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Quorum Sensing by Super Bugs and their Resistance to Antibiotics, a Short Review

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Abstract

Bacteria's are the primitive form of the organisms that evolved millions of years ago and still, exist in our society. Like other animals, bacteria's have the power of sensing or adaptation. It can detect odd, harsh environment and survive accordingly. Quorum sensing is a well-known field that scientists have explored for long years. Bacteria's flagella can touch and sense odd molecules and escape the harsh living areas. In the adverse situation, they produce spores to survive from drought or any other natural calamities. The cell membrane is a unique part of a bacterial body that protects the nucleic acid from destruction. The nucleic acid is pH sensitive, temperature sensitive and it degrades when cell wall or membrane is absent. Like plants, bacteria also have pores in their membranes.

Through these pores, they exchange gas, ions and nutrients and genetic materials. In the adverse situation, they close most of the pores and keep one or two pores open to gather nutrients or to transfer genetic materials. This is how they developed horizontal gene transfer mechanism. Cell fusion is the basic idea of horizontal gene transfer. This is also called asexual reproduction. Bacteria's developed resistance against quorum quencher molecules too. The mobile genes or the genes in plasmid those are associated with sensory organelles like flagella helps bacteria to develop resistance against molecules. Natural and artificial chemicals have used against quorum sensing and people found success with it.

Keywords: Quorum sensing; Acylated homoserine lactone; Auto inducer; Liquid chromatography; Double mass spectrometry; High pressure liquid chromatography; Staphylococcus aureus; Quorum sensing inhibitors

Abbreviations: QS: Quorum Sensing; AHL: Acylated Homoserine Lactone; AI: Auto Inducer; LC: Liquid Chromatography; MS/MS: Double Mass Spectrometry; HPLC: High Pressure Liquid Chromatography; MARSA: Staphylococcus Aureus; QSI: Quorum Sensing Inhibitors; NMR: Nuclear Magnetic Resonance; IR: Infrared Spectroscopy; LLE: Liquid-Liquid Extraction

Introduction

Drug-resistant bacteria or super bugs communicate though quorum sensing. Quorum sensing (QS) is a technique that shows how bacteria secret chemical signals to communicate with each other, and followed by gene expression. The constant change of bacterial stains or species is a global problem. Gram-positive and gram-negative bacteria's uses acylated homoserine lactones (AHLs) as anauto chemo-inducer or chemical signal. Although signal relay mechanism varies from species to species. Through quorum sensing circuit, bacteria control variety of physiological mechanisms; such as cell density, competence, virulence, sporulation, biofilm production, conjugation, motility etc. Quorum sensing exists in microorganisms. Recent findings prove that chemical communication is present in viruses too. It also proves that molecules and chemical reactions are the common ground in living objects and its activities.

In human, biosynthetic pathways are the key modulators for cellular energetics; production of essential enzymes, cellular byproducts and the most important molecule is glucose as a source of energy [1-3]. Bacteria's have several different genes for AHLs and produce the variety of AHLs. It is a cytosolic transcription factor. AHL activates the transcription cascade and produces biofilm in various chronic infections. AHL type signaling can be divided into several parts. It produces the Luxl type of protein which accumulates in the intercellular areas. To cure the chronic infection or virulent infection, quorum sensing is a major pathway that needs to be stopped [4].

It has reported that cell density, diffusional characteristics, and environment induce quorum sensing and genetical reprogramming. Quorum sensing helps Staphylococcus aureus sense confinement and trigger virulence and metabolic pathway

that is needed for survival [5]. It has found that bacterial genes involved in pathogenicity are mediated by quorum sensing. AHL (N-acyl homoserine lactone) molecule contain 4-14 carbon acyl side chains [6]. Anti-pathogenic drug targets are the key regulatory system in bacteria that cause virulence. The pathogen produces, detect and respond to small signaling molecules such as fatty acid derivatives, oligopeptides, and furanones. More than 70 species found communicate through quorum sensing. Some are agriculturally important bacteria too, e.g. *A. Tumefaciens*.

