MINIREVIEW

Quorum sensing and fungal–bacterial interactions in Candida albicans: a communicative network regulating microbial coexistence and virulence

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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 behaviour 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. Moreover, 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.

Introduction
Communication is crucial for life. This would appear to be an obvious remark if referred to evolved species. For a long time microorganisms were believed to behave as individual organisms that primarily sought to find nutrients and multiply. However, little over 20 years ago the surprising discovery of density-dependent intermicrobial communication has led to the realization that microorganisms are also capable of coordinated activities. This phenomenon was first described in bacteria where the ability to behave collectively as a group has obvious advantages such as the capacity to migrate to a more suitable environment, to adopt new models of growth (e.g. sporulation or biofilm formation) or to enable a coordinated pathogenic attack (for reviews, see Miller & Bassler, 2001; Whitehead et al., 2001; Donabedian, 2003; Von Bodman et al., 2003). Bacterial intercellular communication is based on small, self-generated signal molecules called autoinducers (Reading & 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 (QS) (Miller & Bassler, 2001).

More recently this remarkable behaviour has also been described in fungi and there is accumulating evidence that different fungi show QS-dependent phenotypes (reviewed in Chen & Fink, 2006; Hogan, 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.

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 (for review, see Atlas & Bartha, 1986). 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. QS molecules are important players in
these interactions in a fascinating and intricate intra- and interspecific system of microbial communication.

This review 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. The latter is a commonly studied pathogen with a well-characterized QS system (Pesci & Iglewski, 1997; Whiteley et al., 1999; Whitehead et al., 2001; Venturi, 2006).

**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 & Fink, 2008). Indeed, since the discovery of QS mechanisms in fungi, it became evident that these organisms have evolved their own systems (Nickerson et al., 2006; Tseng & Fink, 2008). Because of the diversity of secreted molecules and signals, Monds & 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 interkingdom cross-talk. In fact, the diversity of interkingdom signalling occurring in a myriad of environments has been classified into four categories (Cugini et al., 2008): (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; and (4) two-way communication: multiple signals are exchanged between organisms (Fig. 1).

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 & Eberl, 2006). On the other hand, several studies show that fungi are able to interfere with bacterial QS by producing AHL antagonists (Rasmussen et al., 2005) as well as through the effects of their own QS systems (Cugini et al., 2008).

**QS in C. albicans**

In the healthy host C. albicans can be found as a benign commensal situated in a variety of body locations (Calderone, 2002). 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 Mitchell, 1998; Klotz et al., 2007; Schelenz, 2008). 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.

**Biofilm formation in C. albicans**

*Candida* infections frequently involve the formation of biofilms on implanted devices such as indwelling catheters or prosthetic heart valves as well as in nondevice-mediated infections (Andes et al., 2004; Pierce, 2005; Kumamoto & Vincens, 2005). Biofilms of *C. albicans* consist of polysaccharide-matrix-enclosed microcolonies of yeasts and hyphae arranged in a bilayer structure, and depend on adhesion to substrates and in-between cells (Douglas, 2003; Soll, 2008). Moreover, the cell surface proteins Hwp1 (Nobile et al., 2006), Als1 and Al3 (Nobile et al., 2008), and the cell wall-related protein Sun41 (Norice et al., 2007) have recently been identified as critical for biofilm adhesion and virulence in *C. albicans*, thus suggesting possible therapeutic targets. In fact, the biofilm protects the pathogen from host defences, antibiotics and conventional antifungal agents and provides it with a degree of spatial stability and autonomy in controlling its own microenvironment. Biofilms can be made up of a single species or of multiple species of fungi and bacteria. Furthermore, the selective advantage in adhesion and biofilm development is highly species specific (El-Azizi et al., 2004). Therefore, heterogeneity of the microbial biofilm can have an impact on the response to antimicrobial therapy.

