Quorum Sensing

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Abstract

Quorum sensing (QS), a density-dependent signalling mechanism of microbial cells, involves an exchange and sense of low molecular weight signalling compounds called autoinducers. With the increase in population density, the autoinducers accumulate in the extracellular environment and once their concentration reaches a threshold, many genes are either expressed or repressed. This cell density dependent signalling mechanism enables single cells to behave as multicellular organisms and regulates different microbial behaviours like morphogenesis, pathogenesis, competence, biofilm formation, bioluminescence, etc… guided by environmental cues. In general, Gram-negative bacteria use acylated homoserine lactones as autoinducers and Gram-positive bacteria use processed oligo-peptides to communicate. Recent advances in the field indicate that cell-cell communication through autoinducers occurs both within and between bacterial species. The discovery of filamentation control in pathogenic polymorphic fungus candida albicans by farnesol revealed the phenomenon of QS in fungi as well. The phenomenon of quorum sensing inhibition or "Quorum Quenching" (QQ) can be achieved through the enzymatic degradation of the auto inducer compound, the blockage of autoinducers production, or the blockage of their reception through the addition of some compounds "inhibitors" that can mimic them.

Introduction

"Quorum" is a Latin word. It means the number of members of a group required to carry out an activity legally. It is a process of cell-to-cell communication in microbes that enables them to coordinate certain behaviors based on their population density (Postat, J., & Bousso,P., 2019). This process relies on the production, release and detection of chemical signaling molecules called Autoinducers. As environmental conditions often change rapidly, bacteria need to respond quickly in order to survive. Different species of bacteria produces different autoinducers. This allows each individual bacteria to count how many other bacteria are there of their own kind. When a bacterial population reaches a high enough density, the Concentration of autoinducers in the environment surpasses a threshold level, triggering a coordinated response from the entire bacterial community i.e., virulence or bioluminescence.

Quorum Sensing

Quorum sensing (QS) is a bacterial cell-cell communication process that involves the production, detection, and response to extracellular signaling molecules called autoinducers (AIs). AIs accumulate in the environment as the bacterial population density increases, and bacteria monitor this information to track changes in their cell numbers and collectively alter gene expression. QS Controls genes that direct activities that are beneficial when performed by groups of bacteria acting in synchrony. Processes controlled by QS include bioluminescence, sporulation, competence, antibiotic production, biofilm formation, and virulence factor secretion (Williams, P., & Cámara, M. 2009).

Discovery

Initially, QS was regarded to be a specialized system of *Vibrio fischeri* wherein LuxI / LuxR transcriptional activator and autoinducer system mediate cell density dependent control of Lux gene expression important for the production of luminescence. It was observed that liquid cultures of *V. fischeri* produced light only when large numbers of bacteria were present (Von Bodman *et al*., 2003). These bacteria exist as free-living cells or as symbionts in the light producing organ of an animal host, such as the Hawaiian bobtail squid.

Quorum Sensing molecules: Each individual bacterium is capable of producing a signaling molecule (inducer) and each bacterium also has a receptor for the inducer. Signals lead to activation and suppression of certain genes leading to changes in metabolic activity, morphology, mobility, aggregation and association with other cells of same species or different species. Three main types of inducers molecules:

1) Acyl-homoserine lactones (AHLs): Commonly used by Gram negative bacteria.

2) Autoinducer peptides (AIPs): Commonly used by Gram negative bacteria.

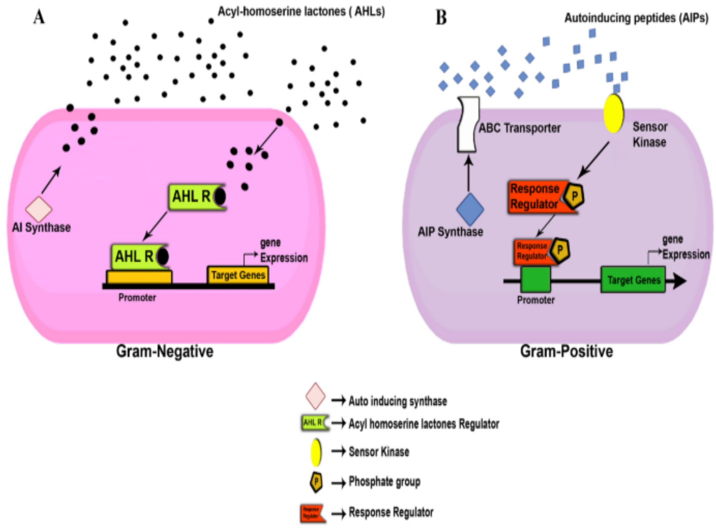
3) Autoinducer-2 (AI-2): A universal signaling molecule used by both Gram positive and Gramnegative bacteria.

