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Quorum Sensing and Fungal-Bacterial Interactions in *Candida albicans*

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Abstract

Microorganisms have evolved a complex signature of communication termed quorum sensing (QS), which is based on the exchange and sensing of low-molecular- weight signal compounds. The ability to communicate within the microbial population gives the advantage to coordinate a groups behavior leading to a higher fitness in the environment. The polymorphic fungus *Candida albicans* is an opportunistic human pathogen able to regulate virulence traits through the production of at least two QS signal molecules: farnesol and tyrosol. The ability to adopt multiple morphotypes and form biofilms on infected surfaces are the most important pathogenic characteristics regulated by QS and are of clinical relevance. In fact, traditional antimicrobial approaches are often ineffective towards these characteristics. Furthermore, the intimate association between *C. albicans* and other pathogens, such as *Pseudomonas aeruginosa*, increases the complexity of the infection system. This review outlines the current knowledge on fungal QS and fungal–bacterial interactions emphasizing on *C. albicans*. Further investigations need to concentrate on the molecular mechanisms and the genetic regulation of these phenomena in order to identify putative novel therapeutic options.

Keywords: *Candida albicans*; Quorum sensing; *Pseudomonas aeruginosa*; Intermicrobial communication.

1. Introduction

Quorum sensing, a mechanism of microbial communication wherein accumulation of signaling molecules enables a cell to sense a cell density. It regulates several ecologically and medically important traits in microorganisms such as competence & bioluminescence, biofilm formation, secretion of virulence factors, sporulation & antibiotic production. Quorum sensing phenomenon which relies on the interaction between small diffusible signal molecules with transcriptional activator proteins, couples the gene expression with cell density (Padder *et al.*, 2018b). Quorum sensing is a well-known and widespread mechanism of cell–cell communication in bacteria,

wherein they communicate through signaling molecules called autoinducers, and contribute to the regulation of the gene expression (Wongsuk *et al.*, 2016).

The oral microbiome plays a vital role in maintaining oral health by preventing pathogen colonization and protecting the mucosa. Several studies have investigated the ecological balance of the oral microbiome, where the modern metagenomic and meta transcriptomic approaches showed presence of much larger number of species, dominated by bacteria, than previously thought (Mahdia *et al.*, 2020) .This also concerns fungi (mycobiome), viruses (virome), and protozoa. The oral cavity is inhabited by more than 75 members of the mycobiome, with the most abundant Candida, Cladosporium, Alternaria, Aspergillus, Fusarium, Cryptococcus, and Aureobasidium (Ghannoum *et al*., 2010)

One of the most common fungi that contribute to the natural human microbiota inhabiting the oral cavity, usually without disease symptoms in healthy individuals, are Candida species (30%–60%). They reside in the oral cavity as commensals, mostly in planktonic cell form, colonizing variety of surfaces, ranging from delicate host epithelia to hard surfaces of teeth or artificial dental appliances or dentures (Rapala-Kozik *et al.*, 2023). However, when the balance between the host and colonizing microbiota is disrupted, opportunistic *Candida* fungi can induce local or systemic infections (Mavor *et al.*, 2005). This problem affects mainly individuals with weakened immune system function, in general immunosuppressed, HIV-positive patients, as well as patients after long-term antibiotic therapy or chemotherapy (Ghate *et al.*, 2015).

Additionally, risk factors also include diabetes, nutritional deficiencies, use of dentures and orthodontic appliances, stress, smoking, ageing, and poor oral hygiene. The nature of yeast-induced infections and the ability to colonize host tissues depend on strain-specific characteristics, including adherence properties, the ability to biofilm formation, as well as the potential of secreted degradative enzymes (Blaikie *et al.*, 2014). More recently this remarkable behavior has also been described in fungi and there is accumulating evidence that different fungi show QS-dependent phenotypes (De Sordi and Mühlschlegel, 2009). However, the majority of fungal autoinducers, as well as their molecular mechanisms of action, remain unknown. Understanding how QS systems affect fungal physiology can lead to a better understanding of pathology, thus providing knowledge to develop new systems for control. Microorganisms are frequently found in mixed communities in their natural environment. In fact, predation,

symbiosis, parasitism and many other relationships naturally occur in ecological niches, allowing the entire community to survive in equilibrium (Kuyukina *et al.*, 2003)

Bacterial intercellular communication is based on small, self-generated signal molecules called autoinducers (Reading and Sperandio, 2006). Through the production and sensing of autoinducers, bacteria can activate or repress target genes according to population density and dimensions of the environment. This ability has been called quorum sensing (Miller and Bassler, 2001).

