



*Review*

## ***Quorum sensing mechanisms in fungi***

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**Abstract:** In the environment, cells from microorganisms can communicate to each other through the secretion of signal molecules, so-called autoinducers, which accumulate in the medium as the population density grows. When the concentration of these molecules reaches a threshold, different genes are induced or repressed, and processes such as sporulation, pathogenesis or symbiosis are initiated. These mechanisms, known as *quorum sensing* (QS), were first discovered in bacteria, and more recently have been identified in fungi. The model eukaryote organism for this kind of studies is the dimorphic pathogenic yeast *Candida albicans*. However, QS mechanisms have been described in a variety of fungi with clinical or biotechnological interest. Hence, the study of these mechanisms may be useful to prevent fungal infections, and interesting for its exploitation in industrial biotechnology.

**Keywords:** *quorum sensing*; *Candida albicans*; dimorphic; filamentous fungi

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### **1. Introduction**

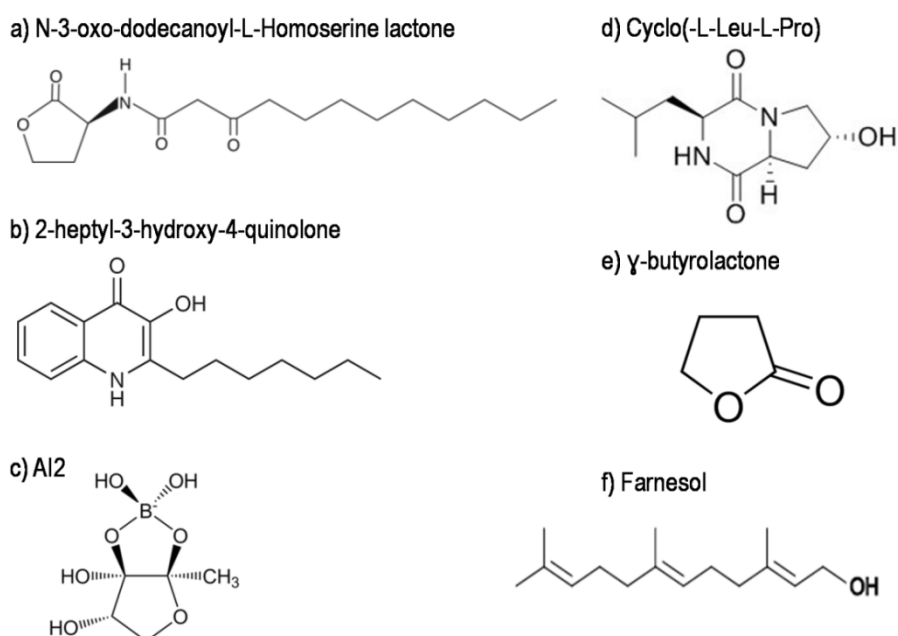
*Quorum sensing* (QS) is a phenomenon of microbial communication and regulation of gene expression. From the 1960's it is known that unicellular microorganisms do not live isolated in their environment, but there is a communication between single cells that allows the population to coordinate their behavior [1]. This sophisticated cell to cell signaling is mediated by small diffusible molecules produced by the microbial population, which accumulate throughout the microbial growth and act as "autoinducers" [2]. Each individual cell senses the concentration of QS molecules (QSM) present in the medium. When the signal molecule reaches a threshold concentration, a number of cell density related processes are initiated [3]. Hence, microbes monitor their population density through QS mechanisms that regulate gene expression of the population in a coordinated manner.

QS mechanisms have emerged among the most important aspects in the study of bacterial behavior. These mechanisms allow the coordination of the physiology of the community and have

supposed an advantage for the adaptation to the rapid changing conditions of the environment. Furthermore, some authors propose the role of these processes as neo-Darwinian mechanisms of evolution with an important participation in the appearance of the earliest multicellular organisms [4,5].

