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Nanoparticles as Emerging Therapeutics for Coping Antimicrobial Drug Resistance

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Abstract

Emergence of antimicrobial drugs resistance to traditional antibiotic compounds is a global problem with considerable challenges predict ted for treatment of many serious bacterial infections. The drug resistance against common antibiotics has gain resurgence in developing novel therapeutics such as nanoparticles against microbe. Some nanoparticles have been observed previously to have antimicrobial properties. Although the biological basis for this effect is currently unknown, it is hypothesized that quantum interactions within the cell play vital role in the regulation of RNA transcription relating to both coding (relating to genes) and non-coding (structural RNA) regions of the genome. These transcripts interact and establish an intracellular communication in the bacterium *Escherichia coli*. Their interaction can be unfolded by the application of nanoparticles. The response in terms of bacterial growth and RNA expression upon the exposure of the nanoparticles can be evaluated. Furthermore, the site of nanoparticle incorporation within the bacterial cell and the potential intracellular transcript interactions has been hypothesized.

Keywords: Nanoparticle; Transcriptome; Bioinformatics; Quantum phenomena; *Escherichia coli*

Introduction

According to World Health Organization (WHO), antimicrobial resistance is resistance of a microorganism against an antimicrobial drug that was originally effective for its treatment. The global Antimicrobial Resistance (AMR) surveillance was conducted by WHO in 2014. The outcomes of the AMR surveillance revealed that antibiotic resistance are the serious threat in treating the microbial infections [1]. These microorganisms communicate with each other both by quorum sensing and inside the cell at the transcriptome level. The latter are quantum communications involving continuous waves of energy in the time scale of attoseconds.

In 2012 WHO reported a gradual increase in resistance to HIV drugs, which may procure expensive drugs in the near future. In 2013, there were about 480,000 new cases of multidrug resistance tuberculosis (MDR-TB) [1]. MDR-TB requires therapeutic for extended duration and impose less potency than those for non-resistant TB. Patients with infections caused by drug-resistant bacteria are at risk of worse clinical outcomes and death, and require more medications than patients infected with the same bacteria that are not resistant [2]. Few bacteria which became resistant to the drugs are as follows: *Escherichia coli.* resistant to 3rd gen. cephalosporins and fluoroquinolones, *Klebsiella pneumoniae* resistant to 3rd gen. cephalosporins and carbapenems, *Staphylococcus aureus* resistant to methicillin [3]. One of the mechanisms of AMR is efflux pump. Efflux mediated resistance is characterize by up-regulation of genes associated to the expression of transporter proteins extruding drugs from the cell to create intracellular sub-therapeutic concentrations leading to resistance [4].

The antimicrobial resistance to the bacterial disease required attention of the scientific community to explore the wide scale mechanisms of antimicrobial resistance. Many scientific studies have been initiated in this direction to further readdress the AMR mechanism. Scientists are working to find the signaling cascade in the microbe which enables them to become resistant. Laboratories are also conducting experiments to prepare some novel therapeutic to fight against the AMR.

Major developments

In present scenario several institutions are leading project on microbial resistance. Their primary objective is to find the signaling cascade of the microbe which enables them to become resistant against antibiotics. Since mankind has discovered and developed the antibiotics against microbes, it appeared that the fight against the microbes has been ended. However, the bacteria were quietly evolving and acquiring the resistance genes and resistance gene arrays, which provide them protection against the antibiotics [5].

Global attention has taken on the AMRs. Several research laboratories are working to troubleshoot the microbial resistance either by targeting the biochemical pathways involved in this resistance or using the combinational drug therapy with nanoparticles. The drug potency associated with nanoparticles can be explained by studying the quantum properties of these nanoparticles. Moreover, the quantum biology could be able to provide the insight of their bioactivity. The Quantum Biology deals with the application of quantum theory to unfold the biological mechanisms. Furthermore the recent progresses in this area have been highlighted by several researchers considering the Quantum interference, entanglement, coherences, and tunneling [6,7].

Recently the development of genomic and evolutionary insights could predict the antibiotic resistance in bacterial infections [8]. Applying this approach the diagnosis and treatment have been transformed. Genotype based antibiotic resistance profiling has been promising for example, rifampicin resistance in *Mycobacterium*

tuberculosis caused by a nucleotide substitutions, and methicillin resistance in *Staphylococcus aureus* caused by a resistance cassette. Current predictability of AMR relies more on genotypic profiling rather than its phenotypic. Moreover, the importance of mathematical modeling in context of reducing the resistance in hospital has been reported [9]. This report focused on the control of nosocomial transmission of bacteria by reducing the antimicrobial resistance in nosocomial pathogens. These mathematical models are highly sensitive to the complexity of microbe community variation of disease and treatment among patient in any real hospital.

