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Review Article

Antibiotic Overusage Causes Mitochondrial Dysfunction Which May Promote Tumorigenesis

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Abstract: Mitochondria are dynamic intracellular organelles involved in many vital cellular functions. It is important to maintain good mitochondrial biogenesis and health. Mitochondrial dysfunction is known to be associated with many neurodegenerative diseases, such as, Parkinson's, Alzheimer's and amyotrophic lateral sclerosis. In the 1930's Warburg described a link between mitochondrial function and tumorigenesis. Modern Medicine has fallen prey to the overusage and misuse of antibiotics. This minireview postulates that this misuse may attack the mitochondrion and alter host-antibiotic interactions that might cause serious pathophysiologic conditions. One such condition may be cancer which was proposed by Warburg and supported by our work on normal mitochondria organelle transplantation in cancer. Some groups of antibiotics attack targets that are shared by prokaryotes and mitochondria. This leads to mitochondrial dysfunction possibly promoting tumorigenesis and neurodegenerative conditions.

Keywords: Antibiotics, Mitochondria, Warburg Effect, Tumorigenesis

1. Introduction

Mitochondria are dynamic, active, mobile intracellular organelles that undergo constant fission and fusion; and are involved in many vital cellular functions. Otto Warburg described a link between defects in mitochondrial function and tumorigenesis in the 1930's. He noticed an increase in glycolysis and lactate production of cancer cells in the presence of oxygen without an increase in oxidative phosphorylation (OXPHOS). He said this was caused by a defect in cellular respiration. This aerobic glycolysis became known as the "Warburg Effect" [1-2]. Our results of transplantation of normal mitochondria into cancer cells causing inhibition of glycolysis suggested mitochondrial dysfunction in cancer cells and supported Warburg's observation [3-4].

Mitochondria are probably descended from free-living bacteria that survived endocytosis by an eukaryotic host cell over a billion years ago; and this theory was postulated by the great work of Lynn Margulis [5]. Michael Gray has done tremendous work on mitochondrial evolution. He described DNA evidence and hard science describing evidence affirming a bacterial origin of mitochondria. They are probably an alpha-class of proteobacteria (alpha-proteobacteria) the specific bacterial lineage from which they originated [6]. The fact that mitochondria are evolutionary bacteria supports the probability that their function could be affected by antibiotics; just as are bacteria. We will present evidence during this communication to support this possibility.

2. Some Common Problems Caused by Antibiotics

Most physicians are aware of the serious problem of bacterial antibiotic resistance. The use and misuse of antibiotics has created a global health crisis; and antibiotic resistant bacteria are increasingly making it difficult to treat infections. Hiltunen, Virta, and Laine have published a great paper entitled "antibiotic resistance in the Wild; an eco-evolutionary perspective". They discuss how this problem

can be studied, how it arises and the impact on human and animal health. This article is highly recommended [7]. Woolhouse and Word have emphasized how solving antimicrobial resistance in a single environment, as in the clinic setting, will be ineffective because in bacteria, mobile genetic elements (MGEs) and drugs themselves move among human, animals and environmental compartments [8]. The emergence of increased bacterial resistance has prompted the development of stronger antibiotics, which in turn probably produce more severe resistant bacterial strains. These powerful antibiotics probably also impact the health of normal intracellular mitochondria leading to mitochondrial dysfunction and defective cellular respiration due to damage to the electron transport chain (ETC).

3. Effect of Antibiotics on Host Immunity

Antibiotics can also cause other serious problems that impact the host immunity of humans. This is especially true if the person already has occult cancer that is in the equilibrium phase of cancer immunoediting. Antibiotic damage to the host mitochondria might be just what tips the balance towards the escape phase. Clostridium difficile (C. Diff) infection is a serious diarrhea and 20% of these cases are antibiotic associated. It can produce serious complications, such as, pseudomembranous colitis, toxic megacolon, perforation of the colon, and sepsis. These conditions impair host immunity increasing cancer risk.

Another serious condition that is also frequently precipitated by antibiotic use is vaginitis. The condition is caused by disruption of the healthy vaginal microbiota. One of the main organisms of the vaginal microbiota that supports a healthy vaginal mucosa is the Lactobacillus species and its eradication by antibiotics can cause a serious vaginal yeast infection caused by the yeast "Candida Albicans. This problem can also contribute to stress and an impairment of host innate immunity.

4. Antibiotic Effect on Gut Microbiota and Immunotherapeutic Efficacy of Cancer Immunotherapy

Essential for precision medicine is an understanding of the interactions between metabolites, microbes, and the immune system. This is especially true for certain cancer immunotherapeutic drugs. Evidence shows that there is a complex interaction between cancer, metabolites, and the microbiome and a positive result of some cancer immunotherapy drugs. Johnson, Spilker, Goetz, et al. have published a great paper on the metabolite and microbiome interplay in cancer immunotherapy [9]. This is a very good, complex paper that discusses how bacteria use host metabolites to build biofilm to propagate cancer, host versus bacterial metabolite origin, data to knowledge, and microbial metabolic influences on immunotherapeutic efficacy and future directions. This is a must read to later understand how the effect of antibiotics on the microbiome could also affect the evolutionary bacteria's relative "the mitochondrion."