More recently this remarkable behavior has also been described in fungi and there is accumulating evidence that different fungi show QS-dependent phenotypes (Reading and Sperandio, 2006). However, the majority of fungal autoinducers, as well as their molecular mechanisms of action, remain unknown. Understanding how QS systems affect fungal physiology can lead to a better understanding of pathology, thus providing knowledge to develop new systems for control (Blaikie *et al.*, 2014). Microorganisms are frequently found in mixed communities in their natural environment. In fact, predation, symbiosis, parasitism and many other relationships naturally occur in ecological niches, allowing the entire community to survive in equilibrium (De Sordi and Mühlschlegel, 2009). In this context, the concept of QS assumes a more complex meaning. In a network of coexisting organisms, both endogenous and exogenous signals mediate different responses. Molecules are important players in these interactions in a fascinating and intricate intra- and interspecific system of microbial communication (Padder *et al.*, 2018a).

This review article aims to highlight the progress in the research on fungal QS and on the interactions between fungi and bacteria. Emphasis will be laid on Candida albicans. An important aspect of C. albicans research is its interaction with other microorganisms and we will focus on the relationships existing between C. albicans and the bacterial opportunistic pathogen Pseudomonas aeruginosa.

2. QS and Interspecies Interaction

Although the nature of bacterial autoinducers is very diverse, none of the known molecules or genes mediating bacterial QS seems to be found in fungi, regulating fungal cell–cell communication (Tseng and Fink, 2008). Indeed, since the discovery of QS mechanisms in fungi, it became evident that these organisms have evolved their own systems (De Sordi and

Mühlschlegel, 2009). Because of the diversity of secreted molecules and signals, (Monds and O'Toole, 2008) have recently proposed guidelines to recognize the compounds mediating an intercellular signal: (1) The signal is secreted and has been identified; (2) Mechanisms exist to sense and respond specifically to the signal; (3) the concentration of the signal required to elicit the response is not toxic to the cell; (4) The response evoked is separable from the primary metabolism of the signal; (5) Purified signal can reproduce the biological response at a physiologically relevant concentration; and (6) The signal network is adaptive at the level of the community.

In many cases, autoinducers and other molecules are not only responsible for same-species communication but also for the more complex interspecies cross-talk. In fact, the diversity of interkingdom signaling occurring in a myriad of environments has been classified into four categories (Casiraghi *et al.*, 2008). (a) One-way sensing: one organism senses and responds to a diffusible signal produced by a second organism; (b) Co-opting for a signal: one organism uses the signal produced by another to regulate its own gene expression; (c) Modulation of a signal: one organism alters the production or stability of a signal from another organism; and (d) Two-way communication: multiple signals are exchanged between organisms (Fig. 1)

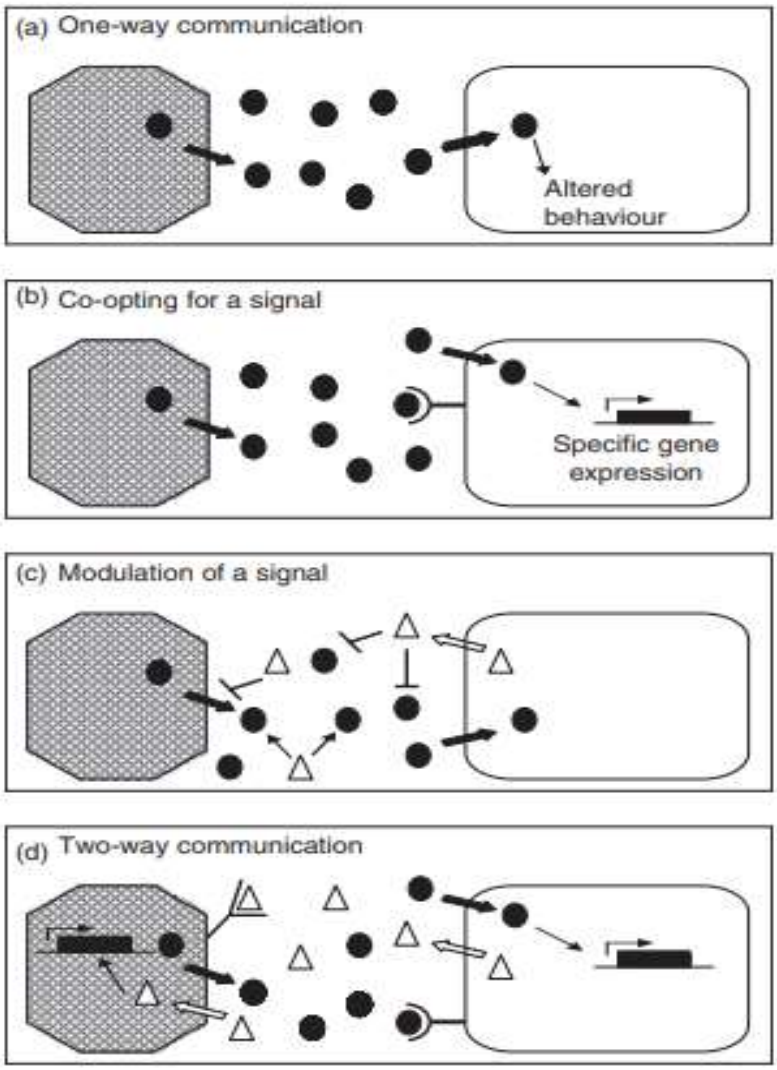

Fig.1 Examples of uni- and bidirectional signaling interactions. (1) One-way sensing: one organism senses and responds to a diffusible signal produced by a second organism; (2) co-opting for a signal: one organism uses the signal produced by another to regulate its own gene expression; (3) modulation of a signal: one organism alters the production or stability of a signal from another organism; (4) two-way communication: multiple signals are exchanged between organisms (Casiraghi *et al.*, 2008).

