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Side effects of antibiotics during bacterial infection: Mitochondria, the main target in host cell

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ABSTRACT

Antibiotics are frontline therapy against microbial infectious diseases. Many antibiotics are known to cause several side effects in humans. Ribosomal RNA (rRNA) is the main target of antibiotics that inhibit protein synthesis. According to the endosymbiont theory, mitochondrion is of bacterial origin and their molecular and structural components of the protein expression system are almost similar. It has been observed that the rate of mutations in mitochondrial rRNA is higher as compared to that of nuclear rRNA. The presence of these mutations may mimic prokaryotic rRNA structure and bind to antibiotics targeted to ribosomes of bacteria. Mitochondrial functions are compromised hence may be one of the major causes of side effects observed during antibiotic therapy. The current review had summarized the studies on the role of antibiotics on mitochondrial functions and its relevance to the observed side effects in physiological and pathological conditions.

1. Introduction

Since the development of antibiotics, it had been the first line of treatment against many Gram positive and negative bacterial infections since the early twentieth century. The compounds that specifically target fundamental cellular processes of bacteria, with negative consequences for pathogen survival, and no plausible side effects in host are considered as potentially useful antibiotics (Dimauro and Davidzon, 2005; Fischel-Ghodsian, 2005; Wang et al., 2006). It has been observed that more than 40% of antibiotics interfere with bacterial protein biosynthesis machinery and more specifically the ribosome is one of the most important targets (McCoy et al., 2011). The two ribosomal subunits (30S and 50S) play an important role starting from initiation of elongation to termination of the translational process. The 30S subunit is responsible for codon–anticodon interactions. In the prokaryotic system, the translation is a complex process and involves several steps like initiation, elongation and termination which had been well established. The initiation of the translational is initiated by a complex of IF1, IF2 (a GTP-binding protein), IF3, mRNA and the initiator fMet-tRNA^{fMet} which binds to the 30S ribosomal subunit, forming the 30S initiation complex (30S IC). In the next step, the 50S subunit joins the 30S IC and GTP is hydrolyzed. This leads to the disassociation of the initiation factors and fMet-tRNA^{fMet} is positioned in the P site. This complex is called as 70S initiation complex (70S IC). After binding of the first aminoacyl-tRNA and formation of the first peptide bond, the 70S IC enters the elongation cycle of translation and finally termination. The 50S subunit is responsible for the catalytic activity of the peptide bond formation. It had been observed that different steps of translational process are the direct target of different antibiotics. The mode of action at different steps of translation had been summarized in Table S1.

The peptidyl transferase center (PTC) is the most conserved rRNA nucleotide in the entire ribosome. The recent findings revealed an unexpected high level of variation in the mode of antibiotic binding to the PTC of ribosomes from different organisms (Polacek and Mankin, 2005). The antibiotics chloramphenicol and oxazolidinones act on the PTC and cause myelosuppression, lactic acidosis and optic and peripheral neuropathies similar to phenotypes frequently found in mitochondriopathies (Bacino et al., 1995; Bitner-Glindzicz et al., 2010). Similarly, another group of antibiotics, erythromycin, tetracycline and aminoglycosides, which target large and small subunits of rRNA also showed similar side effects (Pasquale and Tan, 2005). These are also known to act on mitochondria and may cause bioenergetic crisis in a patient with Leber's hereditary optic neuropathy (LHON) disease (Thyagarajan et al., 2000). Mitochondria are now known to be involved in many other cellular processes other than energy metabolism like apoptosis and regulation of inflammation during viral and bacterial infections (Zhao et al., 2004). However, the action of antibiotics in the context of the newly discovered role of mitochondria has not been studied. The antibiotics had been extensively used as front-line therapy against many bacterial infections and are considered as life saving drugs. The side effects of

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antibiotics are emerging which have been summarized in Table S2. The majority of the antibiotics target the ribosome of bacteria to inhibit its translation, hence its growth. Due to the similarity of bacterial and mitochondrial ribosomes most of the antibiotics show side effects similar to mitochondrial myopathies. In the current review, we summarize the available literature in the area and emphasized the needs for further investigation to understand the side effects of antibiotics in human cells with special focus on mitochondria.

2. Antibiotic therapy in microbial infection and its side effects

The emergence of antibiotic resistance in majority of pathogenic bacteria is a cause of major concern in infectious bacterial diseases therefore it is of urgent need to identify the antimicrobials which are more susceptible for microbial infections with minimal side effects on the host cell. The mechanism of acquisition of antibiotic resistance should be further investigated while developing new antibiotics taking their side effects into consideration. Protein synthesis is a key and universal process in all unicellular to multicellular organisms. The functional sites are highly evolutionary conserved within rRNAs. These sites are targeted by ribosomal drugs, which implies limitations with respect to selectivity and toxicity (Xing et al., 2006).

The LHON patients when given erythromycin showed bilateral vision loss with optic nerve atrophy. The transmitochondrial cybrids derived from the patient showed bioenergetic crisis, impairment of cell growth in galactose medium and mitochondrial protein synthesis defects (Luca et al., 2004). Tetracycline is also known to cause several side effects by targeting cytochrome oxidase activity in thymocytes (Tanimoto et al., 2004) and HepG2 cells (Bottger et al., 2001). The aminoglycoside group of antibiotics is associated with both nephrotoxicity and ototoxicity (Polacek and Mankin, 2005). It has been shown that renal impairment is, in general, mild and reversible while ototoxicity is irreversible.

