Review Article

Role of SOS response in Bacterial Drug Resistance

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ABSTRACT

SOS response is a global regulatory response to protect cell from severe DNA damage. Induction of SOS response involves more than forty genes, and products of these genes maintain the integrity of cell by enhancing the adaptation through mutagenesis. Recent studies reported that certain antibiotic induces SOS response by activation of chromosomal DNA damage. In this paper we are reviewing the current information about SOS system, providing resistance to bacteria by enhancing repair and recombination.

Keywords: SOS regulator, Quinolones, β-lactamases.

INTRODUCTION

Many species of bacteria have preferentially evolved to invade and multiply within human and animals, making them a potential threat to the host if they cause a persistent infection that leads to illness or death. Bacteria are outnumbered than the human body cells (host) and average approx. 10:1. Pathogenic bacteria drastically prevent colonization of the normal microbial inhabitants thus affecting digestion and uptake of essential nutrients as well[1]. Unfortunately, the commensal bacteria, which are normally kept in check by the host's immune system, can become pathogenic under opportunistic conditions. It was thought that, such pathogens might be controlled with introduction of antibiotic, but unfortunately not exactly happened like that; because bacteria have evolved resistance mechanism against antibiotics. Abraham and Chain[2], for the first time reported the occurrence of microbial resistance against antibiotics. Major causes of transmission of drug resistance in bacteria are selective pressure of antibiotic used and social and technical changes that enhance the resistance in microorganisms. The mechanisms underlying bacterial resistance to antimicrobials reside in the ability of bacteria to degrade antibiotics by enzyme, quickly modify their Genome is a consequence of not only spontaneous mutations or genome rearrangements that can occur during the bacterial life cycle, but also of exogenous gene acquisition through genetic exchange between bacteria and gene capture in integrons[3, 4]. Several bacteria acquire antibiotic resistance by inducing stress response leading to expression of several genes, provide resistance for particular antibiotics.

SOS response is stress response in bacteria, activated under stress condition by antibiotics that induces DNA damage[5]. SOS response maintains the integrity of cell by DNA repair and removal of mutagen from system. In this review, we have tried to reveal some important aspects of SOS response, conferred resistance to bacteria against certain antibiotics.

1. Resistance mechanism in bacteria

Antibacterial resistance in bacteria may be intrinsic or acquired[6]. Intrinsic resistance mechanism in bacteria is a natural occurring trait, generated by modification in genome, makes bacterial target site less accessible for antibiotics[7], for example obligate anaerobes are resistant to aminoglycosides as they lack the electron transport system essential for antibiotic uptake[8, 9]. Gram negative bacteria are resistant to macrolides and certain β-lactam antibiotics as the drugs are too hydrophobic to traverse the outer membrane[10]. While, acquired resistance is a trait in which bacteria previously sensitive to an antibiotic, display resistance further, either by mutation or acquisition of DNA or a combination of the two[11]. Methods of acquiring antibiotic resistance in bacteria are further given below:

Mutation: Krasovec and Jerman[12] reported that mutation in bacteria can be either spontaneous or adaptive. Spontaneous mutation may be either by replication error or due to DNA damage in actively dividing cell responsible for antibiotic resistance[13]. Several studies reported that mutations in the genes encoding the targets of rifamycins and fluoroquinolones, i.e. RpoB and DNA-topoisomerases respectively, results in resistance against those compounds[14, 15]. Prolonged exposure of bacterial species to sublethal concentration of antibiotic switches a small population of bacteria to generate a brief state of high mutation[16, 17]. This stage of mutation in bacteria is called 'hypermutation' in which they acquire to relieve the selective pressure, they grow, reproduces and exits the state of high mutation rate[18, 19]. Krosovec and Jerman [12] reported that, bacteria overcome such selective pressure related problem by induction of a special type of SOS inducible mutator DNA polymerase (pol) IV. Hypermutators in bacteria play a significant role in the evolution of antibiotic resistance and may also be

responsible for the multi-resistant phenotype which has been reported in several literatures [20-23, 14]. These mutations, known as adaptive mutations, have been associated with the evolution of antibiotic resistant mutants under natural conditions[24-26]. Adaptive mutagenesis is regulated by the stress responsive error prone DNA polymerases V (umuCD) and IV (dinB) [27, 9, 28]. Piddock and Wise[29] demonstrated that some antibiotic like quinolones induce a SOS mutagenic response and increase the rate of emergence of resistance in *E. coli*.