In this context, QS plays a major role. For example, N-acyl-L-homoserine lactone (AHL) bacterial QS molecules not only direct the synthesis of compounds active towards other organisms but are also directly recognized by eukaryotic cells, including animal cells, plants, seaweed and fungi, reviewed in (Dudler and Eberl, 2006)). On the other hand, several studies show that fungi are able to interfere with bacterial QS by producing AHL antagonists (Bjarnsholt *et al.*, 2005) as well as through the effects of their own QS systems(Casiraghi *et al.*, 2008).

2.1. Quorum Sensing in *C. albicans*

In the healthy host C. albicans can be found as a benign commensal situated in a variety of body locations (Calderone and Clancy, 2011). However, in immunocompromised individuals, bloodstream infections, which are frequently nosocomial, can be associated with considerable mortality rates despite the existence of robust antifungal treatment strategies, reviewed in (De Sordi and Mühlschlegel, 2009). Different endogenous and exogenous signals enable C. albicans to colonize a plethora of environments and promote pathogenesis. Among these, biofilm formation and morphogenesis are well-studied characteristics of C. albicans.

2.2. *Candida albicans* Infections and Biofilm Formation

Candida albicans is an opportunistic pathogen. One of its most critical virulence traits is captured by the real estate agent's mantra: 'location, location, location.' That is, C. albicans is a typical component of gastrointestinal and genitourinary tract flora in healthy individuals, where it generally exists without noticeable symptoms. Alterations in host immunity, bacterial flora or other environmental factors permit C. albicans overgrowth, causing a wide range of infections (Pappas, 2006). Implant-related infections in particular are a significant problem in this context. These infections are associated with indwelling medical devices, such as catheters, pacemakers and prosthetic joints, which provide surfaces for biofilm formation (Nobile and Mitchell, 2006). C. albicans cells may reach an indwelling device through occasional breach of the gastrointestinal tract barrier(Saiman *et al.*, 2000) or, perhaps, through external contamination.

Our understanding of C. albicans biofilm ultrastructure began with scanning electron microscopic visualization of yeast cells, pseudo-hyphae and hyphae in C. albicans biofilms(Hawser and Douglas, 1994). This and subsequent studies (Nobile and Mitchell, 2006) show that biofilm formation in vitro can be broken down into three basic stages: (1) attachment and colonization of yeast cells to a surface, (2) growth and proliferation of yeast cells to allow formation of a basal layer of anchoring cells and (3) growth of pseudo-hyphae and extensive hyphae concomitant with the production of extracellular matrix material (Fig.2). Recent studies of C. albicans biofilms from denture stomatitis patients confirm the presence of yeast, hyphae and extracellular matrix in vivo (Ramage *et al.*, 2004) Furthermore, biofilm architecture in two animal catheter models appears to include numerous yeast cells in the basal

region, as well as extracellular matrix. Hyphae are also present in both in vivo biofilm models (Nobile *et al.*, 2012).