This phenomenon was first studied in bacteria [4,6] and it is known to be involved in the regulation of processes such as pathogenesis, symbiosis, competence, conjugation, nutrients uptake, morphological differentiation, secondary metabolites production, biofilms formation, etc. [7].

The pioneer studies on Gram-negative bacteria showed that QS was controlled by a two components system integrated by a synthase (LuxI), responsible for the production of the QSM N-acyl-homoserine-lactone (AHLs, Figure 1), and a sensor receptor (LuxR), responsible for the detection of the molecule in the environment [8]. After this, quinolones (Figure 1) were found as QSM in other Gram-negative bacteria such as *Pseudomonas aeruginosa* [9]. Later on, QS mechanisms mediated by peptides and the autoinducer 2 (AI-2) were discovered in Gram-positive and Gram-negative bacteria (Figure 1) [4]. More recently,  $\gamma$ -butyrolactone (Figure 1) was found as the QSM used by species of the genus *Streptomyces* [7].



**Figure 1. Examples of QSM from different microorganisms a) AHL b) Quinolone c) Autoinducer 2 d) Cyclic Peptide e)  $\gamma$ -butyrolactone and f) Farnesol.**

QS mechanisms are not restricted to prokaryotes: more recently this phenomenon has been described in eukaryotes, particularly in the pathogenic yeast *Candida albicans* [10], where the sesquiterpene alcohol farnesol (1-hydroxy-3,7,11-trimethyl-2,6,10-dodecatriene) was described as the QSM (Figure 1) [11]. Over the years, other molecules, such as aromatic alcohols, tyrosol, dodecanol,  $\gamma$ -butyrolactone, or  $\gamma$ -heptalactone, have been identified as mediators of QS processes in eukaryotic organisms as we will see later.

The fact that that this kind of microbial communication is not restricted to member of the same species, and even of the same kingdom, is well known nowadays. Cross-talking has been described between different species of bacteria, bacteria and fungi, and even between bacteria or fungi with

their plant [12] or mammalian [13] hosts. It is known that opaque cells of *C. albicans* are able to attract leukocytes to the site of infection [14], or that certain plants produce bacterial QSM [15].

On the other hand there are organisms that have evolved strategies to disrupt the QS signaling of other microorganisms. The phenomenon, called quorum quenching [16], usually leads to inactivation/degradation of the QSM [17]. This strategy prevents the accumulation of QSM in the microorganism environment, preventing the initiation of QS mediated processes [18].

The study of QS mechanisms in fungi has been a very hot topic during the past 15 years, there are more than 230 papers dealing with this topic indexed in the Web of Science (WOS) with an increasing number of citations over the years, currently higher than 8000.

The main objective of this review is to provide a general overview about QS mechanisms described in fungi, and their potential biotechnological applications such as improvement of industrial processes or prevention of fungal infections.

## 2. *Quorum Sensing in Candida Albicans*

The model for the study of QS mechanisms in fungi is the yeast *C. albicans*. This dimorphic fungus is found in human as a commensal or as an opportunistic pathogen in immunocompromised individuals. Is a common mycosis, and may also occur in animals suffering malnutrition and poor management, or treated previously with antibacterial and/or immunosuppressive therapy [19]. In healthy individuals *C. albicans* resides in the gastrointestinal, vaginal, and oral tracts, where it is considered to be part of the normal flora. However, in certain situations *Candida* is able to invade the mucosal surface and disseminate into the bloodstream causing systemic disease [19].

The dimorphic nature of *C. albicans* consists of the switching from yeast to hyphal growth under certain conditions, which is crucial to its pathogenicity and may limit nutrient foraging behavior. This switch in morphology is governed by many environmental signals acting through several well-established signaling cascades [20]. QS mechanisms are also involved in the morphological transition. Two signals with opposite effects have been described as QSM in this yeast: farnesol and tyrosol [10,21]. Farnesol prevents the differentiation from yeast to hyphal growth and, therefore, the synthesis and release of this molecule could play a role in pathogenesis.