Horizontal gene transfer: Transfer of genetic material consisting of single or multiple mutation in between bacterial cells by conjugation, transduction and by transformation is known as horizontal gene transfer responsible for the spread of antibiotic resistance. These transferred genes may also be associated with plasmids and/or transposons. In addition, Simjee and Gill[1] reported that high level resistance to gentamycin and other aminoglycosides (except streptomycin) in *Enteroccoci*, was found to be associated with narrow and broad host range plasmids.

2. Role of SOS response in bacteria

SOS response is a stress regulator found among all bacterial species, come into play when huge number of damaged DNA is found in the cell[30, 31]. SOS response works together with two proteins RecA and LexA[32]. Function of RecA protein is to assemble on ssDNA to form a nucleoprotein filament known as the presynaptic complex[6]. This filament is an adaptable structure, capable of performing three separate functions: homologous recombination (interaction with double-stranded DNA, dsDNA), SOS induction (cleavage of the LexA repressor) and SOS mutagenesis (interaction with the processed Umu(D') 2C complex (DNA polymerase V)[14]. The active nucleoprotein filament is a helical complex of RecA protein monomer wrapped around ssDNA at a stoichiometry of three nucleotides per monomer and about six monomers per turn[33]. ssDNA and RecA filament bind around the LexA and facilitate autocleavage of LexA repressor, and autocleavage of LexA protein causing induction of more than 40 genes of SOS regulon involved in damage repair and recombination[34, 35].

3. Quinolones and their mode of action

Quinolones are those antibiotics which destroy bacteria by targeting nucleic acid structure such as gyrase and topoisomerase II[36]. Fluoroquinolones are synthetic antibiotics developed in the 1970s, used as human medicine to treat infectious diseases [37]. To the date, four generations of quinolones have been discovered, 1st generation of quinolones was nalidixic acid, 2nd generation norfloxacin and its derivatives ciprofloxacin and ofloxacin formed by substituent fluoro at 6th position and saturated nitrogen containing heterocycle at 7th position. The first representative of this generation was norfloxacin, thus norfloxacin and its derivatives ciprofloxacin and ofloxacin have broad spectrum of activity. 3rd generation of fluoroquinolones are levofloxacin and 4th generation of fluoroquinolones are moxifloxacin, furthermore, fluoroquinolones have broad spectrum of activity against gram negative and gram positive bacteria [37, 11].

4. SOS response mediated resistance of bacterial cells against quinolones drugs

Quinolones are very good inducer of SOS response in bacteria. DNA damage in bacterial cell triggers the production of various repair proteins by activating SOS gene network [32, 23, 38-40]. Qnr is protein family, protecting DNA gyrase from the quinolones[18]. Several similar proteins have been identified such as QnrA as well as QnrB, QnrC, QnrD and QnrS [41]. QnrB protein, coded by *qnrB* gene in bacteria that provides resistance against quinolones, reside on the plasmid [39]. The LexA binding site is located in the sequence upstream from *qnrB,* so that *qnrB* is regulated by the SOS-system, in response to DNA damage[42]. The peptide QnrB protects bacterial DNA-topoisomerases from quinolone inhibition and provides low-level quinolone resistance by a mechanism termed "plasmid mediated fluoroquinolones resistance"[43, 44]. The Qnr determinants facilitate the emergence of high-level antibiotic resistance in bacteria. In *E. coli*, this effect depends on the increased mutation ability conferred by the nonessential polymerases Pol II, Pol IV, and Pol V on LexA-cleavage-mediated de-repression of their respective genes (*polB*, *dinB,* and *umuDC*)[38]. Quinolones resistance gene *qnrB* is upregulated by ciprofloxacin in a RecA/LexA dependent manner. Quinolones resistance development in *qnrB* harboring bacteria is an integral part of their mode of action[45]. Ciprofloxacin resistant mutants could be elicited much more frequently in LexA positive wild-type strains than in LexA mutant strains and preventing LexA cleavage make bacteria sensitive for fluoroquinolones[46, 47]. In addition, SOS response induces persistence to fluoroquinolones[48]. Quinolone resistance is not only acquired via target site mutations, but also via SOS system by de-repression of genes whose products increase mutation rates.