In spite of the fact that the bacterial genome was the first completely sequenced genome among free living organisms, however, there have been few bioinformatics tools developed to curate the genomic database related to its pathogenicity [10]. In particular there are few tools to study the genetics and genomics of the antibiotic resistance how it impacts bacterial population, and their clinic. There has been a Comprehensive Antibiotic Research Database (CARD) developed, which provide the Antibiotic Resistance Ontology (ARO), and can quickly identify putative antibiotic resistance genes in new unannotated genome sequences. In bacteria most of the antibiotics targets are 16S rRNA. Therefore the transcripts are the best target for finding any novel signaling cassette attributed to antimicrobial resistance. Signaling cassette associated with multi proteins involved in a single cellular signal processing from external environment to the nucleus of the cell.

At least 130 different cassettes that carry known or predicated antibiotic resistance genes were identified, along with many cassettes of unknown function [11]. The MRI studies revealed new resistance gene cassettes, including those conferring to additional class of antibiotics. Although the analysis of MRI sequences provided a few hints, particularly the wider genetic contexts of cassette arrays, is needed.

Researchers have also focused to develop Antimicrobial peptides (AMPs), an oligopeptides with a varying numbers of amino acids. These peptides are wide-spread in all forms of life, from virus to parasites including bacterial cells [12]. The AMPs target broad spectrum of organisms used to interfere with microbial growth. Several AMPs have been shown to be effective against multi-drug resistant bacteria and have low propensity to resistance development, probably due to their unique mode of action, different from well-known antimicrobial drugs. Cationic AMPs are currently the potential alternatives for antibiotics, which disrupts the various key cellular processes [13]. There is a class of antimicrobial peptide known as bacteriocins which can inhibit the growth of other closely related species of bacteria can be potential drug against microbial growth.

Although many mutations attributed to antibiotic resistance have been revealed, the connection between the mutations and its phenotypic changes accountable to the resistance has yet to be fully elucidated. Previously the mapping of phenotype and genotype for drug resistance has been analyzed by phenotypic and genotypic changes in *Escherichia coli* [14]. The phenotypic expressions connected to few number of genes were quantitatively computed the antimicrobial resistance. Several genotypic changes contributing to the resistance were identified. However, phenotype-genotype mapping were complex. This complexity comes from the various mutations that cause similar phenotypic expression changes. Moreover, the integration of transcriptome and genome data disclosed the indispensable phenotypic changes for drug resistances.

The National Centre for Disease Control (NCDC) published a National Policy for Containment of Antimicrobial Resistance India. In this policy the alarm of AMR has been raised, and several task forces has been established to assure the proper administration of antibiotics [15]. In another study this problem has been considered globally for the developing countries. The global problem of antimicrobial resistance is particularly critical in developing countries, where the infectious disease trouble is elevated and cost constraints prevent the widespread application of newer, more expensive agents. Gastrointestinal, respiratory, sexually transmitted, and nosocomial infections are leading causes of disease and death in the developing world, and management of all these conditions has been critically compromised by the appearance and rapid spread of resistance [16,17].

A study has been conducted in south India on Enterococcus species which is resistant to vancomycin. The study characterizes the phenotypic and genotypic associated to its resistance [18]. Especially few studies have been also conducted on the AMR of *Escherichia coli* and its genotypic profiling in Indian clinics [19]. In Ujjain, central India, a work on *E. coli* isolates from Indian children has shown antibiotic resistance profile [20].

AMR detections techniques and therapy

There are several biochemical techniques by which the antimicrobial resistance of a microbe for an antibiotic can be detected. The Sensitivity of the microbe to the antibiotic can be tested by several methods. These techniques are dilution method, disk diffusion method, E-test, and automated antimicrobial susceptibility testing systems. The mechanism-specific tests are there, for the detection of a few antibiotics. Moreover, the genotypic methods can test the specific genes that are related to antibiotic resistance. Polymerase chain reaction (PCR) is a molecular technique for detection of a gene concern to antibiotic resistance activity [21]. DNA hybridization is another technique of genotype detection of AMR. Use of oligonucleotide coated with 5'-fluoresence, DNA chips, and DNA arrays etc. are many others developed techniques. Moreover, the mechanism of Antimicrobial Resistance in microbe is yet to be fully elucidated (Figure 1).