*E,E*-farnesol is a sesquiterpene alcohol, which is an alcohol made up of three isoprene units. It is an intermediate in sterol biosynthesis, but the subsequent pathways to secrete the molecule are unknown. On the other hand, tyrosol [2-(4-hydroxyphenyl)] stimulate germ-tube formation and hyphal development in the early and intermediate stages of *C. albicans* growth [21]. This alcohol is related to the amino acid tyrosine, and requires the biosynthetic pathways of the aromatic amino acid. Exogenous addition of tyrosol inhibits biofilms formation in *Candida* species, and enhances their susceptibility to antifungals [22]. In addition, dodecanol, a 12-carbon alcohol which is not a physiologically relevant QSM, as well as 3-oxo-C12-HSL (QSM secreted by *P. aeruginosa*, with also a 12-carbon backbone), have activity against *C. albicans* filamentation [23]. Both appear to influence morphogenesis inhibiting the AMP (cAMP)/protein kinase A (PKA) signaling pathway [24].

The morphological changes in *C. albicans* are regulated at different levels, connecting diverse signal transduction pathways dependent on external stimuli.

Hyphal development can be regulated through the modulation of the cAMP/PKA pathway. It has been postulated that farnesol can affect filamentation by inhibiting the cAMP pathway through the inhibition of the activity of the *Candida* adenylyl cyclase, Cyr1p [25]. Activation of the cAMP-

PKA pathway down-regulates the expression of NRG1, the major repressor of hyphal development. Moreover, farnesol is able to block the protein degradation of Nrg1, repressing the expression of Sok1, the kinase required for Nrg1 degradation [3]. The transcription repressor Cup9 has also been found to be responsible for the regulation of SOK1 expression in response to farnesol inhibition. Interestingly, farnesol inhibits Cup9 degradation mediated by the N-end rule E3 ubiquitin ligase, Ubr1 [3].

The *CEK1* mitogen-activated protein kinase (MAPK) pathway is also implicated in the response to farnesol [26]. The histidine kinase (Chk1) and the zinc finger 1 (Czf1) from *C. albicans* [24,27] have also been identified as additional factors important for the response to farnesol [28]. Farnesol also modulates the transcription levels of *tup1*, a major repressor of the morphological transition [27]. And more recently, it has been shown that farnesol reception requires a signaling pathway that includes the conserved small GTPase Ras and its downstream effector, suggesting that there is a considerable amount of cross talk between the systems [29].

cDNA microarray analysis of *C. albicans* biofilms exposed to farnesol showed a total of 274 responsive genes, with 104 of them up-regulated and 170 down-regulated [30]. Important changes were detected in the hyphal formation-associated genes (*tup1*, *crk1*, and *pde2*), and a number of other genes with roles related to drug resistance, cell wall maintenance, iron transport and genes encoding heat shock proteins.

In addition, formation of biofilms in *C. albicans* has been documented as a form of resistance. Different approaches have been tested to enhance the susceptibility of these structures to antimycotic drugs since traditional antimicrobial approaches are often ineffective [31]. Farnesol inhibits biofilm formation by *C. albicans*, being this regulation of clinical relevance [32].

The morphology and biofilms formation in this fungus is regulated in a population-density manner due to the availability of nutrients as the population density grows, and the competition for a natural niche [11,31].

Furthermore, the association between *Candida* and other pathogens, such as *P. aeruginosa*, increases the complexity of the infections. Farnesol can inhibit the virulence factors from some bacteria [33], and has also been reported that co-cultivation of *C. albicans* and the nonpathogenic filamentous fungus *Aspergillus nidulans* results in an farnesol-dependent inhibition of *A. nidulans* growth [34].

