# Mitochondrial Retrograde Signaling in Fluoroquinolone Associated Disability, A Disease Theory

**D. Melvin**
**Email: david@myquinstory.info**

This article is available at: https://www.myquinstory.info/downloads/


## Abstract

Despite warnings from regulatory agencies urging conservative usage due to the potential for major adverse events, Fluoroquinolones remains one of the most commonly prescribed antibiotics worldwide. A large number of people who take this class of antibiotics become chronically or permanently disabled suffering from what the Federal Drug Administration has observationally identified as Fluoroquinolone Associated Disability or FQAD. FQAD is an idiopathic pathological presentation of numerous, disparate, symptoms that can literally number into several hundred. FQAD, in affected individuals, can cause an intractable long-term, progressive, multi-system condition that can be severely disabling or fatal. This multisystem involvement of symptoms is usually suspected as being genetic in origin. Despite this, most clinical genetic testing fails to identify any pathological phenotypes that would explain a progressive disease. Due to the lack of further research, the exact mechanism of FQAD remains unknown, even though many disparate pieces of academic research exist documenting the genotoxicity of fluoroquinolones. Based on over ten years of anecdotal evidence by citizen scientists, and the results of some recent research findings, this paper proposes a theory that, if proven true, would elucidate the mechanism behind FQAD in an otherwise healthy population in the absence of genetic predispositions.

### Introduction

Fluoroquinolones (FQs) are a broad class of antibiotics that are one of the most commonly prescribed antibiotics within the United States. The FQs are typically prescribed for bacterial infections, however, they are very often prescribed off-label or for prophylaxis. Because this class of antibiotics brings the potential for major side effects, the FDA urges doctors not to over-use them. In fact, the agency has restricted the recommended uses for these drugs and has required several updates to the drugs' labels to warn of life-altering risks.

The FDA has proposed the existence of a permanent disability that can come from FQ usage (Fluoroquinolone Associated Disability; FQAD). The FDA identified FQAD in a Briefing document for a joint meeting of the Antimicrobial Drugs Advisory Committee and the Drug Safety and Risk Management Advisory

Committee during a formal review of the FQs on Nov. 5, 2015. FQAD is defined as a constellation of adverse event symptoms that have been identified as leading to disability. The FDA made it known that FQAD was not a formal diagnosis just an observational identification, one that is yet to be formally recognized by the medical community [1].

Despite increased awareness, the medical community still tends to dismiss patients who report symptoms of FQ toxicity. This is especially true of patients who reported being affected by FQAD. One of the main reasons for this dismissal is the great variability and severity with which the FQAD symptoms present themselves. Many of these patients are often unfairly diagnosed with umbrella diseases such as fibromyalgia, chronic fatigue, and others [2], despite the fact that symptoms often surpass those classifications and there exists both clinical and laboratory evidence that links the FQ with cellular toxicity in and of itself [3].

This article introduces a hypothesis that, if proven true, would explain the wide variety of symptoms that manifest in the condition referred to as Fluoroquinolone Toxicity or FQAD.

**Overview**

The most common demographic to receive a prescription for FQs usually consists of individuals who are 45 years of age or older [4]. Although some strong exceptions exist, anecdotal evidence collected over the last decade has shown that more middle-aged and older people become permanently disabled by FQAD. It is suspected that the underlying reason for this has to do with the bioenergetic phenotype of the mitochondria of older individuals versus the young [5].

In FQAD, it is common to see a constellation of symptoms that include fatigue, weakness, muscle atrophy, neurological problems, digestive problems, cranial cervical pathologies, cardiac conduction abnormalities, and many more. These symptoms often present themselves in a puzzling array confounding many medical practitioners. Often, standard genetic sequencing does not provide any insight that would reveal a predisposed pathogenic condition or genetic variant(s) that would explain the onset and duration of FQAD. Despite this lack of a known genetic predisposition, patients manifest obvious signs of a pathophysiology that has a genetic component.

Based on the large amount of anecdotal data collected over several years, combined with recent clinical diagnostics from a few cases of FQAD, suggests a novel hypothesis.