Albuquerque and Casadevall detailed four criteria that must be fulfilled for a compound to be classified as a signaling molecule (Albuquerque & Casadevall, 2012).

1. Accrue in the extracellular environment throughout microbial growth
2. A mass in a concentration that is proportional to the density of the population cells
3. Result in a coordinated response across the population
4. When appended to the culture exogenously, propagate the QS phenotype.

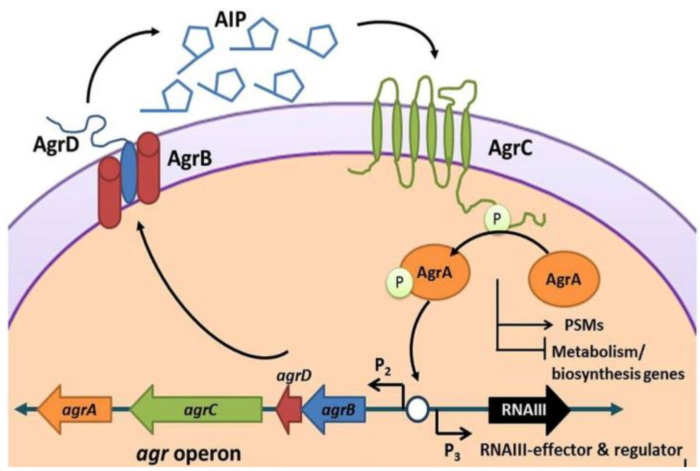
Mechanisms

Synthesize and release of signaling molecules into the environment. These molecules can be species specific or universal to allow communication across species. In Gram negative bacteria, acyl-homoserine lactones (AHLs) are the primary autoinducers, whereas Gram positive bacteria often use small peptides. As the bacterial population grows the concentration of autoinducers in the surrounding environment increases. These molecules diffuse through cell membranes and accumulate in the environment or within bacterial cells. When the concentration of autoinducers reaches a critical threshold, it triggers the next steps in quorum sensing. Bacteria have receptor proteins, usually located on their cell surface or within the cell, that detect the presence of autoinducers. In Gram negative bacteria, the receptor is typically a cytoplasmic protein that binds to AHLs, while in Gram-positive bacteria, the signaling peptides bind to membrane bound receptors. Once the receptor binds to the autoinducers, it leads to the activation or repression of specific genes. The activation of specific genes leads to a coordinated response across the bacterial population, allowing them to perform complex, multicellular behaviors that increase their survival and adaptability.



(Source: Suresh, S. *et al.*, 2021)

QS mechanism in *Staphylococcus aureus*



(Source: Quave, C. L., & Horswill, A. R., 2014)

AgrA - response regulator; AgrB - exporter (transmembrane protein); Agrc - sensor kinase receptor (transmembrane protein); AgrD - encodes for the production of Autoinducing peptides.

Staphylococcus aureus is a type of pathogen that causes infection to the skin and soft tissue and can lead to a variety of more severe diseases such as osteomyelitis, pneumonia and endocarditis. *S. aureus* uses biofilms in order to increase its chances of survival by becoming resistant to antibiotics. Biofilms help *S. aureus* become up to 1500 times more resistant to antibiofilm agents, which try to break down biofilms formed by *Staphylococcus aureus* (Wu, X., *et al*., 2024).