Interkingdom communication through QS mechanisms has been reported between the caries-promoting bacterium *Streptococcus mutans* and *C. albicans* in polymicrobial biofilms, which are of medical importance [35]. Dual-species biofilms reached higher biomass and cell numbers than mono-species biofilms. *Candida* was able to stimulate the QS systems of *S. mutans*, changing the virulence properties of the bacterium. In another example of interkingdom communication, the Gram-positive bacterium *Enterococcus faecalis* inhibits hyphal morphogenesis and virulence of *C. albicans* [36]. Both are found as commensals in the same niches and frequently induce polymicrobial infections. Using a *Caenorhabditis elegans* model of infection, it was shown that *E. faecalis* and *C. albicans* negatively impact each other's virulence, and the inhibition was partially dependent on the Fsr QS system [36].

Finally, recent evidences suggest that other yeasts with biotechnological relevance, like *Saccharomyces cerevisiae*, exhibit QS type of regulation, and that the signal molecules are aromatic alcohols [37]. Opening the door to the modification of these mechanisms to improve industrial processes carried out by the yeast. In this case, while the dimorphic pathogen *C. albicans* produces tyrosol, the budding yeast *S. cerevisiae* produces tryptophol and phenylethyl alcohol. Interestingly,

the signaling network controlled by tryptophol and phenylethylalcohol in *S. cerevisiae*, presents many similarities with the QS pathways described in Gram-negative bacteria [37].

### 3. Other Dimorphic Fungi

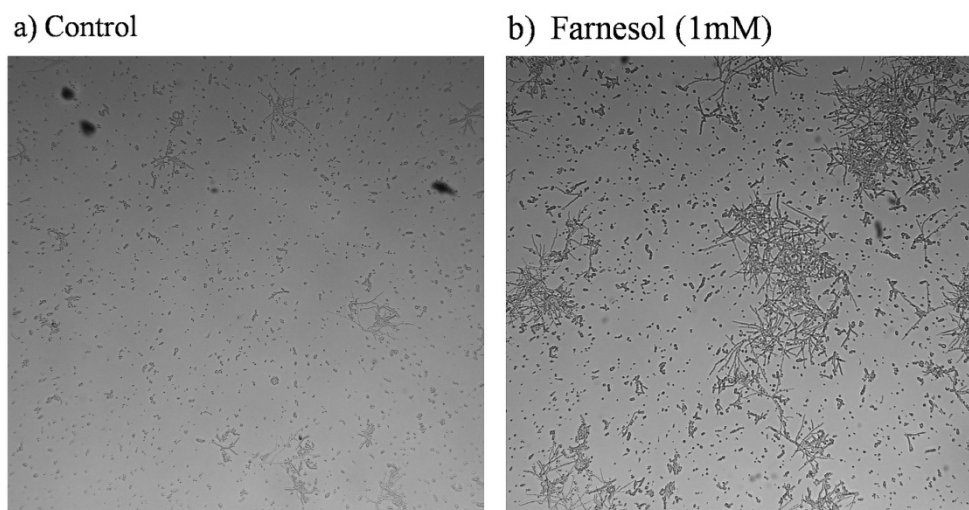
Fungal dimorphism is an environmentally controlled reversible interconversion of morphology, particularly between yeast and mycelial morphologies [38]. The study of this phenomenon is interesting, because many dimorphic fungi are of plant or animal pathogens. Numerous environmental parameters can induce the yeast-mycelium morphological transition, including temperature, pH, nutrient levels, nitrogen source, carbon dioxide levels, transition metals, chelating agents, and inoculum size or initial cell density [39].

The effect of inoculum size has been well studied in fungi such as *Ceratocystis ulmi*, *Ophiostoma piceae*, *Ophiostoma flocculosus*, *Histoplasma capsulatum*, *Mucor rouxii*, *Penicillium isariaeforme*, *Penicillium marneffeii*, *Neurospora crassa*, *Cryptococcus neoformans* and *C. albicans* [40]. However, the QS mechanisms underlying this morphological transition have only been studied in a few fungi.

