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Commentary

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Bacterial Stress Response and Cross Resistance to Antibiotics in the Light of Natural Selection

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Abstract

Bacterial cells have to face many challenges to survive in the form of environmental stresses. These environmental stresses elicit a strong protective response. It has been understood that these protective responses negatively influence the susceptibility of stress-exposed bacterial cells to antibiotics. This concept of stress-induced cross resistance to antibiotics is probably a consequence of natural selection or due to directed mutagenesis. According to the theory of natural selection, it might be due to the activation of non-specific stress responses following exposure to one type of stress while directed mutagenesis explains it as a consequence of accelerated random mutations following stress exposure. The activation of stress response systems in biofilms increase the frequency of genetic transfers that help them acquire resistance. However, these hypothesized cross-talks should be precisely studied for definitive conclusions.

Keywords

Environmental stress; Bacterial stress response, cross resistance; Adaptive resistance; Adaptive mutagenesis

Introduction

Antimicrobial resistance is an emerging menace in the effective management of infectious diseases. This global issue has triggered tireless efforts and exhaustive funding from many global health agencies with an ultimate motive of bringing it to an end [1]. While much studies have been directed towards understanding this issue and on ways to tackle it, a few others are in hunt for alternative modalities to address it [2-4]. The initial step towards tackling antimicrobial resistance would be to understand the mechanisms of emergence and spread of antimicrobial resistance. In the recent times evidences have accumulated establishing the role of environmental stress in the emergence of antimicrobial resistance.

Environmental Stress and Antimicrobial Resistance

When bacterial cells are exposed to stress, they undergo a series of complex genomic, phenotypic and physiological alterations that enable endurance [5]. And these consequential maneuvering of bacterial cells in response to domestic environmental stress also induce cross-resistance against antibiotics [6-10]. Hence, it is clear that antimicrobial resistance is not just a consequential event following the exposure to antibiotics. This concept of environmental stress-induced cross resistance to antibiotics provides a valid explanation about the occurrence of drug-resistant strains in the domestic surroundings and health-care environment. A paper was recently published by Ebinesh [11] explaining this phenomenon according to which this concept of stress-induced cross resistance 'questions the validity of the theory of natural selection'. But it necessarily does not question the validity of the theory of natural selection. Adaptive cross resistance is either consequence of natural selection or a stratum ahead of it. To decipher this question on evolution, a deep insight into the relation between bacterial stress response and antimicrobial action is essential. Though many workers have demonstrated stress-induced phenotypic and genotypic alterations that promote antimicrobial resistance, the sub-cellular intermediate interactions between stress response and antimicrobial action have not been understood. The possible intermediate sub-cellular mechanisms linking bacterial stress response and resistance to antimicrobial action are as follows.

Sequential response

In 1988, Heidenreich demonstrated that the mutation rates are higher in respiration-deficient *Saccharomyces cerevisiae* when compared to respiration-competent strains [12]. Applying the above quoted work to bacteria, it can be inferred that the nature selects a clone of bacterial cells among the existing population. Following exposure to stress, these selected clones of bacterial cells activate stress-specific protective responses. Ultimately, the cells enter a state of transient hypermutability bringing about multiple random mutations [11]. Occasionally, these random mutations are advantageous rendering refractoriness to antibiotics also. It is also clear that only few specific factors produce mutations [13]. There also remains a question whether it is due to a process of evolution or merely the inability of bacterial cell to repair its own DNA when subjected to stress as a measure of energy conservation.

Collective response

Al-Mahin [14] designed a recombinant strain of *Lactococcus lactis* NZ9000 which was capable of expressing *E. coli dnaK* gene on exposure to stress. They observed that this strain of *Lactococcus lactis* was resistant to multiple stresses in comparison to other non-recombinant strains of *Lactococcus lactis*. They attributed this measure of resistance to the production of dnaK protein which is homologous to hsp70. It is clear that inducing the expression of a single type of molecular chaperone might result in the development of cross resistance to multiple other stresses. Exposure to a single type of stress activates a stress sensor molecule such as heat shock proteins. These sensors in turn non-specifically activate collective stress responses. As result of activation of multiple non-specific stress response cascades, a collection of alterations occur in the bacterial cell that make them resistant to various other stresses without prior exposure

Recombinant response

It is well-known that biofilm formation is one of the major bacterial survival strategies. Planktonic form of bacterial cells on exposure to an adverse environment form matrix-enclosed accretions called biofilms [15, 16]. It has been well documented that these

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biofilm are highly refractory to the action of antimicrobials than the planktonic forms. The stability of these biofilms are enhanced by high frequency of genetic combinations and gene transfers [17]. Stewart [18] demonstrated a positive correlation between the expression of stress response genes (such as *anr, rpoS,* and *relA spoT* that regulate hypoxic stress, stationary-phase growth and osmotic stress respectively) by *Pseudomonas aeruginosa* biofilm and the degree of antimicrobial resistance they exhibited. They also compared the ciprofloxacin susceptibility of wild type *Pseudomonas aeruginosa* biofilms with the biofilms formed by mutant strains deficient in *anr, rpoS,* and *relA spoT***.** The biofilms formed by mutant strains were more susceptible to the antimicrobial action of ciprofloxacin than the wild type biofilms. This makes it clear that stress response systems impact the ability of biofilms to tolerate antibiotics. However, they were not able to determine the specific underlying mechanisms. It can be hypothesized that activation of these stress response systems increase the frequency of genetic transfer and recombination as a result of which the biofilms acquire multiple resistance determinants [19].

