COMMENT
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Combating mitochondrial toxicity: looking at the past and where to go

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Mitochondria are the main sources of intracellular energy and reactive oxygen species (ROS), which play an important role in the regulation of cell survival and death under pathological conditions. Mitochondria are important targets of drug toxicity [1]. Some antiviral drugs, antitumor drugs and antibiotics can significantly induce mitochondrial damage in target organs such as the liver and heart [2]. Drug-induced mitochondrial damage may involve multiple pathways and mechanisms. Mitochondria are important targets of drug toxicity. In the process of drug research and development, mitochondrial toxicity has become an important factor for many drug development failures or clinical application limitations. Some large international pharmaceutical companies and regulatory institutions have successively used mitochondrial toxicity evaluation as an important part of the preclinical safety evaluation of drug candidates. In recent years, mitochondrial damage caused by poisoning has become a research hotspot, and mitochondria have been identified as an important target of toxicity of many drugs. Studies have found that the poisoning of some fat-soluble compounds, such as organophosphorus pesticides, bupivacaine, and amitriptyline, can lead to mitochondrial damage.

Mitochondrial toxicity can affect different parts of the body, including the heart, nerves, muscles, pancreas, kidneys, and liver. Conditions resulting from mitochondrial toxicity can include muscle weakness [3], inflammation of the pancreas (pancreatitis) [4] at high levels (lactic acidosis), changes in the distribution of lactic acid in the blood and the amount of body fat (abnormal lipid metabolism) [5] and fatty liver (fatty liver). Some antiretroviral therapies (ARVs) use drugs that may cause mitochondrial toxicity [6].

At present, studies on mitochondrial toxicity mainly focus on the following aspects: changes in ultrastructure, including the number, size and volume of mitochondria, bilayer structure, length and density of cristae, intracellular distribution, and relationship with suborganelle nuclei and endoplasmic reticulum; mitochondrial function, including membrane potential and permeability transition pore activity, energy metabolism (mitochondrial respiratory chain control rate (RCR) and respiratory chain complex I-V enzyme activity), ATP level, and ATPase activity. The inhibition of mitochondrial respiratory chain complex activity can lead to serious mitochondrial dysfunction, and long-term inhibition of mitochondrial respiratory chain complex activity may lead to neurological diseases such as Parkinson's disease, Down's syndrome, Leigh's syndrome, etc [7]. Therefore, mitochondrial respiratory chain complex activity is often used as an indicator of mitochondrial virus-induced diseases [8].

Beatrice Golomb of the University of California, San Diego, has been studying the side effects of fluoroquinolones for more than a decade. In 2007, David Melvin, a police officer and cyclist, was forced to use a wheelchair because of side effects from levofloxacin, suspected of epididymitis [9]. Golomb says there is growing evidence that fluoroquinolones can damage mitochondria in human cells. Mitochondria in human cells came from bacteria billions of years ago. Antibiotics that work on bacteria can also affect cells in our own bodies, which is why diseases worsen over time [10]. Many drugs have mitochondrial toxicity, says Mike Murphy, who studies mitochondrial biology at the University of Cambridge [11]. Because mitochondria retain some similarities to bacterial ancestors, antibiotics pose a particular threat to them. For example, the aminoglycoside antibiotic gentamicin can cause deafness by damaging the mitochondria of hair cells in the inner ear [12].

Since the 1980s, studies have shown that fluoroquinolones impair mitochondrial function, but the most convincing 2013 study by Collins and his colleagues reported that antibiotics cause the accumulation of reactive oxygen species in mitochondria, which leads to the suppression of mitochondrial function [13]. The effect is very large, and the range of effects is very large, the most significant of which is the quinolones. A 2010 report by toxicologist Yvonne Will examining mitochondrial damage found that some antibiotics can affect some people's mitochondria [14]. All fluoroquinolones have a powerful damaging effect on the mitochondria of human hepatocytes at therapeutic concentrations.

Antibiotic damage to mitochondria is not widely accepted, Collins said, and it is generally believed that antibiotics do not affect mammalian cells. At present, there are no reliable biomarkers to test mitochondrial damage in humans. Nor is it known how precisely to measure the extent to which fluoroquinolones damage human cells [13]. A 2013 FDA safety review of antibiotics cited a 1996 study in which ciprofloxacin caused mitochondrial DNA breaks in mammalian cell lines [15]. However, Neil Osheroff, a biochemist at Vanderbilt University in Tennessee who studies fluoroquinolones, is skeptical of the results. His tests found that the drug had very little effect on human DNA at therapeutic concentrations. Mitochondrial damage is not the only theory. A 2015 study suggested that fluoroquinolones bind to iron atoms at the active sites of several DNA-modifying enzymes, causing epigenetic changes that may be responsible for the side effects [16].

A study led by researchers from the Federal Institute of Technology in Lausanne, Switzerland, suggests that adding tetracycline arbitrarily may have a negative effect on biological experiments: tetracycline alters the expression of the mitochondrial genome and disrupts the function of the cell's respiratory chain [17]. This study suggests that these antibiotics can cause a monocyte protein imbalance by affecting mitochondrial translation, an effect that may reflect the evolutionary relationship between mitochondria and Proteobacteria. Even at low concentrations, tetracycline can induce toxic stress on mitochondrial proteins, leading to changes in nuclear gene expression and altering the dynamics and function of mitochondria in commonly used cell types as well as in nematodes, fruit flies, mice and plants. Because tetracycline antibiotics are so widely used in scientific research, scientists should be aware of their potential confounding effects on experimental results. Adding tetracycline arbitrarily may have negative effects on biological experiments: tetracycline can alter the expression of the mitochondrial genome and disrupt the function of the cellular respiratory chain. Furthermore, these results caution against the widespread use of tetracycline in animal husbandry because of its potential effects on the environment and human health. It was found that methylene blue can reduce the decrease in ATP levels, inhibit the opening of mPTP and reduce the production of ROS in hepatocytes of mice with acetaminophen poisoning [18]. Curcumin can inhibit the decrease in ATP production and $\Delta\psi m$ induced by paracetamol and the decrease in the activity of mitochondrial respiratory chain complex enzymes, which can induce the protective effect of paracetamol-induced liver cell mitochondria [19]. Mitochondria-targeted antioxidants and N-acetylcysteine amides reduce oxidative stress damage by reducing ROS production and increasing glutathione levels, thereby reducing the toxicity of fat-soluble compounds to mitochondria [20].

Mitochondria play a regulatory role in maintaining the normal

operation of organ functions. Mitochondrial damage may play an important role in organ function damage caused by compound poisoning, but the detailed mechanism of mitochondrial damage is not very clear. The relationship between mitochondrial damage and compound poisoning is still worth further investigation, and its mechanism of action has become a research hotspot in recent years. Mitochondrial damage may also provide directions for the clinical treatment of compound poisoning. It is believed that in the near future, the protection of mitochondria to maintain the normal operation of mitochondria may be a new method to rescue compound poisoning clinically.

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Competing interests

The authors declare no conflicts of interest.

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Abbreviations

ROS, reactive oxygen species; ARVs, antiretroviral therapies; RCR, respiratory chain control rate.

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