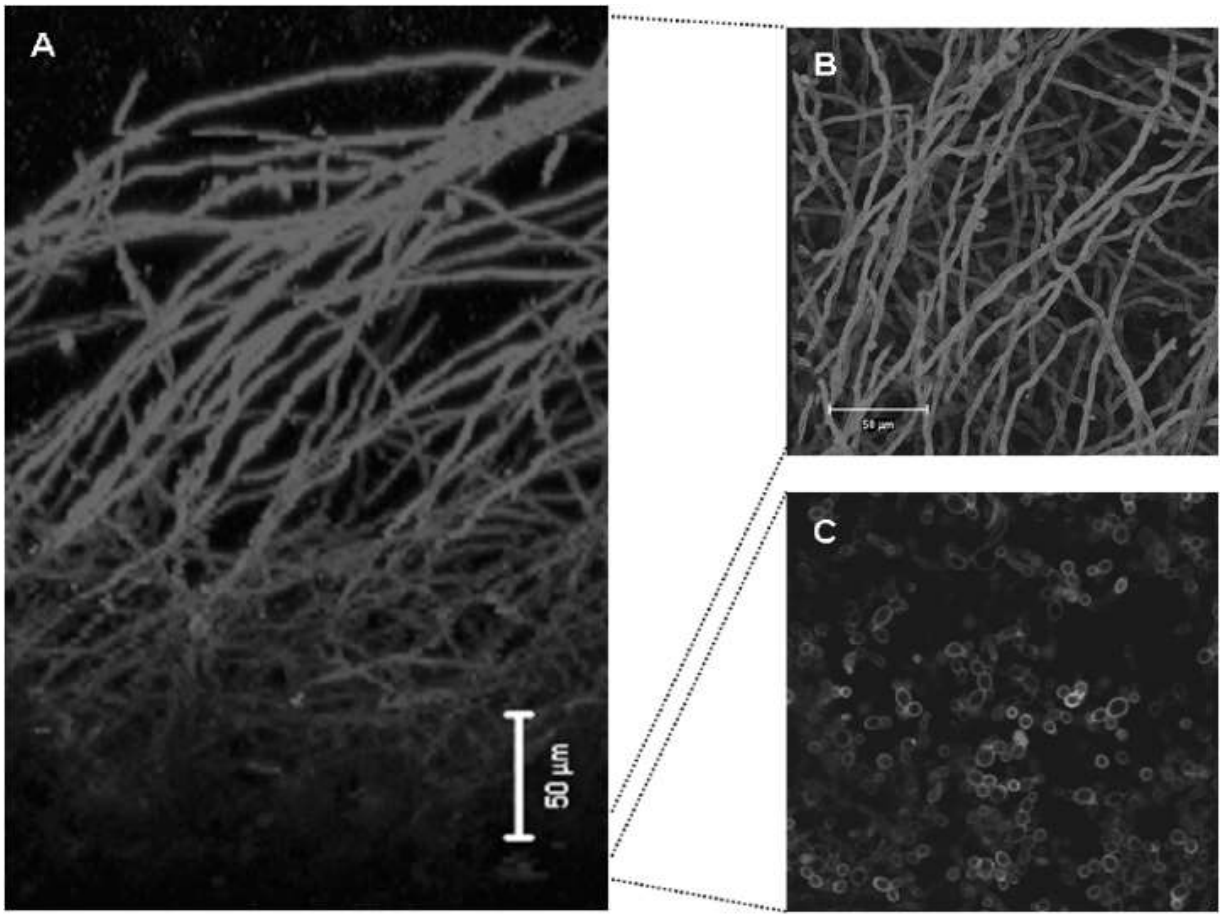

Fig.2 Biofilm produced by reference Candida albicans strain DAY185 on silicone substrate in vitro. The biofilm was visualized through confocal scanning laser microscopy after staining with fluorescent concanavalin A. The side view (A, x–z plane) shows a well -stained upper hyphal layer atop a poorly visualized basal layer. The basal layer may stain poorly due to presence of extracellular matrix material. The top view (B, x–y plane) emphasizes abundance of hyphae, and reveals few yeast cells or pseudo hyphae in the upper layers of the biofilm. A slice taken at 20 microns above the substrate (C, x–y plane) reveals primarily yeast cells; a few elongated cells are apparent at the top of the panel (Ramage *et al.*, 2004).

2.3. Genetic Control of Biofilm Formation

The analysis of gene function serves as a cornerstone of mechanistic hypotheses, an assertion that has proven true in studies of bacterial biofilm formation (Davey and O'Toole, 2000). Genetic analysis of C. albicans is slower and more limited than that of many bacterial species, but the completion and annotation of the C. albicans genome sequence (Achterberg *et al.*, 2006) has

facilitated numerous reverse genetic strategies. Thus, we now have a modest but growing list of genes whose products have been shown to impact biofilm development in vitro (Table.1).

Table.1 Phenotypes are summarized for homozygous null mutants unless otherwise noted (Achterberg *et al.*, 2006)

Gene	Mutant phenotype	Reference
ACE2	Reduced adherence, reduced biofilm biomass, altered biofilm structure	Kelly *et al*. (2004)
ALS3	Severe defect in biofilm formation	Nobile *et al*. (2006)
BCR1	Severe defect in biofilm formation	Nobile and Mitchell (2005); Nobile *et al*. (2006)
CDR1	*cdr1*/*cdr1 cdr2*/*cdr2* double mutant has increased azole susceptibility in immature biofilms	Mukherjee *et al*. (2003); Mateus *et al*. (2004)
CDR2	*cdr1*/*cdr1 cdr2*/*cdr2* double mutant has increased azole susceptibility in immature biofilms	Mukherjee *et al*. (2003); Mateus *et al*. (2004)
CHK1	Forms a biofilm in the presence of farnesol	Kruppa *et al*. (2004)
CPH1	*efg1*/*efg1 cph1*/*cph1* double mutant is defective in biofilm formation	Lewis *et al*. (2002); Ramage *et al*. (2002a)
EAP1	Null mutant not reported; overexpression improves adherence of *efg1*/*efg1* mutant	Li and Palecek (2003)
EFG1	*efg1*/*efg1* single mutant and *efg1*/*efg1 cph1*/*cph1* double mutant are defective in biofilm formation	Lewis *et al*. (2002); Ramage *et al*. (2002a)
GCN4	Reduced biofilm biomass	Garcia-Sanchez *et al*. (2004)
KEM1	Severe defect in biofilm formation in SD medium, reduced hyphal content in biofilm in Spider medium	Richard *et al*. (2005)
MDR1	*mdr1*/*mdr1 cdr1*/*cdr1* double mutant and *mdr1*/*mdr1 cdr1*/*cdr1 cdr2*/*cdr2* triple mutant have greatly increased azole susceptibility in immature biofilms	Mukherjee *et al*. (2003); Mateus *et al*. (2004)
MDS3	Severe defect in biofilm formation	Richard *et al*. (2005)