**Mitochondrial Retrograde Signaling In FQAD**

This paper puts forth a postulation that the FQs are making changes to nuclear genomic loci without altering the underlying nucleic acid sequence while still impacting gene expression and functional regulation. These pathological changes are driven by a phenomenon known as mitochondrial retrograde signaling.

In mitochondrial retrograde signaling, information flows in the opposite direction to that of the more familiar and understood anterograde regulation which is characterized by the transfer of information and material from the nucleus to mitochondria. This retrograde signaling can culminate in wide-ranging changes in nuclear gene expression.

Mitochondria play a significant role not only in energy production but also in the integration of metabolic pathways in addition to signals for

apoptosis and autophagy. These semi-autonomous organelles have their own genomes, which in humans typically appear as small double-stranded closed DNA circles.

Only recently has it become apparent that mitochondria in mammalian cells play critical roles in the initiation and propagation of various novel signaling cascades [6]. Scientific research has shown that reverse or retrograde communication does exist between the nuclear and mitochondrial genomes [7,8]. This unique signaling pathway appears to influence many cellular and organismal activities under both normal and pathophysiological conditions [9].

It is now known that mitochondrial metabolic, respiratory, and genetic instability are all communicated to the nucleus as an adaptive response through retrograde signaling [6]. When mitochondria become dysfunctional, they communicate through retrograde signaling to the nucleus in an adaptive response that results in altered nuclear gene expression and cell physiology and morphology.

Again, collected anecdotal data, along with some limited clinical data, are revealing that this unique communication pathway could be the main driving factor in the complex syndrome that is known as Fluoroquinolone toxicity Syndrome (FQTS) or the more chronic sense, FQAD.

Although many theories have been put forth as to the causal mechanisms of certain aspects of FQAD, such as long-term upregulated metalloproteinase, GABA receptor inhibition, and increase ROS, it is believed these are the result of the downstream nuclear signaling cascades driven by mitochondrial retrograde signaling.

While many specific mechanisms are yet to be fully elucidated, the mitochondrial retrograde signaling cascade's influence would explain the disordered and varied nature of FQTS and the complexity of the resulting syndrome that many medical practitioners find preposterous.

**General Discussion**

Truly little was known about mitochondria themselves when the Fluoroquinolones were approved for use years ago. The fact that mitochondrial instability could directly influence disease states through retrograde signaling was also largely unknown to medical science until recently.

Evidence is emerging that points to the fact that the FQs are changing mitochondrial DNA (mtDNA) topology which in turn impacts nuclear DNA (nDNA) expression and ultimately DNA methylation.

Mitochondrial retrograde responses are initiated and sustained by metabolic pressures such as toxic exposure. The FQs have been documented to impact the normal maintenance and transcription of mitochondrial DNA (mitostasis) by changing mtDNA topology, causing impaired mitochondrial energy production and blocking cellular growth and differentiation [10].

Through this feedback loop, the mitochondria are directing the changes in nuclear gene function. This communication is happening as a direct result of the mitochondrion's role in generating and regulating high-energy molecules, such as ATP, acetyl-CoA, AKG, etc.

One documented way that the FQs are changing mtDNA topology is through the inhibition of isoforms of Topoisomerase 2, Top2α, and β [12]. Top2β in when exposed to an FQ has an immediate effect on mtDNA biogenesis,

indicating that this isoform is involved in mtDNA maintenance [12]. Through this method, the FQs have a dramatic effect on mtDNA topology, blocking replication, reducing copy number, and inhibiting mitochondrial transcription.

Evidence of the retrograde signaling shows up when eukaryotic cells are exposed to FQs and they exhibit signs of immediate retardation of cell division that is only present in cells with functional mitochondria, implying a retrograde signal from mitochondria to nucleus either caused by oxidative stress or impaired mtDNA replication [12].

Impaired mitostasis has been suggested to induce cellular senescence [11]. Deregulation of mitochondrial homeostatic mechanisms which manifests as impaired mitochondrial biogenesis, cellular metabolism, and dynamics, has become a hallmark of cellular senescence, which is believed to be another factor in FQAD.

