QUORUM SENSING: CELL TO CELL SIGNALING MECHANISM

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Introduction

Communication is considered as the strongest and most important property ever evolved by nature for every living creation. It takes place by cell-to-cell signaling process which is prerequisite for development of multicellular organisms such as animals and plants but has also evolved in groups which are not usually described as multicellular, i.e., bacteria and unicellular fungi. It is perhaps an important tool in battle for survival. One of the mechanisms for bacterial cell-to-cell signaling and behaviour coordination under changing environments is referred to as quorum sensing. Quorum sensing was first observed in Vibrio fischeri, a bioluminescent bacterium that lives as a mutualistic symbiont in protophore (or light producing organ) of the Hawaiian bobtail squid. In case of free living Vibrio fischeri, autoinducer (small signaling molecule) is at low concentration and thus cells do not luminance. But when they are highly concentrated in the protophore (about 10^{11} cells/ml) transcription of luciferase is induced, leading to prominent bioluminescence.

Quorum sensing can be defined as the ability to coordinate gene expression in accordance with population density. Quorum systems are found in both gram-negative and gram-positive bacteria. It is assumed that quorum sensing represents both intra (occurs within single bacterial species) and interspecies (between two or more distinct species) signaling. Hence this corporation is for benefit of local or population as a whole. It is a way of individual cell to exchange information using small molecules that bind to sensory proteins and thus directly or indirectly affect transcription and translation process. These small chemical signal molecules are termed as autoinducers whose external concentration increases as a function of increasing cell population density. The corresponding bacterial cells detect the accumulation of minimal threshold stimulatory concentration of these autoinducers and alter gene expression. There are chemically distinct classes of autoinducers have been identified; the structures of few are the following:

Acetyl Homoserine Lactones (AHLs)

AHLs are called as autoinducer 1 type molecules which are composed of homoserine lactone ring with an attached fatty acid chain. This chain will contain carbon atoms numbering between 4 to 8 along with or without keto group on third position, e.g., in Vibrio fischeri, AHL synthase LuxI produces $3OC_6$ homoserine lactone with

keto group on third of 6 carbons, whereas, in case of Agrobacterium tumefaciens, there is production of $3OC_8$ molecule which has keto group on 8 carbon. Most of AHLs cross membranes by diffusion then they bind to LuxR like response regulators, which simultaneously act as sensors and transcription factors. This type of signal transduction where signal binding domain and transcription regulating DNA binding domain are fused called as one component signal transduction system.

Autoinducer 2

These type of autoinducers are compounds containing furanosyl borate diester whose precursor is 4, 5-dihydroxy-2,3-pentanediene (DPD). It is synthesized by LuxS from S-adenosyl methionine (SAM).

Oligopeptide Autoinducers

These are processed peptides containing amino acid residues with length ranging from 40 to 65. For peptide communication except peptide signal itself, the cell must contain membrane bound histidine kinase and response regulator with an aspartate phosphorylation residue. Hence, it constitutes a component signal transduction system. Peptide signals can be more flexible than small communication molecules as they do not require any special synthase and can change to adapt to ecological niches by simple codon mutation. Oligopeptide autoinducers are mostly used by gram positive bacteria, e.g., Staphylococcus aureus, which has autoinducing peptides derived from precursor accessory gene regulator (AgrD).

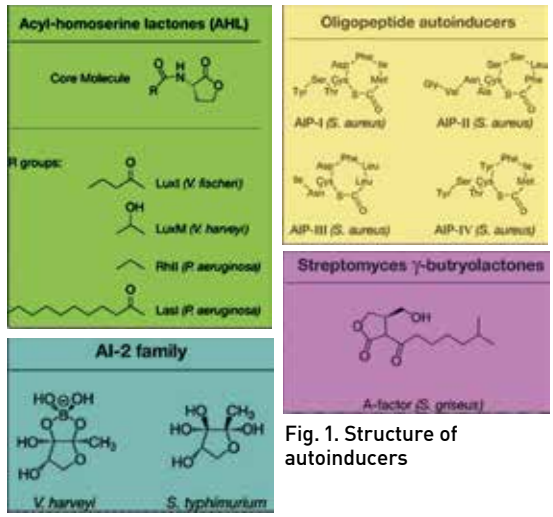

Fig. 1. Structure of autoinducers

Quorum Sensing in Gram Positive Bacteria

Quorum sensing system among the gram positive bacterium is studied best in Staphylococcus sp. They communicate by using processed oligopeptides as autoinducers and two component-type membranes bound sensor histidine kinases as receptors. In this class of bacteria, as peptides signals are not diffusible across the membrane, hence, signal release is mediated by using oligopeptide exporters. Further the sensing is mediated by phosphorylation cascade that influences the activity of DNA binding transcriptional regulatory protein termed as response.

The accessory gene regulator (Agr) system regulates toxin and protease secretion in Staphylococcus. In Staphylococcus aureus autoinducing peptides (AIP) is encoded by AgrD gene. Agr B then adds a lactone ring to this peptide and transports AIP out of the cell. Further AIP continues with its receptors,

i.e., sensor kinase Arg C and Agr C's cognate response regulator, Agr A. After binding with Agr C it transfers a phosphate group to Arg , which further activates transcription of arg operon for autoregulation. This leads to activation of RNA III, regulatory RNA which in turn leads to repressed expression of cell adhesion factors and induced expression of secreted factors.