Auto inducer

The quorum sensing molecules are diffusible auto inducers. It was first discovered in marine bioluminescent bacterium *V. fischeri*. They live in various marine animals. It produces light that helps the host to find food, mate or protect themselves from predators. In return, bacteria get nutrient rich environment to live in sea animals. "Milky Sea" is a good example of quorum sensing bacteria in north western Indian Ocean. Biopolymer or exo-polysaccharide helps to form biofilm; some people also found that breakage of peptidoglycan helps to form biofilm. Adhesion and biofilm formation mainly takes place with gram-positive bacteria's e.g. *L. monocytogenes, S. Aureus, S. Epidermidis, S. Gordonii*. Peptido glycan in gram positive bacteria is made of N-acetyl glucosamine-N- acetyl muramic acid-disaccharide penta peptide which forms internally then get transported outside. In gram-positive bacteria's signaling molecules are 5-25 amino acid long. Cytoplasmic response regulator protein help cells to respond to signaling molecules via gene expression. Auto inducer type quorum sensing is present in gram-positive and in gram negative-bacteria [7-9].

Auto inducer 2 (AI 2) helps inter species signaling. It was first discovered in *V. harveyi*. AI-2 is a furanosyl borate and it controls cell density dependent bioluminescence. Fatty acids also take part in quorum sensing. Cholera-causing bacteria *V. cholerae* regulates several behaviors by quorum sensing (QS) [10]. Vibrio's QS-regulated by two auto inducer molecules. CAI-1(product of CqsA synthase) and AI-2 (product of LuxS synthase). This auto inducer molecules help them to pick up extracellular molecules. QS also controls the transcription of competence gene and helps with DNA uptake by the bacterial cell. Proper timing of biofilm formation also plays a key role in horizontal gene transfer [11].

Biofilm

Biofilm helps the bacteria to tolerate heat, cold, other physical stress, chemical hazard, pH, and oxygen. Polymeric matrix binds water and prevents dehydration. Two component mediated quorum sensing has observed in gram positive and gram-negative bacteria. Biofilm or group of bacteria works against host cell defense to establish chronic or lethal infection when single bacteria are vulnerable to attach to the host cells. Biofilms are the unique structure that helps the bacteria to attach in biological or non-biologicals surfaces and help them to grow. It is made of proteins, nucleic acid and, carbohydrates. It has found that low level of aminoglycoside antibiotic can induce bacterial biofilm formation in the case of *P. Auroginosa*. Adverse environmental signal triggers the bacterial biofilm formation which is highly complex, that's how bacteria develop drug resistance. They come to free-swimming (planktonic) state when environment is suitable to live. If biofilm gets observed under microscope, it shows the very well-organized structure with very special configuration. Like the multicellular organism, they can form structures and communicate with each other by secreting small molecules [12]. In nature, high cell density and proximity of various microorganisms motivates microorganism either compete or form a symbiotic association. In the dental biofilm, bacteria produce bacteriocin. It takes a major role in interspecies competition and coexistence. Chronic biofilm associated infections are hard to treat. They are antibiotic resistance. This biofilm-related infection can occur in any part of the body, such as bone, air way/lung tissue, mouth, eye, gastrointestinal tract etc. When bacteria produce biofilm, they are virulent and pathogenicity associated with it. Cell or tissue damage takes place [13-16].

Horizontal gene transfer

Horizontal transfer of resistance genes in bacterial colony either by intra or inter-species helps to degrade antimicrobial compound. Decreased permeability is the reason of biofilm. It is already well characterized between free-swimming bacteria and the bacteria's in a biofilm. Chronic infection and biofilm are correlated to each other. Horizontal gene transfer can be possible by plasmid and mutation in chromosomal genes [17]. Horizontal resistance occurs by changing the drug binding site and modulating essential enzyme's binding site. *S. Aureus* is a nosocomial pathogen (MARSA). It has observed that *Staphylococci* and *enterococci* can transfer mobile genetic elements i.e. DNA [18]. Antibiotic resistance can be acquired or lost during horizontal gene transfer. Horizontal gene transfer also helps with adaptation. The mobile genetic element that produces the key protein to develop antibiotic resistance, virulence and host adaptation [19-21].

