are also involved in the parasite-host communication [98]. *A44* gingipain adhesine peptide is responsible for the hijack of clathrin-dependent endocytosis system of the host, allowing the internalization of peptides and intact bacterial [98]. Boisvert and Duncan [99] (2010) have showed that *A44* peptides can be translocated to mitochondrial level, using confocal microscopy and cell fractionation assays. It has been demonstrated that these peptides interfere with the mechanisms which control programmed cell death, by triggering upregulation of antiapoptotic genes *bcl-2* and *bcl-XL* and prevent staurosporine-induced apoptosis [99]. The mechanism described allows bacteria to persist, due to the fact that they are protected in the cellular microniches, which allows infection spread.

All this studies confirm once again the great importance of prokaryotes microorganisms for superior eukaryotes. From promoting the takeover of nutrients by plants to the induction of malignant transformation; or from stimulation of cytokines production, to the complete hijack of signaling pathways of the host, sometimes reaching its death, the bacteria manage to impose its "personality" all over. Currently, scientist accepts the idea that relationships between microorganisms and the host organism represents one of the most important links of evolution. Even though the mechanisms that build the base of these relationships (mechanisms that couldn't be possible without the existence of a well constructed communication system understood by all the participants), are not fully understood, multiple researchers focused on this direction have started to come up with quite results. A recent study that supports these hypotheses is represented by the research of Sharon and his collaborators [100]. Considering the fact that mating preferences represent an early event in the speciation process, these researchers have shown that commensal bacteria can influence mating preferences of fruit flies (*Drosophila melanogaster*).

The authors used a wild type line of flies, kept in the laboratory on a molasses medium, from which they later broke of two groups: one was maintained on the molasses medium, while the other group was transferred on a starch medium. After a certain number of generations, all the flies were mixed and left to reproduce on a molasses medium. The authors observed that the flies manifested mating preferences (males kept on the molasses medium preferentially mated with the females kept on the molasses medium, while males kept on the starch medium preferentially mated with females kept on the same tip of medium). Mating preferences appeared after only two generations, and the effects were maintained for at least 37 more generations. In order to confirm the results, a treatment using antibiotics was achieved. The results showed that the flies treated with antibiotics mate randomly, despite the growth medium. Through molecular rRNA 16s studies, several commensal bacterial strains have been identified, from which only *Lactobacillus plantarum* was proved to be involved in mating preferences in *D. melanogaster* [100]. Moreover, the study showed that only one bacterial species is needed (*L.plantarum*) for mating preferences to manifest in *D. melanogaster*.

Although the mechanisms responsible for these effects still remain unknown, one possible explanation could be the modification of hydrocarbons composition of the flies cuticles, as the authors have observed differences regarding this aspect, for the flies grown on the molasses medium versus the starch medium; differences which faded after the administration of antibiotics.

Such studies represent arguments that support the hologenome theory of evolution, considering thatthe holobiont (the host organism and the associated microorganisms) acts as selection units on the evolutionary scale.

# 4. Conclusions

Intermicrobial communication and the QS mechanisms are intensively studied processes; the results obtained up until now being very useful for understanding microbial behavior in processes of clinical interest, like the production of biofilms or infections, and more.

Researchers have managed to partially identify and highlight the molecules and mechanisms of intra and interspecies communication. However, research in the domain of intra and inter-kingdom communication has only just begun. Even though it is certain and accepted the fact that prokaryotes and eukaryotes are capable to recognize and respond to both their own signals as well as to crossed signals, presently we can only manage to issue hypotheses regarding the importance of understanding these relationships and interactions, as well as the possibility of exploiting them. In the near future we expect the diversification of knowledge in this multidisciplinary field, and also the clarification of many aspects that are still unresolved about infectious disease. The central objectives of these studies are the elaboration of novel therapeutic strategies (more efficient from the medical and economical perspective), the development of the biotechnological domain, as well as the elucidation of aspects regarding co-evolution of prokaryotes and eukaryotes. In order to obtain more efficiently valuable results, besides microbiology and immunology, related domains, like genomics, transcriptomics, proteomics, metabolomics and bioinformatics are being endorsed.

Through cumulated efforts of all of these domains, we find ourselves one step closer to deciphering the mechanisms of intra and inter-kingdom communication, and the expected results will definitely not be postponed.

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