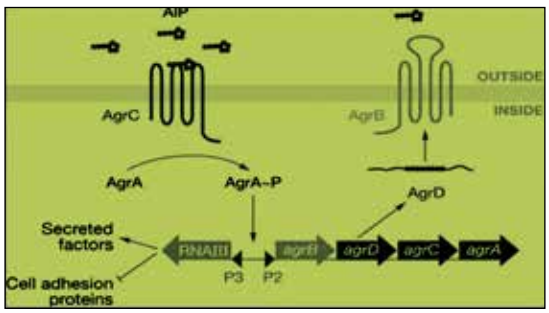

Fig. 2: Using a two-component response regulatory system, Staphylococcus aureus detects and responds to an extracellular peptide. Small red circles indicate the AIP. P2 and P3 designate the promoters for agrBDCA and RNAIII, respectively.

Quorum Sensing in Gram Negative Bacteria

It is carried out by production and reception of diffusible molecules of signal in the form of acylhomoserine lactones (AHLs). These signals are released by AHL synthase encoded by homologues of AHL synthase gene. LuxR is a family of response regulator proteins which perceives AHLs. After attaining a threshold concentration of AHL signal molecules form complex with receptor protein which become activated. These activated complex in turn dimers or multimers with other activated LuxR—AHL complexes. These products function as transcriptional regulators controlling expression of quorum sensing regulated target genes. A large number of gram negative proteobacteria have LuxR/I type of proteins and communicate with AHL signals. These systems are used for intraspecies communications as extreme specificity exists between Lux R proteins & their cognate AHL signals. Lux I type proteins link and lactonize methionone moiety from SAM to specific fatty acyl chains carried on acyl carrier proteins. Best described Lux I/R type quorum sensing is in Pseudomonas aeruginosa. It uses quorum sensing to activate several genes for colonization and persistence within host. Pseudomonas aeruginosa produces to AHLs N-(-3-oxodecanoyl)-L-homoserine lactone ($3OC_{12}HSL$) and N butanoyl-L-homoserine lactone (C_4HSL) which binds to LasR & RIhR transcription factors respectively.

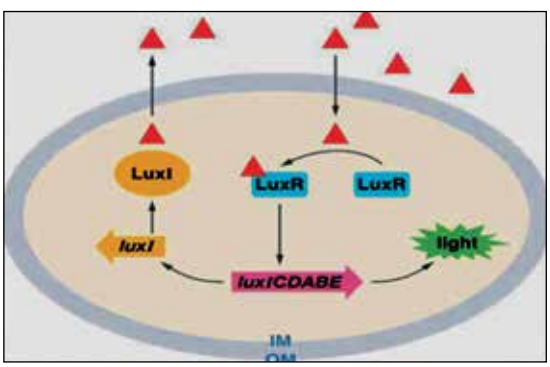

Fig.3: Quorum sensing in Vibrio fischeri; a LuxIR signaling circuit. Red triangles indicate the autoinducer that is produced by LuxI. OM outer membrane; IM inner membrane.

Properties Exhibited by Quorum Sensing

Bacterial groups exhibit remarkable social behavior by using quorum sensing system, e.g., Myxococcus Xanthus cells show socially dependent swarming across surfaces which allows population to seek out bacterial prey.

There are many other phenotypes regulated by quorum sensing which include bioluminescence, exopolysaccharide production, virulence, conjugal plasmid transfer, antibiotic and exoenzyme production, biofilm formation and growth inhibition. Antibiotic resistance is cooperative behavior by species of E.coli, Klebsiella through quorum sensing which is exhibited by production of extracellular enzymes, e.g., β lactamase to breakdown antimicrobials. Quorum sensing has the property of modulating immune response to facilitate survival of microbes within host, e.g., P.aeruginosa, Porphyromonas gingivalis, and Helicobacter pylori. Some data show that some bacteria may also regulate transition into stationary (a phase of quiescent) which alters patterns of gene expression to allow extended cell survival in the absence of nutrientss.

Applications

- This study of communication and its effects on transcription in unicellular organisms promises a variety of practical applications. It could be a novel target for antimicrobial drug therapy.
- Inhibition of quorum sensing offers an alternative to traditional antibiotics because these strategies are not bactericidal and occurrence of bacterial resistance therefore could be reduced.
- Quorum sensing associations may improve industrial scale production of natural and engineered bacterial products.
- By using RNA III inhibiting peptide (RIP) as quorum sensing inhibitor on Staphylococcus strains (i.e. S.aureus & S.epidermidis), which cause biofilm production various surfaces.
- Bacillus thuringenesis show the biocontrol activity through AHL lactonase, AHL degrading enzyme.
- There are few bacteria which can disrupt quorum sensing by degrading AHL autoinducers e.g. soil bacterium Bacillus produces lactonase enzyme which hydrolyzes lactone ring of AHLs. The activity interferes with AHL signaling of other bacterial species. in addition transgenic plants expressing Bacillus lactonase show resistance to quorum sensing dependent bacterial infection.
- It is reported that AHLs have the ability to modulate gene expression of mammalian organisms. Administration of $3OC_{12}$—HSL in an in vitro model of B cell activation leads to production of IgG1 antibodies and elevated IgE. Hence AHL acts as modulator of T cell mediated immune response

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