Microbial co-metabolism can affect T-cell signaling pathways by production of amino-acids, fatty acids and butyrate especially production of proinflammatory Th17 and anti-inflammatory Tregs [10-11]. This co-metabolism can determine the result of immunotherapeutics and cancer cell survival [12-14]. Certain bacterial species of the microbiota play important roles in modulating the host immune system. Viaud and investigators showed that bacteria immunomodulation is done by the drug Cyclophosphamide. They found the drug changed the microbiome of the small intestine of mice with translocation of Gram positive bacteria to the spleen and mesenteric lymph nodes initiating production of helper T-cells, Th1 and Th17 promoting immune medicated cancer cell death [15]. Immunomodulation of the microbiome also effects Toll-like receptor (TLR) against CpG oligonucleotides. This immune response is complex and involves both humeral and cellular immunity [16].

Recently it has been shown that microbiota plays a tremendous role in modulating cancer response to checkpoint inhibitors especially the checkpoint inhibitor anti cytotoxic T lymphocyte-associated protein 4 (CTLA-4) antibody ipilimumab and also antibodies directed to PD-1/PD-L1. A great article published by Vetizou, Pitt, Daillere, et al. entitled "Anticancer immunotherapy by CTL-4 blockade relies on the gut microbiota" [17]. They emphasize the importance of maintaining appropriate flora of certain bacterial species especially the genus Bifidobacterium and Bacteroides. Antibiotics may eradicate these organisms and decrease checkpoint inhibitor therapeutic efficacy.

5. Adverse Effects of Antibiotics on Mitochondria

There are many classes of antibiotics that lead to mitochondrial damage that can develop into severe pathophysiologic responses. The fact that these organelles are archaic bacterial ancestors explains mitochondrial damage caused by the anti-bacterial effects of the drugs. There are several groups of antibiotics such as fluro-quinolones, aminoglycosides, and chloramphenicol that cause specific single side effects caused by mitochondrial interference. Other drug groups can cause multisystemic toxicity. An example of these types is Linezolid/Oxazolidinone. These drugs are inhibitors of bacterial ribosomes which may also be a direct inhibition of mitochondrial ribosomes. Examples are aminoglycosides and oxazolidinones [18]. Some other targets are gyrases/topoisomerases and bacterial ribosomes which are disrupted by fluoroquinolones and chloramphenicol. It is thought their effect on host mitochondria is based on idiosyncratic damage. It appears that antibiotic side effects on the mitochondrion are because of the shared targets of prokaryotes and mitochondria [19]. These side effects can cause mitochondrial dysfunction and defective cellular respiration; and in our opinion promote tumorigenesis.

Antibiotics inhibit mitochondrial ribosomes and protein synthesis and this inhibits mitochondrial biogenesis. This effect can lead to decreased (OXPHOS) and induce the glycolytic metabolic pathway.

Linezolid is a member of the oxazolidine antimicrobials that inhibit bacterial ribosomes and disrupts mitochondrial protein synthesis which is implicated in side effects of hyperlactatemia, neuropathy and myelosuppression. Garrabou et al. have shown that Linezoid hyperlactatemia is caused by inhibition of mitochondrial cytochrome C oxidase [20]. This is an important enzyme in the final step for ATP synthesis in the electron transport chain. This initiates a compensatory glycolytic response which anaerobically converts pyruvate to lactate resulting in hyperlactatemia.

Seyfried believes that cancer is a metabolic disease and that genomic defects and nuclear instability are downstream of mitochondrial dysfunction and a retrograde response [21]. We totally agree with his observations; and the overuse of antibiotics just might be the precipitating event that causes mitochondrial damage.

6. Chloramphenicol Causes a Decrease in Transferrin Receptor Expression and Ferritin Synthesis

The effect of chloramphenicol on mitochondrial functions is so severe that it deserves a special section of presentation. Chloramphenicol inhibits mitochondrial protein synthesis and also disrupts mitochondrial iron metabolism. Iron is an essential micronutrient for Ribonucleotide reductase an important enzyme in DNA synthesis; and the mitochondrion is the cradle of iron metabolism. Leiter, Thatte, Okafor, et al. [22] have shown that chloramphenicol decreases the expression of the cell surface transferrin receptor and ferritin synthesis in cultured K562 cells. They also noted impressive decreases in cytochrome c oxidase activity, respiratory function, ATP levels and cell growth. Aconitase cytosolic activity was also reduced. All of these decreased functions impacts and reduces cell proliferation. This defect in iron metabolism can cause problems with the iron-Sulphur clusters (FeS) of the electron transport chain especially depletion of ATP. This causes severe defective cellular respiration leading to a compensatory glycolytic pathway. The damage to mitochondrial (FeS) clusters is probably the first insult leading to tumorigenesis. We believe that the repeated indiscriminate unnecessary, overuse of other antibiotics may also damage (FeS) clusters and (ETC); and thus cause defective cellular respiration and energy production leading to cancer.