Bacterial motility, flagella as sensory organ

Chemotaxis is a process by which bacteria can respond to chemical molecules. Flagella works like an antenna. It helps to move at the same time responds to chemicals. Bacterial flagella can sense quorum sensing molecules. Knockout of N-octyl homoserine lactone gene showed that bacteria lose its motility and sensing the power in its absence. The gene QsmR is responsible for flagella formation in *Burkholdaria* bacteria. FihDC from flagella gene cluster found that it is directly responsible for chemotaxis. This gene can be a target for antibiotics and to stop biofilm formation. The luxS gene regulates flagellar expression at the same time produces siga toxin in virulent *E coli*. Knock

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out of luxS gene showed flagella impairment, reduced biofilm formation etc. [22,23].

Human microbiome interacts with mammalian cells with the same quorum sensing peptides. In the case of breast cancer, it starts angiogenesis. Peptides from *Bacillus sp., E. coli, E. faecium* found interacting with mammalian cells. Some research group found that these quorum sensing peptides are stable in blood plasma when in vitro experiment was performed. The cyclic structure of these peptides makes it stable in blood plasma and from cellular restriction enzymes [24].

Methods

Liquid chromatography (LC) and double mass spectrometry (MS/MS) is used to find the presence of L-acetyl homoserine lactone in bacteria's. Together gas chromatography and mass spectrometry (GC)-MS was used to study the enantiomers (C8-HSL). People used thin layer chromatography to study the quorum sensing molecules, where sample concentration was femtomole level [25]. Radiolabeled assay can be employed to detect homoserine lactone (HSL). Radio labeled methionine can be added in bacterial culture. The bacteria can incorporate radiolabeled methionine when they produce homoserine lactone (HSL). Colorimetry method detects the concentration of HSL. It is a simple and fast method to detect HSL. Nuclear magnetic resonance (NMR) or Infrared spectroscopy (IR) can detect the molecular structure of HSL [26]. LLE (liquid-liquid extraction) also another procedure to extract HSL. HPLC is used to extract HSL.

Acetonitrile, dichloromethane, chloroform, ethyl ether etc. can be used as an organic solvent in chromatography. ACN is now widely used solvents with most of the HPLC instruments. This solvent is environment-friendly. HPLC and mass spectrometry can also be used together to get AHL formula along with electrospray ionization analysis. It helps to get the whole molecular structure of AHL. The Presence of other molecules can give higher background. The wider peak can be the reason for column impurities with other molecules. Working with the new sample is always challenging, that's why robust HPLC and Mass spectrometry software are needed that can detect molecular branching point.

Whole genome sequencing and microarray also widely used to study the mutation and sequences of bacteria's. Multiplex PCR can show the relevant abundance of active genes. ELISA is commonly used to see the antigen and antibody reactions. Antibiotic-loaded disk test is widely used to see the antibiotic resistance. Cloning is very simple these days. Various ready-made vector is available in different companies, e.g. TOPO cloning kit is easy to use. This vector's multiple cloning sites can be used to insert the gene of interest. In situ hybridization is a technique that helps to chase a gene in sub-cellular level. Through Micro RNA silencing, quorum sensing can be stopped. Mutagenic PCR is a faster way to induce mutation in a gene or in a plasmid.