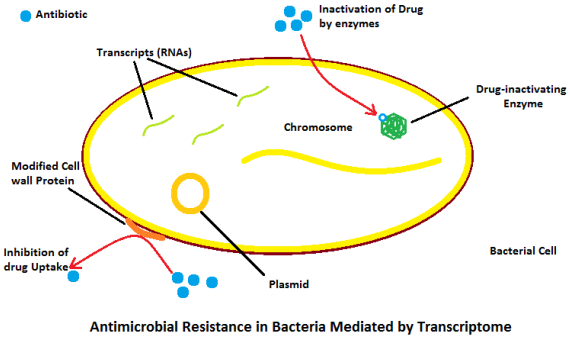

Figure 1: Mechanistic biochemical pathways in bacteria which involved in the antimicrobial resistance.

The signaling cascade which enables them to be resistance against the antibiotics could be a soft target to contour the AMR. In this regard this is utmost important to find the soft target of microbe and fully elucidate the mechanism behind the AMR. Which open an avenue to

researchers to combat against the AMR. Transcripts are prime target of the antibiotics therefore interactions among these transcripts may fully elucidate the novel proteins of the signaling cassette associated to antimicrobial resistance.

Quantum communication among transcriptome

Non-coding RNA (ncRNA) produces functional RNA molecules that act directly as structural, catalytic or regulatory RNAs, rather than expressing mRNAs that encode proteins. It is possible to detect new transcripts (both ncRNA and protein coding RNA) using high-density oligonucleotide microarrays that systematically probe an entire genome or by direct sequencing of the expressed RNA (RNAseq). Most ncRNAs are independently involved in regulation of gene expression or other biological functions and seem to be particularly abundant in roles that require highly specific nucleic acid recognition without complex catalysis, such as in regulating post-transcriptional regulation of gene expression or in guiding RNA modifications [22]. Hence, intracellular communication could be mediated via ncRNA. It has been hypothesised that transcripts communicate by means of a quantum channel established through each microstate of each and every transcript. Each and every quantum microstate corresponds to changes in its spin properties.

Nanoparticles (NPs) are sub-microscopic structures typically in the range of 1–200 nanometres in size. Their size confers different physicochemical properties from individual atoms or the bulk material. Nanoparticles exhibit a high surface to volume ratio, allowing the surface to be coated with a variety of molecules. The interactions between these unique materials and microorganisms are often toxic. Thus they can be used for antimicrobial applications. The interactions that occur in the microbial transcriptome on exposure to nanoparticles with specific reference to ncRNA to be characterized by quantum established through different quantum states. It is believed that specific transcripts interact with the different spin states of nanoparticles or ions and therefore, a differential response of the transcriptome either to the nanoparticle or the associated ion may be induced. Hence, this response would be associated with the mechanism underlying the nanoparticle induction.

There is an important aspect of DNA/RNA dynamic system where they work as an information energy catalyst, able to transmit and receive Bio-quantum signals (e.g. Bio-Photons and associated Bio-Phonons) to and from the proteins and RNA molecules in living cells. This interactive dynamic information exchange in Quantum-Bio-Physics can be termed as Quantum communication in living systems. Based on this aspect of Bio-quantum signal a hypothesis of Quantum communication among the transcriptome of microbe can be proposed. This communication enables them to become resistant against any antibiotics. This emphasize that the quantum signal generated as a result of antibiotics interactions, from one transcript passes to another transcript. This communication makes aware to the other microbe machinery to become inactive against the foreign particles. This communication among the transcriptome can be interrupted by exposure to antimicrobial nanoparticle by changing the quantum state communications occurring within them. Silver and gold nanoparticles have shown their antimicrobial potency by inhibiting the growth of several harmful bacteria. Moreover, some oxide nanoparticles have also shown their antimicrobial potency.

Conclusion

The growing problem of Antimicrobial Resistance is a major concern of medical microbiologist due to ineffectiveness of the drugs against microbe. Although there are many biochemical pathways suggested which are involved in the AMR, however, the bio-quantum communication among the transcripts and proteins is a novel mechanism behind the microbial resistance. This mechanism can be further confirmed by the quantum active inhibition through nanoparticles. Which further strengthens the concept that transcripts communicate by means of a quantum channel established through each microstate of each and every transcript.

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