**Morphology**

*Candida albicans* displays considerable morphotypic flexibility, being able to exist in the form of budding yeast, filamenting hyphae or pseudohyphae (Brown et al., 2007). The ability to undergo reversible transitions among these growth forms has obvious advantages, permitting rapid and efficient adaptation to different environmental conditions. However, the efforts in studying *C. albicans* morphology are predominantly justified by the fact that hyphae formation has been identified as an important virulence determinant (Gow et al., 2002; Saville et al., 2003). Morphological change in *C. albicans* is triggered by various environmental cues, including serum, N-acetylglucosamine, ambient pH above 6.5, low O2 and elevated CO2 concentrations, temperatures above 37 °C, starvation and adherence (Soll, 1986; Mühlschlegel & Fonzi, 1997; Klengel et al., 2005; Biswas et al., 2007; Brown et al., 2007). A pattern of overlapping signal transduction pathways mediates this complex response, including components of the CEK1 mitogen-activated protein kinase pathway, the calcium/calmodulin signalling pathway, the Rim101 pathway and the Chk1 two-component signal transduction pathway (for reviews, see Dhillon et al., 2003; Monge et al., 2006; Biswas et al., 2007; Hall et al., 2009), but a major role is played by the Ras1-Cyr1p (adenyllyl cyclase)-PKA-Efg1 pathway (Rocha et al., 2001). In this pathway, the small GTPase Ras1, when activated, stimulates adenylate cyclase (Cyr1p) leading to the generation of cAMP. This second messenger subsequently promotes PKA-mediated activation of transcription factors, including Efg1, that control the filamentous transition (Castilla et al., 1998; Feng et al., 1999; Leberer et al., 2001; Fang & Wang, 2006).

**Role of QS**

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 (> 10^6 cell mL^-1) and that supernatants of stationary phase cultures could cause the same effect enabled identification of the first fungal QS system (for reviews, see Hogan, 2006; Nickerson et al., 2006; Tseng & Fink, 2008).

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 µM) 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 & Fink, 2008) conferring a selective advantage in the environment. Moreover, farnesol has also been demonstrated to enhance antibiotic susceptibility in *Staphylococcus aureus* and to inhibit biofilm formation and lipase activity in this pathogen (Jabra-Rizk et al., 2006; Kuroda et al., 2007). Farnesol has also been shown to decrease the viability of murine macrophages (Abe et al., 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 (Cao et al., 2005; Enjalbert & Whiteway, 2005). Connecting these facts with the observation that farnesol biosynthesis from farnesyl pyrophosphate inhibits the ergosterol pathway (Hornby et al., 2003) suggests that there may be an important role for QS in *C. albicans* antifungal drug resistance. An interesting study by Westwater et al.
(2005) also suggests a role for farnesol in oxidative stress resistance as it induces the transcription of antioxidant-encoding 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. 2 and Table 1.

At present, little is known about the mode of action of farnesol and tyrosol at a molecular level or the effector proteins associated with the propagation of their outputs. Genetic evidence indicates that the histidine kinase Chk1p is important for mediating the effects of farnesol, as a chk1/chk1 mutant is unresponsive to farnesol’s inhibitory effects on both filamentation and biofilm formation (Kruppa et al., 2004). Moreover, it was recently demonstrated that farnesol action involves the recruitment of the transcriptional repressor Tup1 that negatively regulates the yeast-to-hypha transition (Kebaara et al., 2008). Finally, a link between cells with an increased expression of cAMP-repressed genes and cells repressed for hypha formation has been identified (Davis-Hanna et al., 2008). Because several cAMP-controlled outputs are affected by farnesol and dodecanol, it has been suggested that these compounds modulate the activity of the Ras1-Cdc35 pathway, thus leading to an alteration of C. albicans morphology (Davis-Hanna et al., 2008) (Fig. 3). The heterogeneous involvement of QS in morphology-related signal transduction suggests that QS can play a principal role affecting more than one regulatory system in different ways. Clearly, further studies are required to uncover a more mechanistic understanding of this intriguing system.