Discussion

Quorum sensing or molecular communication has widely discovered across the bacterial spectrum. These aromatic compounds help bacteria to sense adverse or suitable environment to live. Through these quorum sensing molecules bacteria communicate with each other; sometimes they inactivate other species molecules to be virulent or be dominant over other species [27]. In adverse condition bacteria produce biofilm, and this biofilm is hard to cure with antibiotics. Horizontal gene transfer takes place during biofilm formation. It creates more resistant bacteria and takes control over host cells. Cross kingdom interaction of bacteria by quorum sensing molecules help to form symbiotic interaction. These molecules are recognized by higher eukaryotes. Quorum sensing molecule changes the physiology of higher eukaryotes by interfering with their host immune defense, hormonal status and growth factor. Higher organisms have an obligatory association with bacterial world. Various bacteria and their signaling form a holobiont living environment [28].

Mimicry and confusion have widely used in nature. People have found good results by confusing bacteria through disruption of quorum sensing. Although it may not work all the time because bacteria produce the variety of chemical signals in their cells. Small peptides are efficient workers against bacteria. Synchronized quorum sensing signal produces pathogenesis or virulent proteins [29-34]. Anti-quorum sensing therapy is well established, it holds a big volume of future to cure lethal infections. QS pathway is made of three steps-signal productions, signal accumulation, and signal detection. Quorum sensing will be effective when each of these steps gets blocked properly by artificially synthesized peptides. Although this area needs more research and data from all over the world. This can be useful to treat antibiotic resistant bacterial infection too. Chimeric antigen receptor from blood forming stem cells showed the promising effect against HIV. Cell mediated cure of drug resistant infection will be more effective in future [35].

Recent evidence shows that bacteria started developing resistance against quorum-sensing inhibitors (QSI) along with antibiotics. It is a recent development and shows that QSI influence pathogenicity without harming bacterial growth [36]. A report published by Scripps Research Institute that explained structurally modified vancomycin is effective against MARSA. Vancomycin has prescribed for last 50 years against infection, but the change in chemical formula made it more efficient and now lower dosage is also effective. Gram-negative bacterial infection is hard to treat because of their impermeable outer covering. Antiprotozoal drug pentamidine disrupts the outer cell wall of gram-negative bacteria [37,38].

Quorum sensing inhibitors

Quorum sensing molecule activates myriad genes that control bioluminescence, virulence, biofilm formation, sporulation

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etc. Quorum sensing inhibitors or quorum quenchers can control virulent infection. It's also called antipathogenic signal interference. This is the current strategy to combat against virulent bacteria's [39-41]. Discovery of quorum sensing degrading enzyme in mammals shows the effect of innate immunity that can be used against super bugs [42]. A research group reported that quorum quenching and inhibition of iron metabolism by using gallium helped to control biofilm [43]. It has reported that 4 amino quinoline acts as quorum sensing inhibitors in *S. Marcescens* and *P. Auroginosa*. 7-Cl and 7-CF_3 worked as a substitute of N-dodecyl amino-4 amino quinolone [44-47]. Quorum quenching enzymes are present in quorum sensing and non-quorum sensing microbes. They can control virulent pathogenic gene expression [48]. Host innate defense and enzymes can be used to fight against pathogenic bacteria, those uses quorum sensing as a tool for communication.

Quorum quenchers can be divided into signal supply inhibitors and signal response inhibitors. Signal response inhibitors can be antagonistic receptor binding drugs. It can be analog of the signaling molecule [49]. Signal supply inhibitors can stop producing signals. It has reported that phytochemicals from plants are quorum sensing inhibitors. Quorum quenchers generally inhibit biofilm formation by disrupting surface adhesion. A research group reported that a gram-positive bacteria *S. Intermedius*, a zoonotic pathogen excretes two chemical compounds in millimolar level that inhibits quorum sensing in broad spectrum beta and gamma proteobacteria. The compounds were extracted from *S. Delphini.* The chemical formula of the new class of quorum quenchers are N-[2-(1H-indol-3-yl) ethyl]-urea and N-(2-phenethyl)-urea. AHL responding receptor LuxN works oppositely with these chemicals [50] and promoted LuxN mediated phosphorylation of LuxU. In summary, quorum quenchers can be used as drugs, crop production, aquaculture and for anti-biofouling agents [51,52]. Brominated furanone is a pyrimidine analog that inhibits QS and biofilm formation at the same time attenuates the production of pyocyanine and ramnolipids [53].

