CLINICAL INVESTIGATION

Antibiotic induced changes to mitochondria result in potential contributions to carcinogenesis

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Commentary

Mitochondrial job and creation of toxic mix by antibiotic

Mitochondria, a primitive endosymbiotic bacteria, related to extant SARII marine bacteria and Rickettsias, in eukaryotes is responsible for Oxidative Phosphorylation (OP) and ATP and NAD production, when exposed to clinically equivalent doses of antibiotics that target bacteria (cipromycin, ampicillin, kanamycin), exhibited a decline in glutathione titre, an increase in Reactive Oxygen (ROS) and an increase in lipid peroxide [1,2].

Modes of action of antibiotics on mitochondria and microbiome

1. **Quinolones:** Commonly prescribed antibacterial organofluorine compounds that act by inhibition of bacterial DNA synthesis and result in rapid cell death [3]. They could be expected to do collateral damage to mitochondria and the human microbiome. This group contains Ofloxacin, Norfloxacin (Noroxin), Ciprofloxacin (Cipro), Moxifloxacin (Avelox)

2. **Aminoglycosides:** Gentamicin, amikacin which creates holes in the outer cell wall of bacteria suggesting mitochondria and the microbiome might be at risk of similar damage [4]

3. **β-lactams or penicillin:** Its derivatives such as cephalosporins, monobactams, carbapenems, carbacephems that inhibit cell wall synthesis in bacteria and by inference mitochondrial and microbiome reproduction

The harmful impact of liberated substances on dna, p53 tumour suppressor gene, mutagenicity and known effects in other cancers

Glutathione is an antioxidant that soaks up ROS and is essential for many neurological and other body functions. Glutathione is capable of preventing damage to important cellular components caused by reactive oxygen species such as free radicals, peroxides, lipid peroxides, and heavy metals. ROS has been linked to mutation of the cell's DNA protector, the P53 gene and lipid peroxide [5] has been linked to oesophageal carcinogenesis and in the molecular basis of alcoholism and red meat and treated meat carcinogenesis [6]. Lipid peroxide is a mutagen. Kalghatgi also found damage to DNA. This is another finding often associated with carcinogenesis.

Antibiotics render the immune system less effective in infection and inflammation control

Researchers reporting in Frontiers in Microbiology found that Short Chain Fatty Acids (SCFA) from resident bacteria were important in protecting the immune system, and inflammation

control. Both of these side effects have important ramifications for the prevention of cancer initiation. Antibiotics diminished resident bacteria carrying out this role and supplemental SCFA was not effective in ameliorating the effect. Dysbiosis of resident microbes is unequivocally associated with immune-related disorders and opportunistic and pathogenic infections which can themselves set the stage for cancer [7]. If potentially carcinogenic microbes *Helicobacter pylori, Streptococcus bovis, Salmonella typhae, Fusobacterium, Chlamydophyla, Bartonella* or Caries bacteria or any carcinogenic viruses or worms [8] capitalizing on depressed immune systems proliferate as a consequence this can lead to increased risk of cancers.

The evidence of carcinogenesis from research

Seeing that these changes were consistent with steps found in carcinogenesis [9] I asked the question, what is the clinical and epidemiological evidence that antibiotics increase the risk of cancer? It appears others have also addressed this question [10-13]. Velicer et al. [14] found prolonged use of the antibiotic increased the risk of fatal breast cancer. This has broad global ramifications because of the chronic long term exposure of residues in diet from treated foods such as beef, pork, poultry and farmed fish and seafood products.

Antibiotics change tissue environment to favour cancer metabolism by the warburg effect

In addition, one of the antibiotics classes tested was linked to a decline in pyruvate, the feedstock for the Citric acid cycle and ATP and NAD production or OP, thus relegating the cell to a low oxygen environment. This is called the Warburg Effect which cancer cells have been shown to prefer in which they employ glycolysis instead of oxidative phosphorylation for their energy. It can be expected that this ideal environment for glycolysis favouring cancer cells will be the norm whenever and wherever mitochondria are damaged as they are with these antibiotics tested and with common pesticides.

The jyrkkanen carcinogenic mechanism

Since 50% of cancers have a mutated P53 gene from prior studies and lipid peroxide is linked to mutagenesis and carcinogenesis in at least two cancers. I propose the hypothesis that these findings point to the following factors contributing to carcinogenesis:

1. ROS increases DNA and P53 mutations
2. Mutagenic Lipid Peroxide increases cancer contributing mutagens
3. Reduction of oxidative phosphorylation increasing Warburg Effect favouring cancer cells glycolysis resulting from damage to mitochondria
4. Antioxidant glutathione deficiency
5. Antibiotic induced microbiome dysbiosis immune compromise decreasing efficacy of subjects cancer defense mechanisms

Further research suggested by these studies includes testing all antibiotics for their mitochondrial impacts

These findings also raise the question are there pesticides with similar consequences? There are intriguing findings in China. 9/12 common pesticides tested fragmented mitochondria at normal application doses [15]. These results, in turn, raise the obvious question, are the consequences similar in terms of potential long term carcinogenicity? Another interesting question. The heart muscle is full of mitochondria. Do antibiotics and pesticides affect the hearts mitochondria and if so in what way and for how long? I would expect this heart loss of OP combined with ROS and increased peroxides to lead to a condition like chronic fatigue and possibly compromised coronary function.

Cumulative augmentation from environmental cancer causes

Cumulative antibiotic for clinical treatment exposures are unwittingly augmented by chronic low-level residues of other antibiotics from dietary sources like poultry, beef, farmed fish and pork and may not immediately cause a cancer but may contribute to the conditions for one to occur at a later date by facilitating entry of carcinogenic infectious agents other mutagens and carcinogen residues, radiation, chemical and pesticide residues and age stressing the tissues further.

An evolution approach enables these extrapolations

These findings in normal mitochondria of their stress response to antibiotic biocides are consistent with their evolutionary origin from bacteria and are linked to biochemical pathways already shown linked to carcinogenesis and confirmed in the literature. Clearly, regulatory agencies need to pay more attention to these findings.

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