Dysfunctional mitochondria in a senescent cell using retrograde signaling communicate their changing metabolic and functional state to the nucleus as an adaptive response. This retrograde communication becomes a crucial factor in regulating homeostasis and translating extracellular signals into altered gene expression, altered cell physiology, and morphology. This culminates in wide-ranging changes in nuclear gene expression which in turn manifests in the wide variety of symptoms seen in the FQAD syndrome. Often, these changes are very long-lasting and/or permanent.

Changes to mtDNA have been shown to repress specific nuclear gene loci [13]. And although it appears that mitochondrial retrograde signaling can impact nDNA loci genome-wide, in some cases of FQAD, changes are occurring, at least, in part at the genomic loci of the nDNA responsible for mitochondrial mtDNA maintenance. There have been some case reports where FQAD patients have been clinically diagnosed with a mitochondrial disease after undergoing a muscle biopsy and the detected disease state would normally point to or stem from a pathological mutation in the nDNA, however, repeated genetic sequencing has failed to reveal any clinically recognized polymorphisms.

Since mtDNA lacks robust repair mechanisms, insults to the mitochondria from the FQs such as mtDNA lesions, membrane damage, insufficient O2, Top2α and β inhibition, and more can influence retrograde communication to the nDNA, which in turn alters functional regulation (anterograde) in cascading or sometimes vicious cycle.

The specific mechanisms that drive long-term or permanent changes that impact methylation in the absence of clinical genetic polymorphisms need to be fully elucidated. However, it is known that mtDNA damage is more extensive and persistent than nDNA and often these damages escape rescue mechanisms such as autophagy. During periods of chronic oxidative stress, such as those induced by Fluoroquinolone exposure, mitochondria can become extensively damaged [14]. Abnormal mitochondrial dynamics, impaired biogenesis, and defective mitophagy could be the sustaining forces that are driving the anterograde signaling altering nDNA methylation, and producing the syndrome we see in those who are severely disabled by fluoroquinolones.

**Conclusion**

In a normal state, crosstalk between the mitochondrial and nuclear genomes is vital for the proper maintenance, integrity, and function of both genomes which contributes to the

symbiotic relationship between them and the homeostasis of a person's health state.

The heterogenic nature of the symptoms in those who are impacted by FQAD points to an underlying mtDNA-driven dysfunction/disease. Evidence is emerging that FQ-induced changes to the mtDNA can lead to the epigenetic modification of the nuclear genome and/or alterations to DNA methylation through retrograde signaling, thus contributing to the diverse pathophysiology observed in FQAD.

Even today, medical science is limited in its understanding of how mitochondria interact with nDNA, influence methylation, and drive disease. This is evident in the poor patient outcomes in those who have been chronically affected by FQAD.

It is hoped that the hypothesis presented in this paper will provide a foundation for future research into the role of FQs and their ability to triggering chronic illnesses by affecting the communication between the mitochondrial genome and the nuclear genome in a novel fashion, leading to severe acquired human disease.

**References**


1. Melvin, D. (2015, November 5). FDA Briefing Information Nov. 5, 2015. Life After Levaquin. Retrieved April 12, 2023, from https://www.myquinstory.info/wp-content/uploads/2018/06/FDA-Briefing-Information-Nov-5-2015-Meeting-of-the-Antimicrobial-Drugs-Advisory-Committee-and-the-Drug-Safety-and-Risk-Management-Advisory-Committee-FQAD.pdf

2. Ganjizadeh-Zavareh S, Sodhi M, Spangehl T, Carleton B, Etminan M. Oral fluoroquinolones and risk of fibromyalgia. Br J Clin Pharmacol. 2019 Jan;85(1):236-239. doi: 10.1111/bcp.13765. Epub 2018 Oct 14. PMID: 30216492; PMCID: PMC6303210.