Dutch elm disease has been classified as one of the biggest epidemic forestry diseases on a worldwide level. The disease caused by the fungus *Ophiostoma ulmi* and its aggressive variant *Ophiostoma novo-ulmi*, has destroyed the majority of American elms and continues to kill trees every year. The fungus is transported to the elm trees by an intermediate vector, the bark beetle [41]. The spores from the fungus accumulate in the xylem vessels and are dispersed by translocation. The ability to undergo morphological change is a crucial factor for its virulence, and in *Ceratocystis (Ophiostoma) ulmi* the inoculum size affects its morphology. Hornby et al. [42] showed that when inoculated at  $>10^6$  spores per ml in the growth medium, cells develop as budding yeasts, while when inoculated at concentrations  $<10^6$  spores per ml cells develop as mycelia. The cause of this inoculum size-dependent effect was because of the presence of QSM in the medium that accumulated throughout the growth of the fungus. These molecules were extracted with the organic solvent ethyl acetate, and the QS activity acquired by the organic solvent could be added back to fresh medium in a dose-dependent manner. This activity was specific for *C. ulmi* and had no effect on *C. albicans* or the photomorphogenic fungus *P. isariaeforme*. The inoculum size effect is a manifestation of a QS mechanism [42]. Further studies in *O. ulmi*, showed that the QSM mediating these processes could be fusel oils and branched chain amino acids [43]. Addition of the branched-chain amino acids or other compounds detected in the spent medium, 2-methyl-1-butanol, 4-hydroxyphenylacetic acid or methylvaleric acid, decreased germ tube formation by more than 50% in *O. ulmi* cultures. These studies on the morphological transition mediated by QSM may have a great impact on the prevention of plant diseases.

On the other hand, *O. piceae* is a wood-staining dimorphic fungus, causal agent of pine and spruce discoloration [44]. Although not being a pathogenic species, which associates with non aggressive bark beetles, the infection results in substantial economic losses in the forestry industry [44], and its biological control is desirable. The strain *O. piceae* CECT 20416 produces an extracellular sterol esterase (OPE) with activity on triglycerides, and esters of *p*-nitrophenol and cholesterol that presents a great biotechnological interest [45]. The effect of inoculum size on the morphology of this fungus has been described [39]. Furthermore, QS mechanisms mediated by the signal molecule farnesol have been observed (Figure 2). The molecule accumulates in the exponential phase of growth and seems to modulate the expression of the transcriptional repressor

Tup1 [39]. Interestingly, the effect of farnesol was opposite to that observed in *C. albicans*, leading to the development of mycelium. These mechanisms also influence the secretion of OPE increasing its production [39]. This effect of inoculum size on the morphology has also been observed in the albino strain of *O. piceae* PcF2A29.



**Figure 2. Micrographs (10X) of *O. piceae* CECT 20416 fungal cultures at 120 h after inoculation.** Morphological changes in the absence (a), or presence (b) of exogenous farnesol.

In *O. floccosum*, an attractive biocontrol agent against blue-stain fungi, QS mechanisms also control yeast-mycelium dimorphism [46]. In a defined culture medium with L-proline, a high inoculum size was the principal factor that promoted yeast-like growth. Three cyclic sesquiterpenes were found to be QSM responsible for yeast development. These studies have a great potential for the conservation of wood quality.

Finally, the dimorphic pathogenic fungus *C. neoformans*, etiologic agent of cryptococcosis, has been shown to regulate its growth and virulence using QS mechanisms [47] mediated by a variety of peptide QSM [48]. The sequence of these peptides, named QS-like peptide (QSP1-4), and their functional properties are described in the Quorumpeps database [49].

#### 4. Filamentous Fungi

Only recently QS mechanisms have been reported in filamentous fungi. Species from the genera *Aspergillus* and *Penicillium* seem to coordinate processes using signal molecules [50–54]. However, the necessity of this kind of mechanisms is arguable in non-unicellular microorganisms.