The side effects of antibiotics are tissue specific (Borshchev et al., 2012; Marra et al., 2012; Neri et al., 2012; Roca-Alonso et al., 2012; Rouby et al., 2012; Scherzed et al., 2013; Siefker-Radtke et al., 2013). Several examples of the side effects have been summarized in Table S3 and many more examples can be found in the literature. The energy demand of individual organ systems is different (Peters et al., 2011) therefore the side effect of antibiotics related to mitochondria may vary. The nervous system is dependent on mitochondrial energy metabolism therefore it is severely affected by mitochondrial mutations. The pathologies associated with brain like optic neuropathy and sensorineural hearing loss are commonly observed (Table S3) during antibiotic therapy during bacterial infections (Polacek and Mankin, 2005). Remarkably, toxic optic neuropathy and ototoxicity are observed after the administration of different antibiotics, such as macrolides (Cotney et al., 2007) or chloramphenicol (Pacheu-Grau et al., 2010). Recently, 25 transmitochondrial cell lines derived from the platelets from individuals related with the most frequent available European mitochondrial DNA haplogroups. These cell lines were cultured in the presence/absence of antibiotics targeting for ribosomes (Pacheu-Grau et al., 2013). The treatment of linezolid showed low levels of mitochondrial translation products, MT-CO1/SDHA ratio and complex IV activity in the cybrids harboring common mutations. The linezolid also showed side effects obtund and disoriented in time and space (Kofoed and Vester, 2002). These evidences suggest that mitochondrial functions may be compromised during antibiotic therapy during bacterial/viral infections. The cell line study also suggests that mitochondrial mutation may further compound the side effects of antibiotics targeting bacterial ribosomes.

3. Mitochondria: Target of antibiotics

Many of the antibiotics target bacterial protein synthesis machinery specifically ribosomal RNA (Table S1). According to the endosymbiotic theory as well as comparisons of rRNA sequences from bacteria and higher eukaryotes show high degree of similarity. Interestingly, inspite of these similarities there are differences in rRNA sequences, which are highly conserved which may have implication in drug sensitivity and selectivity (Harish and Caetano-Anolles, 2012). It had been observed that some of the resistance mutations in bacteria are present in human wild-type rRNA and can account for the antibiotic selectivity (Polacek and Mankin, 2005). The ribosomal peptidyl transferase center (PTC) plays a important role in protein synthesis and its function is inhibited by antibiotics like chloramphenicol and oxazolidinones (Carelli et al., 2002; Nagiec et al., 2005; Yunis, 1989). The treatment of the human tissues or cells with antibiotics, severely affects mitochondrial parameters and functions since the PTC mimics bacterial PTC (Fig. 1). The cell growth, mitochondrial mass, respiratory complex activities, levels of mtDNA-encoded subunits and mitochondrial protein synthesis are impaired with administration of antibiotics (Duewelhenke et al., 2007). Similarly, patient undergoing linezolid therapy for a long time showed defect in mitochondrial complexes. Similarly, a recent study systematically showed that antibiotics affected the mitochondrial functions in cell line studies and the side effects have been clearly observed in animal model studies as well. Kalghatgi showed that mice treated with clinically relevant doses of bactericidal antibiotics showed signs of oxidative damage on the transport chain, and increased levels of ROS. The antibiotics ciprofloxacin (a fluoroquinolone), ampicillin (a β-lactam), and kanamycin (an aminoglycoside) in the mice showed decreased mitochondrial functions and increased levels of ROS (Kalghatgi et al., 2013).

Interestingly, these parameters revert back to normal once the antibiotic is removed from the culture media (Pereira et al., 2009). The effect of antibiotics on mitochondrial function is also specific. Streptomycin affects mitochondrial translation in HeLa, cervical carcinoma cells having mtDNA 1555G > A mutation (McKee et al., 2006). This effect is specific as it does not happen on the 143B osteosarcoma cells with similar nuclear background and mtDNA mutation (Inoue et al., 1996). The mitochondrial genome encodes only for few functional proteins and many genes had been transferred to nuclear DNA during evolution. Nuclear DNA encodes most of the protein responsible (except 13 encoded from mitochondrial DNA) for mitochondrial function, hence, the nuclear genetic background will probably influence the toxicity produced by antibiotics. TFB1M is a nuclear encoded mitochondrial transcription factor and it is closely related to rRNA methyltransferases. The expression of TFB1M in *Escherichia coli* lacking the *Ksg* rRNA methyltransferase, helps in methylation of two adjacent adenine residues in a stem loop structure of the bacterial 16S rRNA leading to resistance to the antibiotic kasugamycin (Giordano et al., 2002). The polymorphism on chromosome 6 near the TFB1M gene, however not located in the coding region of the gene has been defined as a nuclear modifying locus and is responsible for mitochondrial functional defect leading to deafness (Guan et al., 2001). The 28 nucleotide residues downstream from the pathogenic 1555G > A mutation, are evolutionarily conserved in the mitochondrial 12S rRNA (Cotney et al., 2007). Interestingly, there is evidence that the nuclear genetic background influences the phenotypic expression of this mutation (Seidel-Rogol et al., 2003). Similarly, it had been observed that human cells (MCF12A) treated with doxycycline showed the alteration in nuclear gene expression that alters mitochondrial functions. It was observed that antibiotic treatment leads to a shift from TCA cycle to glycolytic pathway because of the upregulation expression of the gene involved in glycolytic pathway (Ahler et al., 2013). These evidences suggest that nuclear genes are obviously implicated in the modification or interaction with the mt-rRNAs. Hence, should be considered when analyzing the phenotypic effects of particular ribosomal antibiotics on the mitochondrial translation.