Gene	Mutant phenotype	Reference
MKC1	Reduced hyphal content in biofilm, greatly increased azole susceptibility	Kumamoto (2005)
NUP85	Severe defect in biofilm formation (mutation was insertion allele)	Richard *et al*. (2005)
SUV3	Severe defect in biofilm formation	Richard *et al*. (2005)
TEC1	Severe defect in biofilm formation	Nobile and Mitchell (2005)
YWP1	Super adhesive biofilm	Granger *et al*. (2005)

The study of some genes was prompted by specific hypotheses related to biofilm formation. For example, hyphae are abundantly apparent in *C. albicans* biofilms, thus it was hypothesized that hyphae are necessary to develop a biofilm. The transcription factor genes *EFG1* and *CPH1* are positive regulators of hyphal morphogenesis; an *efg1/efg1 cph1/cph1* double mutant is unable to form hyphae under most conditions (Lo *et al.*, 1997). This same *efg1/efg1 cph1/cph1* mutant is unable to form a normal biofilm, thus arguing that hyphal morphogenesis is required for biofilm formation (Nobile and Mitchell, 2006). Similarly, expression profiling revealed that numerous amino acid biosynthetic genes were upregulated during biofilm development, and the fact that mutation of the amino acid gene activator *GCN4* reduces biofilm biomass argues that increased expression of those genes is functionally significant for biofilm formation (García-Sánchez *et al.*, 2004). Other genes were identified through non-hypothesis-driven genetic screens. For example, a random insertional mutagenesis revealed that *KEM1*, *MDS3*, *NUP85* and *SUV3* are required for biofilm formation *in vitro* (Richard *et al*., 2005). There was no prior functional connection among these genes, but all turned out to be required for hyphal formation, thus strengthening the conclusion that hyphal formation is a requirement for biofilm formation. In a second example, the transcription factor genes *TEC1* and *BCR1* were identified through a functional survey of transcription factor gene mutants (Nobile and Mitchell, 2006). *TEC1* is a known regulator of hyphal formation (Hoang *et al.*, 2000), so its identification as a biofilm regulator was not unexpected. However, *BCR1* proved to be a novel regulator of hyphal cell surface properties, thus suggesting that hyphal adherence specifically is critical for biofilm formation (Nobile and Mitchell, 2006).

2.4. Role of Quorum Sensing

Recently, it became increasingly evident that not only external signals could affect C. albicans biofilm and morphology but also secreted compounds autoregulating development. The fact that hyphal formation was repressed at high cell density (4106 cellmL_1) and that supernatants of stationary phase cultures could cause the same effect enabled identification of the first fungal QS system, for reviews, see (De Sordi and Mühlschlegel, 2009).

(Hornby *et al.*, 2001) identified the QS molecule E, E-farnesol, which represses filamentation in C. albicans despite the presence of filamentation-inducing compounds such as serum and N-acetylglucosamine. In the same study, these authors revealed that the molecule has no effects on the fungal growth rate and that its production and concentration in the medium (10–50 mM) do not depend on the nature of the nutrients (Hornby *et al.*, 2001). Moreover, it has been demonstrated that farnesol reversibly inhibits biofilm formation but does not block the elongation of pre-existing hyphae (Ramage *et al.*, 2002). However, although farnesol does not affect C. albicans growth, a strong antifungal and antibacterial activity has been reported against several other organisms including Aspergillus nidulans and Saccharomyces cerevisiae (Tseng and Fink, 2008), conferring a selective advantage in the environment. Moreover, farnesol has been demonstrated to enhance antibiotic susceptibility in Staphylococcus aureus and to inhibit biofilm formation and lipase activity in this pathogen (Kuroda *et al.*, 2007). Farnesol has also been shown to decrease the viability of murine macrophages (De Sordi and Mühlschlegel, 2009). Furthermore, microarray analyses carried out in the presence of farnesol revealed not only a decrease in the expression of genes associated with hyphae formation, but also an increased expression of genes related to drug resistance (Tseng and Fink, 2008). Connecting these facts with the observation that farnesol biosynthesis from farnesyl pyrophosphate inhibits the ergosterol pathway (Roberts *et al.*, 2003), suggests that there may be an important role for QS in C. albicans antifungal drug resistance. Also suggests a role for farnesol in oxidative stress resistance as it induces the transcription of antioxidantencoding genes (Westwater *et al.*, 2005).