5. Induction of bacterial resistance by SOS regulon against cell wall stress promoter antibiotics

Quinolones as well as β-lactams activate SOS regulon[49]; zidovudine or trimethoprim and rifampin activate the SOS gene network as well[50, 45]. Bacteria resistance against cell wall inhibitors induces SOS response via DpiBA pathway[51]. When cell wall integrity is affected by penicillin binding protein 3 (encoded by ftsI) which is specific target of pipericillin and cephalexin, either chemically (by exposure to some β-lactams) or genetically (by introducing a temperature-sensitive ftsI allele), activate the DpiBA two-component signal transduction system[52, 51]. RecA protein forms filament with damaged DNA, rendering the activation of the DNA damage-responsive SOS network of genes[25] owing to expression of SulA, a key component of the SOS network that inhibits septation and leads to cell elongation and inhibiting polymerization of septation triggering FtsZ monomers[53, 22]. Interestingly, β-lactams

that inhibit PBP3 and induce filamentation have been shown to stimulate the DpiAB two-component system, which can activate the SOS response[51]. β-lactam lethality can be enhanced by disrupting DpiAB signaling or by knocking out SulA. This indicates that SulA may protect bacteria against β-lactam killing by shielding FtsZ and limiting a division ring interaction among PBPs and peptidoglycan hydrolases[51]. In support of this idea, SulA expression limits the lysis observed in a strain of *E.coli* that expresses FtsZ[54], consequently delay in cell division provides temporary protection from β-lactam's lethality[49]. In the long term, development of resistance against sublethal exposure to the cell wall stressor could be favored by SOS-mediated mutagenesis, and it was indeed shown that error-prone DNA polymerase Pol IV (DinB) activity, which is part of the SOS regulon, is also induced by β-lactam antibiotics[10].

6. SOS response mediated induction of persister cells

Presence of antibiotic leads to formation of persister cells by inducing SOS response[48, 55]. Persisters are antibiotic tolerant cells that are not killed during treatment with antibiotics and resume growth when antibiotics are removed. Persisters are not pre-existing dormant cells, but rather that their formation is induced by the SOS response[48]. Persister cell formation can occur through the induction of toxins from the toxin-antitoxin family, such as TisB from the SOS regulon, which decrease the growth rate (drop of ATP, inactive peptidoglycan synthesis, no ribosome, no replication), causing tolerance to multiple antibiotics[55]. Interestingly, 15 toxin-antitoxin modules are present in the *V. cholerae* SI[34]. Hence, sub concentration of antibiotics causes induction of SOS response by leading to formation of persisters, which eventually contribute to the development of multiple drug resistance in bacteria.

CONCLUSION

The role of SOS response is very divergent under stressed condition; bacteria facing myriad of stress during daily life. To protect the integrity of cell, SOS mechanism comes in to play. In this review, we have studied about antibiotic mediated stresses causing induction of SOS response, leading to antibiotics resistance in bacteria. SOS response not only protects cell from stress conditions, but also confers resistance against many class of antibiotics. Thus, by controlling key regulators of SOS response, we can limit the spread of multiple drug resistance in bacteria.

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