The above mechanisms bring about a series of complex alterations in the genotype and phenotype of bacterial cells. The phenotypic changes such as change in membrane fluidity, reconstitution of membrane cholesterol content, etc are transient. But the genotypic alterations bring about a permanent change in the physiology of bacterial cell [6,8]. Environmental stresses influence the antibiotic-bacteria dynamics. This interaction results in a heterogeneous population of bacterial cells that are resistant to antibiotics [20]. These interactions resulting in cross resistance to antibiotics can be a component of natural selection through the activation of non-specific collective response or adaptive mutagenesis. Therefore, in relation to the theory of natural selection, the concept of stress-induced cross resistance to antibiotics might be the result of activation of multiple non-specific cascades that enable endurance to other factors as well. If interpreted with accordance to directed mutagenesis, it is probably due to an increased rate of random mutations after selection is applied on a population of bacterial cells. In biofilms, activation of stress-response systems increase the frequency of genetic recombination. The sequential cascade of molecular interactions following stress exposure that alter the susceptibility of bacterial cells to antibiotics need further precise exploration. Above discussed are the possible mechanisms of cross-talk between the functioning of stress response systems and mechanisms of antimicrobial action. However, they should to be precisely defined by robust scientific methods. Understanding the cross-talk between stress response systems and antimicrobial action will provide putative sites to interfere the emergence of antimicrobial resistance.

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References

1. Ebinesh A, Kailash TV (2016) Looking into antibiotic failure: a deemed threat, indeed not! Int J Appl Res Studies (iJARS) 5: 1247
2. Ebinesh A, Kailash TV (2016) Bacteriophage- mediated microbiome manipulation: A novel venture in fostering infant gut health. Int J Med Biotechnol Genetics 4: 34-39.
3. Ebinesh A, Kailash TV (2016) Horizon of New Hope towards a Robust infantile Gut: Advent of Bacteriophages in Tuning Gut Microbiome. Arch Clin Microbiol 7: 27.
4. Westwater C, Kasman LM, Schofield DA, Werner PA, Dolan JW et al. (2003) Use of genetically engineered phage to deliver antimicrobial agents to bacteria: an alternative therapy for treatment of bacterial infections. Antimicrob Agents Chemother 47: 1301-1307.
5. Boor KJ (2006) Bacterial stress responses: What doesn't kill them can make them stronger. PLOS Biol 4: 23.
6. Poole K. (2012) Bacterial stress responses as determinants of antimicrobial resistance. J Anitmicrob Chemother 196: 1-21.
7. Dorr T, Lewis K, Vulic M (2009) SOS response induces persistence to fluoroquinolones in Escherichia coli. PLOS Genet 5:1000760.
8. McMahon MAS, Jiru Xu (2007) Environmental stress and antibiotic resistance in food related pathogens. App Environ Microbiol 73: 211-217.
9. Faezi Ghasemi M, Gazemi S (2015) Effects of sub-lethal environmental stresses on cell-survival and antibacterial susceptibility of Listeria monocytogenes PTCC1297. Zahedan J Res Med Sci 17: 1-6.
10. Al-Nabulsi AA, Osaili TM (2015). Effects of osmotic pressure, acid or cold stresses on antibiotic susceptibility of Listeria monocytogenes. Food Microbiol 46: 154-160.
11. Ebinesh A (2017) Conspiracy of domestic microenvironment, bacterial stress response and directed mutagenesis towards antimicrobial resistance: Lessons for health care. J Infectious Disease Med Microbiol 1: 1-3.
12. Heidenreich E, Wintersberger U (1988) Replication-dependent and selection-induced mutations in respiration-competent and respiration-deficient strains of Saccharomyces cerevisiae. Mol Gen Genet 260: 395–400.
13. Foster PL (2000) Adaptive mutations: implications for evolution. Bioessays. 22: 1067-1074.
14. Al-Mahin A, Sugimoto S, Higashi C (2010) Improvement of multiple-stress tolerance and lactic acid production in Lactococcus lactis NZ9000 under conditions of thermal stress by heterologous expression of Escherichia coli dnaK. Appl Environ Microbiol 76: 4277-4285.
15. Hall-Stoodley L (2004) Bacterial biofilms: from natural environment to infectious diseases. Nat Rev Microbiol 2: 95-108.
16. Yang X (2008) The R1 conjugative plasmid increases Escherichia coli biofilm formation through an envelope stress response. Appl Environ Microbiol 74: 2690-2699.
17. Madsen JS (2012) The interconnection between biofilm formation and horizontal gene transfer. FEMS Immunol Med Microbiol 65: 183-195.
18. Stewart SP (2015) Contribution of stress responses to antibiotic tolerance in Pseudomonas aeruginosa biofilms. Antimicrob Agents Chemother 59: 838-847.
19. Marks RL (2012) High levels of genetic recombination during nasopharyngeal carriage and biofilm formation in Streptococcus pneumoniae. mBio 3: e00200-12.
20. Harms A (2016) Mechanisms of bacterial persistence during stress and antibiotic exposure. Science 354: 6318.

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