Another QS molecule produced by C. albicans is tyrosol. This aromatic alcohol is able to specifically shorten the lag phase of growth in a low-density culture without having any effect on exponential growth (Chen *et al.*, 2004). Moreover, tyrosol stimulates the formation of germ tubes in yeast cell (Chen *et al.*, 2004) and the development of hyphae in the early stage of biofilm formation (Alem *et al.*, 2006). Thus, the two QS molecules farnesol and tyrosol have antagonistic

effects. However, in the later stages of biofilm development, the presence of farnesol appears to exert dominant effects (Alem *et al.*, 2006), indicating a possible temporal link between the two systems. A schematic representation of the QS effects conferred by farnesol and tyrosol is shown in Fig. 3 and Table 2.

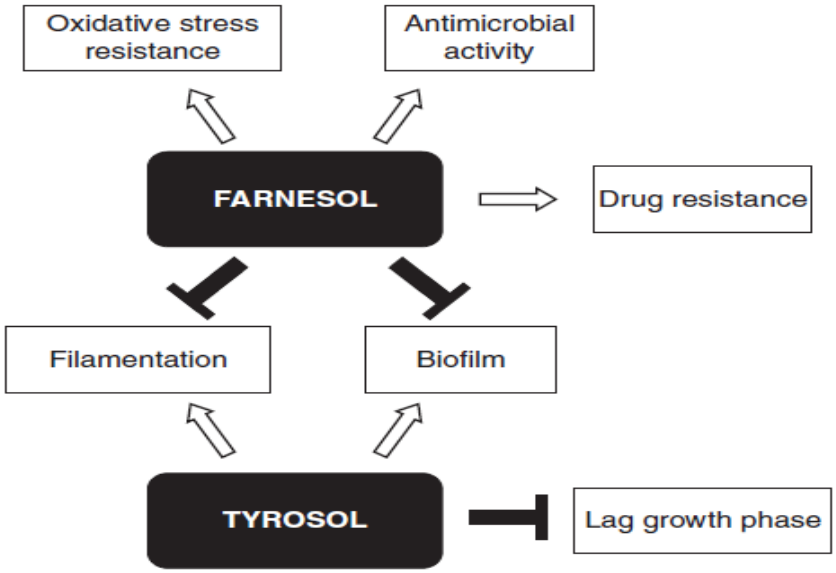

Fig.3. Schematic representation of farnesol and tyrosol's effects on Candida albicans physiology. Arrows indicate positive regulation of the phenotype whereas short parallel lines mean negative regulation (Alem *et al.*, 2006).

Table.2 Farnesol and tyrosol's effects on Candida albicans (Alem *et al.*, 2006)

Molecule	Effect	References
Farnesol	Inhibition of filamentation	Hornby *et al.* (2001)
	Inhibition of biofilm formation	Ramage *et al.* (2002)
	Antimicrobial activity	Tseng & Fink (2008)
	Drug resistance	Cao *et al.* (2005), Enjalbert & Whiteway (2005)
	Oxidative stress resistance	Westwater *et al.* (2005)
Tyrosol	Shortened lag phase of growth	Chen *et al.* (2004)
	Stimulation of germ tube in yeast cells	Chen *et al.* (2004)
	Stimulation of hyphae in the early stage of biofilm formation	Alem *et al.* (2006)

2.5 *Candida albicans* vs. *Psudomonas aeruginosa*: the Relevance of QS in Microbial Coexistence

In many cases, C. albicans infections originate from a disequilibrium in the patient's own microbial communities (Fridkin and Jarvis, 1996). Furthermore, (Xu *et al.*, 2008) recently reported that bacterial peptidoglycan-like molecules promote C. albicans filamentation through direct activation of the fungal adenylyl cyclase Cyr1p (Xu *et al.*, 2008). Thus, it appears that bacteria are sensed by the fungus and the mechanisms mediating this detection have elements common to the perception of bacterial peptidoglycan by human immune effector cells, where these molecules bind the intracellular leucine-rich domains of Nod1 and Nod2 (Girardin *et al.*, 2003).