The drug-resistant bacteria's produce metallo-beta-lactamase enzyme that makes them resistant to common antibiotics, such as penicillin and cephalosporin (Texas Tech University, Baylor University research group). Aptamers made of nucleic acids can bind with metalloenzyme and make it inactive. This observation showed that the application of aptamer helps common antibiotics to work [54,55]. Cross-kingdom interaction of bacteria by quorum sensing molecules help to form symbiotic interaction. These molecules are recognized by higher eukaryotes. Quorum sensing molecule changes the physiology of higher eukaryotes by interfering with their host immune defense, hormonal status and growth factor. Higher organisms have an obligatory association with the bacterial world. Various bacteria and their signaling forms a holobiont living environment [56].

Effective phytochemicals against bacteria

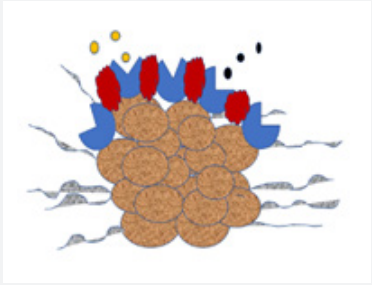

Figure 1: cartoon of biofilm absorbing food and releasing gas.

Table 1: Compounds effective against resistant bacteria.

Source of Antibiotic	Chemicals	Species
Soil bacteria	Teixobactein	*S. Aureus* (MRSA)
Soil bacteria	Teixobactein	*S.Pneumoniae*
Synthetic	Aganocide	*S. Aureus*
Gram positive and Gram-negative bacteria	DPD(4-5 dihydroxy-2, 3-pentanedione)	Active against 70 bacterial species
Synthetic	Lysine conjugated aliphatic non-Spermidine analogue	MRSA, Ebola

Table 2: List of drug resistant bacteria.

Bacteria	Antibiotic
A. baumannii	Carbapenem resistant
P. Aeruginosa	Carbapenem resistant
Enterobacteriaceae	Carbapenem resistant
E.Faecium	Vancomycin resistant
S. Aureus	Methicillin resistant, vancomycin resistant
H. Pyroli	Clarithromycin resistant
Campylobacter sp.	Fluoroquinolone resistant
Salmonellae	Fluoroquinolone resistant
N.Gonorrhoeae	Cephalosporin resistant, Fluoroquinolone resistant
S.Pneumoniae	Penicillin non-susceptible

Aloe vera, Neem, Tulsi plants contain flavonoids and tannin. They are effective against *S. Aureus, K. Pneumoniae*, and *E. coli*. Essential oil from *Hyptismartiusii* shows antimicrobial and antifungal effect. The oil contains following compounds-δ-3-carene, 1-8 cineole, trans-caryophyllene, caryophylline oxide, bycyclogermacrene [57]. Several natural chemicals or compound found effective against biofilm formation. Carotenoid, zeaxanthin found effective against *P. Aeruginosa*, a gram-negative bacterium [58]. Zeaxanthin's effect was found by quantitative reverse transcriptase PCR assay, and it showed the level of gene expression. Piper betle leaf extraction also effective against biofilm (Figure 1). Quorum quenching is present in

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plant proteobacteria too e.g. *A.Tumifaciens. Agrobacterium* contains BlcC enzyme that works as a quorum quencher [59]. It has reported that minimum inhibitory concentration reduced when azithromycin, zentamycin, and curcumin added together. Curcumin has big synergistic effect with other antibiotics (Table 1 & 2) (Figure 2 & 3).

