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Quorum Sensing: Survival Strategy of Microbes

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A B S T R A C T

Sounds strange that bacteria can talk to each other, though not verbally like humans but with the help of chemical signals which bacteria produce by forming biofilm, producing virulence factors or developing antibiotic resistance. The process starts only when the bacterial cell reach a threshold density enough to produce signals which can be detected by the receptors. This unique communication system is very specific to every bacteria and therefore a clear understanding of the quorum sensing mechanism of bacteria helps in developing various techniques for combating the attack of deadly pathogens, production of antibiotics and also using quorum sensing in different sectors of microbiology.

Introduction

Bacteria can sense an increase in the cell population density by the production and excretion of low-molecular-weight signaling molecules (autoinducers, AI). When bacterial population reaches the critical level of density, AIs bind to specific receptor regulatory proteins, which induce the expression of target genes. By means of Als, bacteria transmit information between bacteria belonging to the same or different species, genera, and even families (Asad and Opal, 2008). This type of mechanism is called Quorum Sensing (Diggle and Williams, 2017; Waters and Bassler, 2005). Bacteria of different taxonomic groups use the Quorum sensing (QS) systems in regulation of a broad range of physiological activities. These processes include virulence, symbiosis, conjugation, biofilm formation, bioluminescence, synthesis of enzymes, antibiotic substances (Papenfort and Bassler, 2016). Here we review different Quorum sensing systems of bacteria and the role of QS in bacterial communication. This unique communication system is very specific to every bacteria. A clear understanding of the quorum sensing mechanism will help in designing activities to inactivate the signals of disease-causing pathogens, food spoilers, fermenters and biofilm formers(Hughes and Sperandio, 2008).

Communication among Gram negative bacteria

Among the Gram-negative spectrum of bacteria, a variety of acyl homoserine lactones (AHL's) is produced for inter-species, intra-species, and inter-kingdom communication (de Kievit and Iglewski, 2000).

Vibrio fischeri

The idea about bacterial communication came into existence nearly 40 years ago with *Vibrio fischeri*. Bioluminescence in *Euprymnascolopes* (Hawain squid) is due to quorum sensing mechanism of the *Vibrio fischeri* (Nealson *et al.,* 1970) which is living in symbiotic association with squid. When the bacteria multiply and reach at a particular threshold density chemical signals in the form of proteins are produced i.e., LuxI and LuxR controlling the expression of luciferase operon (light production) (Waters and Bassler, 2005). Among the two proteins, LuxI produces N-(3-oxododecanoyl)-L-homoserine lactone (3OC6-HSL) and LuxR is a transcriptional precursor which is activated by this auto inducer to increase transcription of the luciferase operon. When the produced signals reach maximum level they form LuxR-AHL complex activating the luciferase enzyme encoded by luciferase operon (Stevens *et al.,* 1994) and thus causing the light organs to illuminate.

E. coli

Quorum sensing in *Escherichia coli* has been observed for invading the host environment employing chemical signals like indole, which results in increasing the antibiotic resistance or expression of virulence among its bacterial population (Vega *et al.,* 2013). Homologues of LuxR (Wang *et al.*, 1991) and noradrenaline (NA) (Hughes and Sperandio, 2008) results in abnormal division in cell causing bloody diarrhoea due to enterohaemorrhagic *E. coli* (EHEC), (Knutton *et al.,* 1987; Moon *et al.,* 1983). EPEC contains a Shiga-like toxin which leads to apoptosis of the endothelial cells causing bloody diarrhea (Karmali *et al.,* 1983; Tu *et al.,* 2003). Around the world these chemical signals activate the virulence gene required for invasion of the host cell (Sperandio *et al.*, 2003; Tannock *et al.*, 2005).

Salmonella

This facultative anaerobic bacterium (Daoust, 1997; Ibarra and Steele-Mortimer, 2009) uses the mechanism of bacterial communication for antibiotic resistance, expression of virulent genes for host cell invasion. In the case of *Salmonella,* several auto inducing molecules like SdiA control some genes directed for resistance (Ahmer *et al.,* 1998; Walters and Sperandio, 2006). Indole also acts as a signaling molecule, but the interesting part is though *Salmonella* does not produce indole but in mixed cultures, if indole is present it tends to increase the tolerance against a wide spectrum of antibiotics making the disease control tactics difficult (Vega *et al.*, 2013). LuxS (signaling molecule) act as a precursor for the transcription of a number of virulent genes. It activates the Type III secretion system required by the bacteria for injecting the virulent genes (Mota and Cornelis, 2005) in the host's defense system for colonization the host cell (Wang *et al.*, 2001)

Burkholderia thailandensis

This Gram-negative, non-fermenting, motile bacillus is a natural inhabitant of soil and aetiological agent of melioidosis, well known to form bio-film helping the bacteria to subsist in the host and natural environment. Bio-film formation is mediated by AHL quorum sensing mechanism for signal production (LuxI) and signal receptor (LuxR59) also acting as transcriptional factor. The signals so produced are a combination of three acyl- homoserine lactones (QS-1, QS-2 and QS-3). Of which QS-1, a pair of BtaI1-BtaR1 which aids in development of biofilm. QS-2 is a pair of BtaI2-BtaR2 and *N*-3-hydroxy-decanoyl homoserine lactone (3OHC10-HSL) and QS-3 consists of BtaI3-BtaR3 and *N*-3-hydroxy-octanoyl homoserine lactone (3OHC8-HSL) (Tseng *et al.,* 2016).

