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Review

Mitochondrial DNA mutations associated with aminoglycoside induced ototoxicity

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Abstract

Aminoglycosides (AmAn) are widely used for their great efficiency against gram-negative bacterial infections. However, they can also induce ototoxic hearing loss, which has affected millions of people around the world. As previously reported, individuals bearing mitochondrial DNA mutations in the 12S rRNA gene, such as m.1555A>G and m.1494C>T, are more prone to AmAn-induced ototoxicity. These mutations cause human mitochondrial ribosomes to more closely resemble bacterial ribosomes and enable a stronger aminoglycoside interaction. Consequently, exposure to AmAn can induce or worsen hearing loss in these individuals. Furthermore, a wide range of severity and penetrance of hearing loss was observed among families carrying these mutations. Studies have revealed that these mitochondria mutations are the primary molecular mechanism of genetic susceptibility to AmAn ototoxicity, though nuclear modifier genes and mitochondrial haplotypes are known to modulate the phenotypic manifestation.

Keywords: Aminoglycosides ototoxicity; Genetic susceptibility; Mitochondrial DNA mutations

Contents

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1. Introduction

Sensorineural hearing loss is a common human disorder affecting approximately 275 million people around the world, which occurs because of damaged or deficient cochlear hair cell function (Mathers et al., 2007). The human cochlea contains only about 5000 hair cells (HCs) and do not have the capability to self-repair. Genetic defects may cause the hair cells to be abnormal at birth. Additionally, there are many environmental factors, including noise, aging, and ototoxic drugs, which can cause damage to the HCs. Aminoglycoside (AmAn) antibiotics are common clinical drugs characterized by amino sugars with glycosidic linkages. These compounds are widely used throughout the world to treat gram-negative bacterial infections, which are not responsive to conventional antibiotics, such as penicillin. However, AmAn is difficult to metabolize and can be concentrated in the perilymph and endolymph of the inner ear (Henley and Schacht, 1988), which results in irreversible auditory and vestibular ototoxicity (Fischel-Ghodsian, 2005; Guan, 2005; Al-Malky et al., 2011; Alharazneh et al., 2011; Huth et al., 2011; Li and Steyger, 2011). The abuse of these drugs such as gentamicin, kanamycin, particularly in developing countries has caused millions of people to suffer from ototoxic side effects. The incidence of ototoxicity has been suggested to range from 2% to 45% for adults and 0–2% for infants (Matz, 1993; Fausti et al., 1999). It has been found that there is unusual susceptibility to AmAn ototoxicity related to genetic background in many individuals. In this mini-review, we briefly introduce the molecular mechanism of genetic susceptibility to AmAn ototoxicity hearing loss.

1.1. Aminoglycosides destroy bacteria without harming mammalian cells by irreversibly binding the 30S subunit of the bacterial ribosome

The ribosome is a complex molecular machine found within all living cells, which serves as the site of biological protein synthesis (translation). Ribosomal proteins and rRNAs are arranged into two distinct ribosomal pieces of different sizes, known generally as the large and small subunit of the ribosome. The ribosomal subunits of prokaryotes and eukaryotes are very similar. Prokaryotes have 70S ribosomes, each consisting of a small (30S) and a large (50S) subunit, while eukaryotes have 80S ribosomes consisting of a 40S and a 60S subunit (Palade, 1955; Czernilofsky et al., 1975; Wimberly et al., 2000). The structural differences between the bacterial 70S ribosomes and eukaryotic 80S ribosomes have been exploited to create antibiotics to combat bacterial infections without harming cells of the infected person (Gutell et al., 1994). Aminoglycosides take effect by directly binding to the base pairs C1409–G1491 at the A-site of bacterial 16S rRNA (Fig. 1A), which acts as an essential part of the decoding site, and this interaction results in protein mistranslation or premature termination of protein synthesis (Davies and Davis, 1968; Noller, 1991).

Ribosomes are also found in chloroplasts and mitochondria of eukaryotes, and are similar to bacterial ribosomes. According to the endosymbiotic theory, these organelles are believed to be descendants of bacteria that became incorporated into eukaryotic cells for the implementation of oxidative mechanisms (Vellai et al., 1998; Selmer et al., 2006). Mitochondria are thought to originate from α-purple bacteria. During the course of their evolution, the endosymbiont transferred many of its essential genes to the nuclear chromosomes of eukaryotes and developed into the present-day mitochondria in the eukaryotic cell. Nevertheless, mitochondria still carry hallmarks of their bacterial ancestors. For instance, mitochondria use fMet-tRNA as an initiator of protein synthesis. Mammalian mitochondrial ribosomes have small 28S and large 39S subunits, forming a 55S protein complex, which is active in mitochondria and functions to translate mitochondrial mRNAs encoded in mtDNA (Collatz et al., 1976). Even though mitochondria ribosomes are similar to bacterial ribosomes, normal cells show low toxicity to regular dosages of AmAn. This is because mitochondria are surrounded by a double membrane which does not easily admit these antibiotics into the organelle. More importantly, mammalian mitochondrial ribosomes possess an A-to-G substitution in the aminoglycoside binding site in 16S rRNA, leading to the significantly reduced toxicity of AmAn in eukaryotic cells (Hutchin et al., 1993; Gutell et al., 1994; Guan, 2005; Ruiz-Pesini and Wallace, 2006; Avent et al., 2011; Du et al., 2014; Huth et al., 2015).

1.2. Mitochondrial DNA mutations m.1555A>G and m.1494C>T are associated with aminoglycoside ototoxicity

Mitochondria have their own genome with a modified genetic code. The mammalian mitochondrial genome is transmitted exclusively through the female germ line. Indeed, pedigree analysis has shown that the aminoglycoside susceptibility exhibits a maternally inherited transmission. The most well studied mutations are m.1555A>G and m.1494C>T in the 12S rRNA gene of the 39S subunit (Moazed and Noller, 1987; Purohit and Stern, 1994; Fourmy et al., 1998). Prezant et al. (1993) first suggested the molecular basis of ototoxic hearing loss by analyzing the mitochondrial genome of three Chinese pedigrees and a large Arab-Israeli pedigree with maternally inherited non-syndromic hearing loss. The m.1555A>G in the 12S rRNA gene was identified in these matrilineal subjects, but not found in 278 control subjects (Prezant et al., 1993). As shown in Fig. 1, the A nucleotide at the 1555 position in the 12S rRNA gene in human mitochondria is equivalent to position 1491 in the 16S rRNA gene in wild-type *Escherichia coli* (Bottger, 2010). When the 1555 A is mutated to G, the secondary structure of 12S rRNA more closely resembles the corresponding region of 16S rRNA in *E. coli* (Fig. 1C). Thus, it was speculated that this newly generated G-C pair creates a binding site for aminoglycoside. Indeed, Guan et al. reported that the m.1555A>G mutation alters the binding properties of aminoglycosides at the A-site of rRNA and leads to conformational changes in 12S rRNA. Families with inherited patterns of deafness carrying the m.1555A>G mutation have subsequently been reported worldwide, including in Asian, Caucasian, and African populations, as well as in many sporadic individuals (Matthijs et al., 1996; Pandya et al., 1997;