Both C. albicans and P. aeruginosa can be frequently identified from cases of hospital-acquired infections (De Sordi and Mühlschlegel, 2009). In fact, they can colonize devices, such as intravenous catheters, that are directly linked to the high rates of serious hospital-acquired infections (Ramage *et al.*, 2005). Notably C. albicans mixed with P. aeruginosa has been found in heterogeneous populations on intravenous catheters (Pierce, 2005). Moreover, C. albicans and P. aeruginosa are routinely co-isolated from the lungs of patients suffering from cystic fibrosis (CF) (Navarro *et al.*, 2001), from the respiratory tract of ventilated patients in intensive care units and from burn victims (De Sordi and Mühlschlegel, 2009). Both microorganism's display (a) an ability to form biofilms on the majority of devices used currently; (b) an increased resistance/tolerance to antibiotics when associated with biofilms; (c) documented infections noted for virtually all indwelling devices; (d) opportunistic pathogenicity; and (e) persistence in the hospital environment, reviewed in (Pierce, 2005), Pseudomonas aeruginosa harbours two intimately linked QS systems, the LasI/R system and the RhlI/R system. The first gene pair, lasI and lasR, controls the expression of the second pair, comprised of rhlI and rhlR (Pesci and Iglewski, 1997). The LasI synthase produces 3-oxo-C12 homoserine lactones (HSLs), while RhlI catalyses the synthesis of C4 HSLs (Whitehead *et al.*, 2001). At early stages of growth, the rsaL gene, located in the intergenic region between lasR and lasI, encodes for the RsaL repressor that negatively regulates the Las system (De Kievit *et al.*, 1999). In addition, the quinolone signal molecule 2-heptyl-3-hydroxy-4-quinolone P. aeruginosa quinolone signal (PQS) adds a further level of control in the QS network as it provides a hierarchic link between the Las and Rhl systems(Venturi, 2006). Figure. 4 provides a scheme of the P. aeruginosa QS system. Both LasR

and RhlR, along with their cognate AHLs, affect, either directly or indirectly, the expressions of over 200 genes(Whitehead *et al.*, 2001), and control biofilm formation as well as the expression of an arsenal of extracellular virulence factors and secondary metabolites including elastase, exotoxin A, alkaline protease, chitanase, lectin, rhamnolipid, pyocyanin, phenazine, hydrogen cyanide, superoxide dismutase and catalase (Juhas *et al.*, 2005).

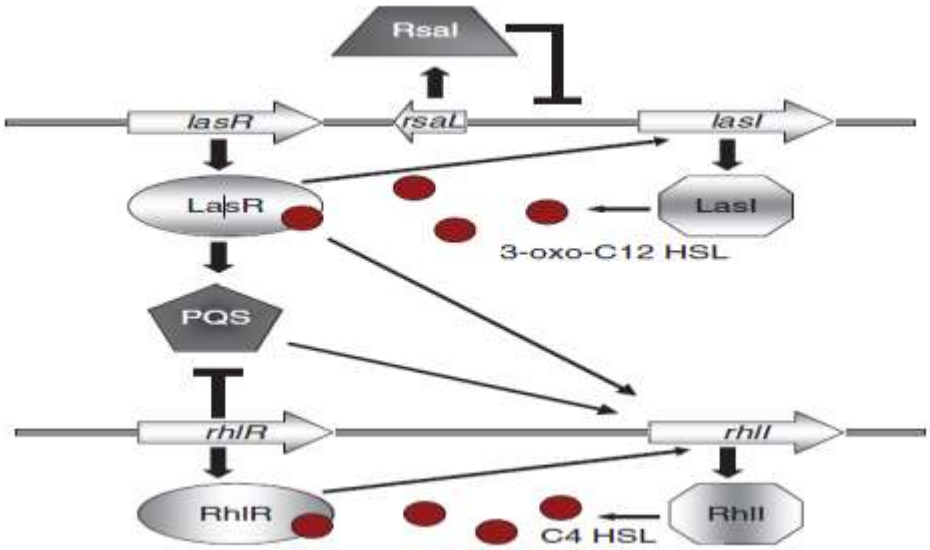

Fig.4. Schematic representation of QS systems in Pseudomonas aeruginosa. The Las system hierarchically regulates PQS production and activation of the Rhl system, which, in turn, represses PQS. A negative control is provided by the Rsal repressor that downregulates the Las system (Whitehead *et al.*, 2001).

Remarkably P. aeruginosa appears to limit the growth of C. albicans in vitro (Kerr *et al.*, 1999) and in burn wounds (Gupta *et al.*, 2005) and eradication of the bacterium by treatment with antibiotics is frequently followed by an increase in the C. albicans population in patients affected by CF(Burns *et al.*, 1999). The P. aeruginosa factors responsible for this effect include pyocyanin, haemolytic phospholipase C, phenazines and several virulence-factor regulators including GacA, LasR, RhlR and RpoN (Hogan *et al.*, 2004) suggesting an ecological role for these elements other than their involvement in causing damage to the human host. Notably, P. aeruginosa only attaches to C. albicans in its filamentous form (Hogan and Kolter, 2002) and this process is mediated by fungal soluble exudates and by the outer glycoprotein-rich layer of the fungal cell wall (Brand *et al.*, 2008) Candida albicans actively responds to this attack: the QS signal molecule, 3-oxo-C12 HSL, which is a component of the LasI/R QS system of P. aeruginosa, blocks the yeast-to-hypha transition or activates the genes promoting the hypha-to-yeast reversion without modifying

fungal growth (Hogan and Kolter, 2002). This fine-tuned response suggests that C. albicans senses the presence of the bacterium and activates a survival mechanism even in conditions normally promoting filamentation. The same study showed that 3-oxo-C12 HSL is effective at a concentration of 200 mM (Hogan and Kolter, 2002). Interestingly, the concentration of HSL in biofilm is around 600 mM, whereas in planktonic cells it varies from 10nM to 5 mM (Charlton *et al.*, 2000). Thus, it is intriguing to speculate that interspecies interaction is restricted to biofilms as the effector molecules are not biologically active in planktonic cultures. Additionally, the C. albicans QS molecule farnesol leads to the downregulation of the P. aeruginosa PQS and, consequently, of pyocyanin production (Cugini *et al.*, 2007). A representation of the cross-talk between C. albicans and P. aeruginosa is shown in Fig. 5.