In these fungi, the secondary metabolism is induced as the population density grows. This phenomenon has already been described in other microorganisms as a competition strategy, aiming the capture nutrients and niche occupation [55].

Multicolic acid and related derivatives are proposed as the QSM in *Penicillium sclerotiorum*. Exogenous addition of an ethyl acetate extract of supernatants from *P. sclerotiorum* Strain M, which produces the secondary metabolite sclerotiorin, to cultures of the same strain, resulted in a significant

(1.8-fold) increase in sclerotiorin yield. However, the greatest enhancement in sclerotiorin production was obtained when spent medium containing  $\gamma$ -butyrolactone from Strain M was added to cultures of *P. sclerotiorum* Strain S, a low sclerotiorin producing strain [50]. Effect of farnesol on the morphology and cellulase production of *Penicillium decumbens* has also been investigated [52]. In this occasion addition of 1 mM exogenous farnesol promoted the growth of hyphae, making possible and facilitating a higher cellulase secretion. Nevertheless, monitoring the accumulation of QSM during the exponential growth phase of the fungi would be desirable.

In the case of species from the genus *Aspergillus*, it has become apparent recently that also QS mechanisms are used to influence population-dependent behavior such as morphogenesis and secondary metabolite production. There are several works reporting the existence of diverse signal molecules.

In *Aspergillus terreus*, a pharmaceutically relevant fungus due to its ability to produce a wide variety of secondary metabolites, it has been described the use of linoleic acid-derived oxylipins to improve the production of the secondary metabolite lovastatin (cholesterol-lowering drug) during fungal fermentations [51]. In this case, lovastatin production was enhanced up to 1.8-fold upon exogenous addition of the oxylipin precursor linoleic acid to low cell density cultures due to transcriptional up-regulation of the genes involved in lovastatin biosynthesis. Linoleic acid-derived signaling molecules are potentially involved in fungal cell–cell communication.

Later on, butyrolactone was proposed as the QSM in *A. terreus* based on its ability to affect both lovastatin and its own production. Exogenous addition of 100 nM butyrolactone I resulted in 2.5-fold increase in lovastatin production regulating the transcription of the genes involved in its biosynthesis, and also resulted in increased endogenous levels of butyrolactone I (2.5-fold), which suggests an auto-stimulatory function [53].

Another strain of *A. nidulans*, producer of the secondary metabolite penicillin, releases at least one small diffusible molecule during its growth cycle, which accumulates at high cell density. This QSM regulates growth profile and secondary metabolite production in cultures at low cell density [54]. Addition of ethyl acetate, extracts from stationary phase culture supernatants to low cell density cultures of *A. nidulans* resulted in the abolition of the lag phase, decrease in the final cell dry weight, and increased penicillin production. The bioactive molecule present in the stationary phase extract was purified and identified as  $\gamma$ -heptalactone [54].

## 5. Conclusions

Study of the QS mechanisms involved in the coordination of important processes of microbial populations is of great interest. Particularly, in fungi we are just beginning to understand the molecular mechanisms implicated and to know the QSM that regulate this phenomenon, and how these mechanisms interact with other regulation pathways in the cell. In the case of dimorphic fungi it has been demonstrated that the accumulation of autoinducers in the medium regulates the population behavior in a cell density-dependent manner. However, is still not completely clear whether in filamentous fungi these mechanisms are auto-regulatory rather than pure sensors of culture density.

The potential of studying QS processes in fungi is huge since among the species that regulate their virulence through these mechanisms there are human, animal and plant pathogens. Moreover, some fungal species with great biotechnological interest regulate the production of enzymes or

secondary metabolites by means of QS mechanisms, opening a window for its exploitation in industrial biotechnology.

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## Conflict of Interest

Author declares no conflict of interests in this paper.

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