7. Antibiotics That Target Mitochondria Can Eradicate Cancer Stem Cells (A Paradoxical Effect)

A recent paper published by Lamb, Ozovari, Lisanti, etal. [23] stated that some antibiotics can effectively target mitochondria and eradicate cancer stem cells of multiple tumor types. This suggest cancer may be treated like an infectious disease. Several classes of antibiotics inhibit mitochondrial biogenesis as a side effect. This side effect could be used as a therapeutic effect. The five classes of mitochondrially targeted drugs are: erythromycins, glycylcyclines, tetracyclines, chloramphenicol and an antiparasitic drug. They suggest that these drugs are non-toxic to normal cells: but we doubt that is the case. The early cancer cell just might be more sensitive to their effect because of already defective respiration; while normal cells are more resistant to injury. Normal cells will mainly be using (OXPHOS) for energy production and probably have more abundant healthy mitochondria. The early cancer cells already harbor less and defective mitochondria with impaired (OXPHOS) making them more sensitive to antibiotic targeting. However, we believe that repeated insult to mitochondria of normal cells by overuse of antibiotics could promote a protumorigenic phenotype. This group also recommends that these drug classes should be used for prevention trials and in the adjuvant setting. We think one should be cautious about using antibiotics in that clinical scenario as these drugs could damage the (ETC) of normal mitochondria. Cancer stem cells are dependent on mitochondrial biogenesis and (OXPHOS) for clonal expansion and survival. These antibiotics inhibit mitochondrial biogenesis by preventing the translation of mitochondrial proteins involved in the mitochondrial OXPHOS complexes. Some of these antibiotics, such as, tetracycline can inhibit tumor growth in pancreatic tumor Xenografts (with PANC-1cells), and doxycycline treatment reduced tumor growth by 80% [24]. These investigators [23-24] think that future clinical trials for testing the efficacy of mitochondrially-targeted antibiotics in multiple cancer types are now definitely clinically warranted. We have ambivalent feelings about that statement, but we will keep an open mind.

8. Conclusion

We believe Warburg [1] was correct and that cancer is caused by defective mitochondrial respiration and energy production. Thus, as Seyfried [21] has stated, cancer is a metabolic disease and he has presented tremendous evidence to support that theory. Our work on normal mitochondria transplantation into cancer cells also gives credit to this theory [3-4]. We have presented the endosymbiotic theory that mitochondria are evolutionary bacteria; and they still have genetic properties, similar ribosomes and proteins of free living bacteria. The fact that mitochondria are engulfed bacteria it is no surprise that drugs that attack and damage bacteria could also damage cellular mitochondria and cause severe mitochondrial dysfunction. The overusage of antibiotics could be agents promoting this problem. The condition of antibiotic resistance, antibiotic induced problems, such as, (C. Diff) and vaginitis were covered. The importance of maintaining a healthy gut microbiota to support innate immunity was emphasized as was the importance of proper gut microbiome to

get the best results and response of cancer immunotherapeutics with checkpoint inhibitors. The adverse effects of antibiotics on mitochondria and that antibiotics decrease mitochondrial biogenesis and inhibits protein synthesis; also, chloramphenicol also disrupts mitochondrial iron metabolism. This is a serious complication that leads to cell death because of inhibited proliferation due to decreased DNA synthesis caused by the important enzyme Ribonucleotide reductase being disabled. We believe and have presented evidence that antibiotics may cause mitochondrial damage promoting tumorigenesis; and also, the paradoxical evidence that they may target mitochondria in cancer stem cells and very early cancer cells causing decreased mitochondrial biogenesis and cell death. Thus, in this case they are therapeutic, while by damaging normal mitochondria they might promote malignant transformation.

We believe that over use of antibiotics do cause damage to mitochondria and contribute to tumorigenesis and bacterial resistance. Our team is involved in a clinical trial of patients at high risk for breast cancer and are breast positive for the (ecto-nicotinamide dinucleotide oxidase disulfide thiol exchanger 2) ENOX-2 protein.

This is an ecto protein that is shed into the blood of cancer patients when the disease is minimal (only about 2 million cells) and is detectable 8-10 years before the disease is detected clinically. We are testing several methods of trying to eradicate this protein, and now we can consider using appropriate antibiotics that have shown efficacy in inhibiting cancer growth. We believe the effect of antibiotics on normal cells and early cancer cells is paradoxical. This indicates that much more work needs to be done studying the role of mitochondrial dysfunction in promoting tumorigenesis and the possible therapeutic effect of antibiotics for treating cancer. Much more to be done so stay tuned.

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