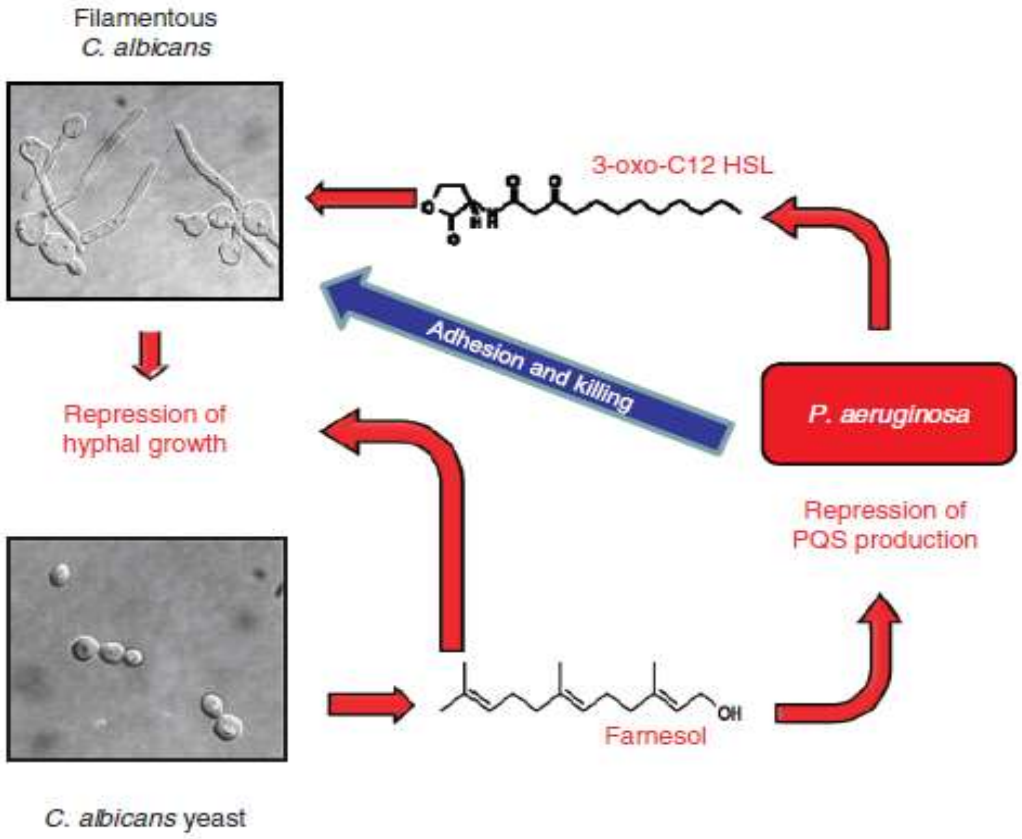

Fig. 5. Schematic representation of the cross-kingdom signaling between Candida albicans and Pseudomonas aeruginosa. QS 3-oxo-C12 HSLs produced by P. aeruginosa inhibit the yeast-to-hypha transition in C. albicans making it impossible for the bacterium to attack the fungus. On the other hand, farnesol further inhibits filamentation in C. albicans and represses the production of P. aeruginosa QS molecule PQS.

3. Conclusions

Once the mechanistic details of fungal QS are established in pathogenic fungi, its value as potential therapeutic target can be assessed. In this scenario, an important further step is to study the fungal pathogen in its natural environment. Therapeutically targeting QS systems may be inefficient if other external inputs in vivo act in an opposite direction. Furthermore, cell morphology, infection spreading and biofilm formation are all influenced by the microbial community coinhabiting the same site. A molecular understanding of bacterial–fungal interactions, such as those between P. aeruginosa and C. albicans, will enable a better approach to study the interface between bacterial pathogenesis and microbial ecology. In fact, virulence traits may derive from two or more synergistic attacks and it is therefore difficult to develop a focused therapy vs. a single virulence component. For this reason, detailed information about fungal–bacterial in vivo interaction is crucial and systems to evaluate those associations need to be developed. However, targeting communication and QS in polymicrobial communities is likely to be a complex affair. Common pathways and cross-signaling will make it difficult to find the right target to generate the desired effect.

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