Pseudomonas aeroginosa

This gram-negative, citrate, oxidase and catalase (Walker *et al.,* 2004) positive group of bacteria resides in soil, water (Wong *et al.*, 2012) having around 100 genes controlled by quorum sensing encoding the virulence (Singh *et al.,* 2000; Yoon *et al.,* 2002). *P. aeroginosa* enters into the lungs, forms biofilm, secretes deadly virulent factors like proteases, hydrolases damaging the lung tissue and thus causing respiratory infection (Smith and Iglewski, 2003). In this bacteria, the whole process of invasion to the host lungs is by using auto inducers LasIR and Rh1IR which activates the target genes of the bacterium for causing infection (Gambello and Iglewski, 1991; Lu *et al.,* 2018; Ochsner *et al.,* 1994).

This bacterium also expresses the cas gene of CRISPR using QS system which can shootup CRISPR-Cas target of foreign DNA and promote CRISPR's adaptation at high cell density ensuring its function under the threat of phage infection. CRISPR-Cas are popular gene editing tools for knocking out / knocking down any gene of interest causing mutation. Therefore, inhibition of quorum sensing can help in restraining CRISPR-Cas adaptive system of immunity for medical relevance (Hogan, 2006).

Communication among gram positive bacteria

Unlike, gram negatives, gram-positive bacteria induce the production of oligopeptides (auto inducing peptides, AIP's) instead of acyl homoserine lactones for communication. These bacteria are known for their high resistant nature by developing spores to survive at times of unfavorable conditions, the strategy for survival is coordinated by bacteria through bacterial communication. A slight difference lies in the mechanism of expression in gram-positive as these peptides cannot penetrate the cell wall on their own and therefore, need an oligopeptide exporter to translocate these signals to the cell wall. One of the best examples of gram-positive bacteria employing the concept of quorum sensing for infection is *Staphylococcus aureus*, other bacteria like *Bacillus*, *Streptococcus* etc also use quorum sensing for their survival (Paharik *et al.,* 2017).

Staphylococcus aureus

Staphylococcus aureus being catalase positive nitrate reducing bacterial pathogen is known to produce lethal staphylococcal toxin and is a very potent pathogenic bacteria causing infection in both humans and animals. This facultative anaerobe, when present in few numbers only express the factors responsible for adhesion and colonization in the host cell whereas when they multiply in numbers and reach a threshold cell density, they start producing the lethal toxin causing meningitis and sepsis in the human body(Lyon and Novick, 2004). Quorum sensing system has been assigned a central role in the pathogenesis of staphylococci, particularly *Staphylococcus aureus* via the accessory gene regulator (agr). Here agr quorum sensing system (agr A, B, C, D) facilitates gene expression. In agr quorum sensing system, agr D encodes the *Staphylococcus aureus* auto inducing peptides (AIP)with respect to the cell density (Ji *et al.,* 1995). The agrB protein helps the *Staphylococcus aureus* AIP's to bind to the thio-lactone ring (Saenz *et al.,* 2000). The moment AIP (chemical signal) bind to the agrC protein, phosphorylation in the agrA commences expressing rRNA III promoting the expression of secreted factors and inhibiting the cell adhesion factors (Novick *et al.,* 1993), activation of agr A protein triggers the agr BDCA gene expression which escalate the AIP level indicating that the cell mass has reached a threshold density(Novick *et al.,* 1995). On account of these autoinducing peptides (AIP's) *Staphylococcus aureus* strains has been categorized (Dufour *et al.,* 2002) and every single AIP's stimulate the associated agr C protein striving with others to unite with the receptor (Lyon *et al.,* 2002) for the genesis of infection in the host cell.

Streptomycetes

Streptomycetes, being the largest genus of *Actinobacteria* tends to live in the soil ecosystem. To transfer their message these group of spore forming gram positive bacteria (Anderson and Wellington, 2001) employ γ-butyrolactones as auto inducers and regulate the production of secondary metabolite through quorum sensing system. This bacterium is known to produce many useful antibiotics like neomycin, chloramphenicol etc (Akagawa *et al.,* 1975; Distler *et al.,* 1987; Dulmate, 1953). A great mystery lies in the cell communication of these bacteria owing to its chemical structure which is similar to the Acyl-homoserine lactones (AHL's) hence a lot of research work is required on this bacteria regarding cell to cell communication.

Quorum quenching

Unlike QS systems which is known to initiate communication between bacterial cells; quorum quenching is a phenomenon of interference in this communication with the help of various compounds (Turan and Engin, 2018). The technique of quorum quenching can be used in therapies against the microbial infestation, colonization, and infection (Czajkowski and Jafra, 2009; Dong *et al.,* 2002; Uroz *et al.,* 2003). The phenomenon of quorum quenching is seen in many groups of bacteria like Bacillus where signal transduction is inactivated by an enzyme (Dong *et al.,* 2001) other than this *A. tumefaction* (Zhang *et al.,* 2002), *S. typhimurium*, *E. coli* (Surette *et al.,* 1999; Taga *et al.,* 2001; Xavier and Bassler, 2003), *P. aeroginosa* (Mathesius *et al.,* 2003) and *S. aureus* (Rothfork *et al.,* 2004) also have quorum quenching mechanism.

It is evident that bacteria use a universal language known as auto inducers for communication with each other through a complex system of activities called quorum sensing. Mechanism of quorum sensing is different in gram negative and gram positive bacteria as signaling molecule AHL's and AIP's respectively are formed for their communication. Another thing that came into prominence through this article is every bacterium has a very specific quorum sensing mechanism which is distinct from other sets of bacteria to compete with other bacterial flora vital for its survival in the host environment.

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