3. Anu Hangas, Koit Aasumets, Nina J Kekäläinen, Mika Paloheinä, Jaakko L Pohjoismäki, Joachim M Gerhold, Steffi Goffart, Ciprofloxacin impairs mitochondrial DNA replication initiation through inhibition of Topoisomerase 2, Nucleic Acids Research, Volume 46, Issue 18, 12 October 2018, Pages 9625–9636, https://doi.org/10.1093/nar/gky793

4. Baggs J, Fridkin SK, Pollack LA, Srinivasan A, Jernigan JA. Estimating National Trends in Inpatient Antibiotic Use Among US Hospitals From 2006 to 2012. JAMA Intern Med. 2016 Nov 1;176(11):1639-1648. doi: 10.1001/jamainternmed.2016.5651. PMID: 27653796.

5. Will Y, Shields JE, Wallace KB. Drug-Induced Mitochondrial Toxicity in the Geriatric Population: Challenges and Future Directions. Biology (Basel). 2019 May 11;8(2):32. doi: 10.3390/biology8020032. PMID: 31083551; PMCID: PMC6628177.

6. Guha M, Avadhani NG. Mitochondrial retrograde signaling at the crossroads of tumor bioenergetics, genetics and epigenetics. Mitochondrion. 2013 Nov;13(6):577-91. doi: 10.1016/j.mito.2013.08.007. Epub 2013 Sep 1. PMID: 24004957; PMCID: PMC3832239.

7. Butow, R. A., & Avadhani, N. G. (2004). Mitochondrial signaling. Molecular Cell, 14(1), 1–15. https://doi.org/10.1016/s1097-2765(04)00179-0

8. Mitochondria-to-nucleus stress signaling induces phenotypic changes … The EMBO Journal. (2001, April 17). Retrieved April 12, 2023, from https://www.embopress.org/doi/full/10.1093/emboj/20.8.1910

9. Butow RA, Avadhani NG. Mitochondrial signaling: the retrograde response. Mol Cell. 2004 Apr 9;14(1):1-15. doi: 10.1016/s1097-2765(04)00179-0. PMID: 15068799.

10. University of Eastern Finland. (2018, October 1). Ciprofloxacin has dramatic effects on the mitochondrial genome: Antibiotics should be used cautiously. ScienceDaily. Retrieved April 12, 2023 from www.sciencedaily.com/releases/2018/10/181001101943.htm

11. Vasileiou PVS, Evangelou K, Vlasis K, Fildisis G, Panayiotidis MI, Chronopoulos E, Passias PG, Kouloukoussa M, Gorgoulis VG, Havaki S. Mitochondrial Homeostasis and Cellular Senescence. Cells. 2019 Jul 6;8(7):686. doi: 10.3390/cells8070686. PMID: 31284597; PMCID: PMC6678662.

12. Anu Hangas, Koit Aasumets, Nina J Kekäläinen, Mika Paloheinä, Jaakko L Pohjoismäki, Joachim M Gerhold, Steffi Goffart, Ciprofloxacin impairs mitochondrial DNA replication initiation through inhibition of Topoisomerase 2, Nucleic Acids Research, Volume 46, Issue 18, 12 October 2018, Pages 9625–9636, https://doi.org/10.1093/nar/gky793

13. Haffner MC, Aryee MJ, Toubaji A, Esopi DM, Albadine R, Gurel B, Isaacs WB, Bova GS, Liu W, Xu J, Meeker AK, Netto G, De Marzo AM, Nelson WG, Yegnasubramanian S. Androgen-induced TOP2B-mediated double-strand breaks and prostate cancer gene rearrangements. Nat Genet. 2010 Aug;42(8):668-75. doi: 10.1038/ng.613. Epub 2010 Jul 4. PMID: 20601956; PMCID: PMC3157086.14 https://pubmed.ncbi.nlm.nih.gov/22474351/

14. Yakes, F. M., & Van Houten, B. (1997, January). Mitochondrial DNA damage is more extensive and persists longer … – PNAS. PNAS. Retrieved April 12, 2023, from https://www.pnas.org/doi/10.1073/pnas.94.2.514