Candida albicans vs. P. 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 & 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 Cyrlp (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; Inohara et al., 2003).

Both C. albicans and P. aeruginosa can be frequently identified from cases of hospital-acquired infections (Pierce, 2005; Azoulay et al., 2006; Klotz et al., 2007). In fact, they can colonize devices, such as intravenous catheters, that are directly linked to the high rates of serious hospital-acquired infections (Lopez-Ribot, 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; Bakare et al., 2003; Valenza et al., 2008), from the respiratory tract of ventilated patients in intensive care units and from burn victims (Memmel et al., 2004; Pierce, 2005; Willcox et al., 2008). Both microorganisms display (1) an ability to form biofilms on the majority of devices used currently; (2) an increased resistance/tolerance to antibiotics when associated with biofilms; (3) documented infections noted for virtually all indwelling devices; (4) opportunistic pathogenicity; and (5) 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 & 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 (Pesci et al., 1999; 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 (Whiteley et al., 1999), 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, chitinase, lectin, rhamnolipid, pyocyanin, phenazine, hydrogen cyanide, superoxide dismutase and catalase (Juhas et al., 2005).

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 (Kerr et al., 1999; Hogan & Kolter, 2002), 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 & 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 LasR/QS system of P. aeruginosa, blocks the yeast-to-hypha transition or activates the genes promoting the hypha-to-yeast reversal without modifying fungal growth (Hogan et al., 2004). 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 μM (Hogan et al., 2004). Interestingly, the concentration of HSL in biofilm is around 600 μM, whereas in planktonic cells it varies from 10 nM to 5 μM (Charlton et al., 2000). Thus, it is intriguing to speculate

![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.](https://academic.oup.com/femsyr/article-abstract/9/7/990/513734/13-9709615815734)
that interspecies interaction is restricted to biofilms as the effector molecules are not biologically active in planktonic cultures. Additionally, the \( \text{C. albicans} \) QS molecule farnesol leads to the downregulation of the \( \text{P. aeruginosa} \) PQS and, consequently, of pyocyanin production (Cugini \textit{et al.}, 2007). A representation of the cross-talk between \( \text{C. albicans} \) and \( \text{P. aeruginosa} \) is shown in Fig. 5.

The two distinct QS-mediated signalling interactions decrease \( \text{P. aeruginosa} \) killing of \( \text{C. albicans} \) and promote the coexistence of these two species. The biological benefit of this reciprocal response to QS molecules in a eukaryote–prokaryote interaction warrants further investigation from both an ecological and a clinical point of view.

Furthermore, other bacteria also release compounds that interfere with \( \text{C. albicans} \) morphology. Similar to what has been shown for \( \text{P. aeruginosa} \) 3-oxo-C12 HSL, the recently identified QS compound \( \text{cis}-\text{2}-\text{dodecenoyl acid} \) (BDSF), secreted by \( \text{Burkholderia cenocepacia} \), strongly inhibits germ tube formation in \( \text{C. albicans} \) (Boon \textit{et al.}, 2008). Peleg \textit{et al.} (2008) have demonstrated that the pathogen \( \text{Acinetobacter baumannii} \) inhibits filamentation of \( \text{C. albicans} \) leading to attenuation of virulence upon coinfection of the nematode \( \text{Caenorhabditis elegans} \). On the other hand, coincubation of the two pathogens showed that \( \text{C. albicans} \) responds by inhibiting \( \text{A. baumannii} \) growth (Peleg \textit{et al.}, 2008).

Finally, the oral pathogen \( \text{Streptococcus gordonii} \) is able to stimulate filamentation and biofilm formation in \( \text{C. albicans} \) through physical and chemical interaction mediated by the signal compound autoinducer-2 (Bamford \textit{et al.}, 2009).