Microorganism	Major Signal Molecules	Regulatory System	Group Derived Benefits
Bacillus subtilis	ComX CSF(PhrC) PhrA, -E, -F, -K, -H	ComP/ComA Rap proteins	Competence, sporulation, Biofilm formation, Antibiotic production.
Myxococcus xanthus	A-signal C-signal	SasSRN	Fruiting body formation or Sporulation
Pseudomonas aeruginosa	3O-C12-HSL C4-HSL	LasI/LasR RhlI/RhlR OscR (orphan)	Structured biofilm formation, Virulence factor
Staphylococcus aureus	AIP-I, AIP-II, AIP-II, AIP-IV	AgrC/AgrA	Biofilm formation, Virulence factors
Streptococcus mutans	CSP (ComC) XIP (ComS)	ComD/ComE ComR	Bacteriocins, Biofilm formation, Competence.
Streptococcus pneumoniae	CSPs	ComD/ComE	Competence, Fratricide, Biofilm formation, Virulence.
Vibrio harveyi	HAI-1, CAI-1, AI-2	LuxLM/LuxN LuxP/LuxQ	Bioluminesence emission, Symbiosis.

(Source: Li, Y. H., & Tian, X., 2012).

Quorum Sensing in fungi

Quorum sensing is also ubiquitous in various fungal species. It was firstly discovered in *Candida albicans* is a dimorphic yeast, that undergoes transformations, e.g; converting from a yeast to hyphal cell morphology under specific conditions.

Farnesol and tyrosol, two signaling compounds produced by *C. albicans* have been reported as QMS with opposite effects. Farnesol, acts as a negative regulator of hyphal formation, whereas tyrosol accelerates hyphal development. Other QS molecules produced by fungi includes Phenylethanol, trypoptol etc.. (Kruppa, M., 2009).

Viruses

The viruses communicate with each other to ascertain their density compared to potential hosts. They use this information to decide whether to enter **lytic** or **lysogenic** life-cycle. (Erez Z *et al*., 2017). By synchronizing their life cycles, bacteriophages can maximize their impact on the host population.

Social insects (Ants)

In ants, quorum sensing is primarily based on pheromones chemical signals that ants release and detect to communicate with each other. Species like *Temnothorax albipennis* (rock ants) use quorum sensing in relocating to a new nest (Pratt, S.C. 2005). In species like *Lasius niger*, quorum sensing helps in selecting the best food sources.

Quroum Sensing in Agriculture

Many plant pathogens, such as *Pseudomonas* and *Xanthomonas* species, rely on QS to regulate virulence factors (e.g., toxins, enzymes) that contribute to disease. By interfering with QS signals, either by disrupting communication or by producing signal molecules that block pathogen QS, researchers can reduce the ability of these pathogens to cause harm. QS regulates biofilm formation by beneficial bacteria, which can help create a protective environment for plants against soil borne diseases.

QS can be used to stimulate natural plant defense mechanisms. For example, plants might produce signaling molecules in response to QS factors from beneficial microbes, inducing resistance against pests and pathogens. QS plays a role in regulating interactions between plants and mycorrhizal fungi, which help plants absorb nutrients, particularly phosphorus.

Quorum Quenching

Quorum quenching is the process of preventing quorum sensing by disrupting signalling. This is achieved by inactivating signalling enzymes, by introducing molecules that mimic signalling molecules and block their receptors, by degrading signalling molecules themselves, or by a modification of the quorum sensing signals due to an enzyme activity. (Pietschke, C *et al.*, 2017). The strategies involved in Quorum Quenching are, 1. Inhibition of synthesis 2. degradation 3. Interference with signal reception. Many quorum quenching chemicals have been identified such as Ajoene, Baicalein and Cinnamaldehyde. These includes halogenated furanones from the seaweed *Delisea pulchra,* which are structural mimics of quorum-sensing chemicals. Enzymes such as AHL-lactonase, AHL-acylase and paraoxonases degrade AHLs.

Conclusion

Humans have become effective communicators during our short time on Earth. However, our communication pales in comparison to bacteria. Quorum sensing using autoinducers allows bacteria to communicate within and between species. With the latter, they can either compete or collaborate with other species based on the autoinducer "message" they receive.

QS is a crucial mechanism through which microbes communicate and coordinate behaviors. This regulation allows bacteria to adapt to changing environments, enhance their survival, and establish infections. QS among various bacterial species and also with their hosts has highlighted their importance in microbial ecosystems and symbiotic relationships. As it affects nutrient cycling, biodegradation, and interactions in microbial communities it plays a significant role in environmental microbiology. As it affects nutrient cycling, biodegradation, and interactions in microbial communities it plays a significant role in environmental microbiology.

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