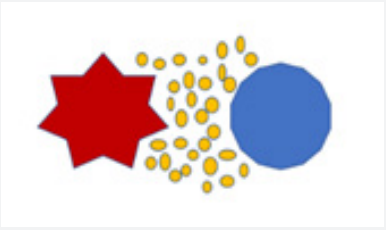

Figure 2: Inter species quorum sensing communication.

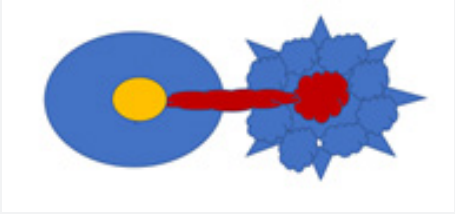

Figure 3: Horizontal gene transfer.

The enantiomer of carbapenem isdoripenem, and it can be used against resistant bacteria's. Generally, bacteria develop resistance to antibiotics by changing protein docking or binding site. In that case previouslyused antibiotic's enantiomer can be used for experimental purposes. Mefloquine is a malaria drug but it shows the potential to inhibit *S. Aureus* and *S. Pneumoniae*. Although mefloquine showed neurotoxicity (Figure 4 & 5). More research needs to be done with a dose-dependent curve. Artificially synthesized peptides also showed an antimicrobial property. This synthetic peptide (RLKLLLLLRLK-NH_2) and its D-enantiomer is effective against *S. Aureus, E. coli*, and methicillin-resistant *S. Aureus*. The middle leucine motif makes it effective against microbes. D-KLKLLLLLKLK-NH_2 peptide has the affinity towards bacteria's cell wall peptidoglycan eventually, it disrupts cell membrane [60] (Figure 6).

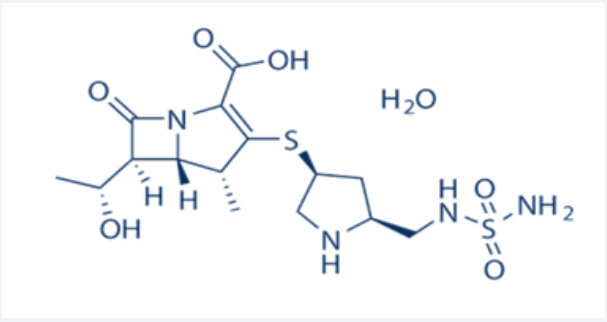

Figure 4: Doripenem.

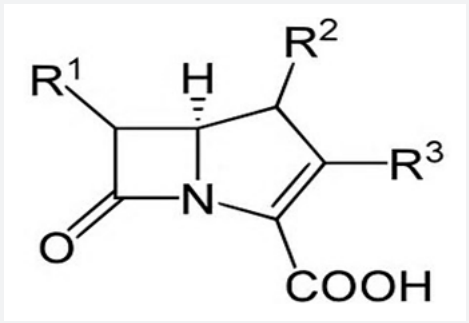

Figure 5: Carbapenem.

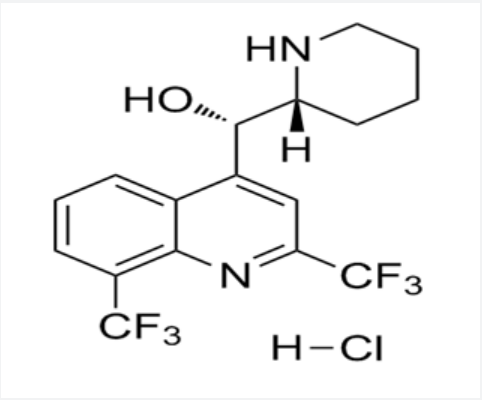

Figure 6: Mefloquine.

Conclusion

Cell signaling or molecular communication is very common in upper eukaryotes. The discovery of quorum sensing in bacteria and viruses makes it an universal language in living organisms. For food and place to live, microorganisms fight with each other to create a symbiotic association. It has reported in bacteria's as well as in other organisms. The very recent development shows that quorum sensing molecule takes part in cancer development.

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