### QS in other fungal species

Recently, Tseng & Fink (2008) suggested that fungal mating pheromones function as another example of QS. In analogy with peptide signalling molecules from gram-positive bacteria, they regulate cell–cell communication leading not only to mating responses but also to phenotypes related to morphogenesis, invasion and virulence. In addition, Lee \textit{et al.} (2007) described the first density-dependent growth phenotype mediated by a peptide in the fungal kingdom. In a strain of \( \text{Cryptococcus neoformans} \) mutated in the global repressor Tup1, these authors could identify a 11-mer peptide enabling the fungus to grow on solid media only when the population density reaches a threshold of \( 10^5-10^6 \) cells per plate (Lee \textit{et al.}, 2007).

A different kind of fungal signalling molecule is represented by volatile compounds. The volatile alkaline molecule ammonium, for example, is transmitted by yeast colonies in pulses mediating an intercolony signal (Palkova \textit{et al.}, 1997). The release of this compound from a colony and the sensing by the neighbouring one resulted in growth inhibition of the facing parts of both colonies. However, the best-characterized QS molecules are small primary alcohols. Similar to what has been observed in \( \text{C. albicans} \), Chen & Fink (2006) demonstrated that phenylethanol and...
tryptophol act in a cell density-dependent way to induce pseudohyphal growth in *S. cerevisiae*. Interestingly, they also described a complex feedback system involving ammonium, acting antagonistically by repressing both filamentation and aromatic alcohol production (Chen & Fink, 2006).

However, the presence of these compounds does not necessarily indicate their involvement in QS in other species. For example, although phenylethanol and tryptophol are also found in *C. albicans* (Chen & Fink, 2006), they do not elicit a density-dependent response. Therefore, fungal QS, similar to the situation found in bacteria, involves different compounds in a species-specific signalling network.

**Other fungal–bacterial interactions**

Many environments offer favourable conditions for the coexistence of different microbial species, genera and kingdoms. The first interactions analysed in depth concerned the plant rhizosphere where arbuscular mycorrhizal fungi and rhizobacteria act together both promoting plant growth and controlling plant pathogens (Whipps, 2001; Artursson et al., 2006; Jäderlund et al., 2008). Predation interactions also take place in soil and other ecosystems; bacteria mycophagy, for example, enables bacteria to obtain nutrients from living fungi and thus allows the conversion of fungal into bacterial biomass. Thus, mycophagy mechanisms such as necrotrophy, extracellular biotrophy and endocellular biotrophy affect fungal activity, turnover and community structure (Leveau & Preston, 2008).

The most intimate fungal–bacterial association is endosymbiosis. In a remarkable study, Partida-Martinez & Hertweck (2005) unveiled the surprising source of the polyketide rhizoxin, a virulence factor of phytopathogenic fungi belonging to the genus *Rhizopus*. *Burkholderia* spp. endosymbionts produce the compound making the fungi pathogenic, whereas symbiont-free *Rhizopus* species are avirulent (Partida-Martinez & Hertweck, 2005). On the other hand, vegetative spore production by *Rhizopus* requires the bacterial endosymbiont. In fact, bacteria become incorporated into single vegetative spores ensuring their persistence in this type of relationship (Partida-Martinez et al., 2007). Thus, reproduction of the host is completely dependent on endosymbiotic bacteria, which in return provide a highly potent toxin for defending the habitat and accessing nutrients from plants. Mutualistic and symbiotic interactions between bacteria and eukaryotes are hypothesized to have driven the evolution of eukaryotes (Valdivia & Heitman, 2007). This evolutionary hypothesis is justified, for example, by the fact that many biosynthetic pathways are well conserved between bacteria and yeasts (Kelley et al., 2003) and that horizontal gene transfer has been demonstrated from bacteria to fungi enhancing the metabolic potential in the recipient fungus (Hall et al., 2005).

**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 cohabiting 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-signalling will make it difficult to find the right target to generate the desired effect.

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