

Mitochondrial Dysfunction, Inflammation, and Cancer Risk — What the Research Shows

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STORY AT-A-GLANCE

- › In laboratory research, suppressing mitochondrial ATP production blocked apoptosis and activated the NLRP3 inflammasome, a key player in inflammation
- › Inhibitors of oxidative phosphorylation (OXPHOS) lead to changes in mitochondrial cristae structure and retention of cytochrome c, which is necessary for NLRP3 activation but not sufficient on its own
- › Activation of the NLRP3 inflammasome requires two signals, one of which is mitochondrial, highlighting the complexity of its regulation
- › Diverse NLRP3 activators share the ability to suppress apoptosis, allowing damaged cells to survive — a mechanism researchers are investigating as a contributor to chronic inflammation and cancer
- › Mitochondrial dysfunction is closely linked to inflammation and various diseases, emphasizing the importance of understanding these mechanisms for optimal health

Chronic inflammation and cancer are health challenges that affect millions of individuals worldwide. Inflammation is your body's natural response to injury or infection, characterized by redness, swelling and pain. However, when inflammation becomes persistent, it is associated with tissue damage and with the development of various diseases, including cancer.

Cancer itself is marked by the uncontrolled growth and spread of abnormal cells, which invade surrounding tissues and form harmful tumors. If left untreated, these conditions significantly impair quality of life and increase mortality rates. Mitochondria, often referred to as the powerhouses of the cell, play a key role in producing adenosine triphosphate (ATP), the energy currency essential for numerous cellular functions.

When mitochondrial function is compromised, ATP production decreases, leading to cellular energy deficits. This reduction in energy impairs the cell's ability to regulate normal processes, which researchers have linked to conditions that favor chronic inflammation.

According to research published in *Immunity*,¹ impaired mitochondrial function activates the NOD-like receptor protein 3 (NLRP3) inflammasome, a key component in the inflammatory response. The researchers propose that this activation sustains inflammation and may create conditions that favor cancer development by allowing damaged cells to survive.

An important note: This work was carried out in cultured cells and in frog tadpoles, so its findings describe a mechanism, not a demonstrated effect in people.

Mitochondrial Function Is Intricately Involved in Inflammation and Cancer

The impact of mitochondrial dysfunction on inflammation and cancer is significant. Studies show that approximately 20% of all cancers are linked to chronic inflammation, highlighting the strong connection between these conditions.² Additionally, individuals with mitochondrial disorders are at a higher risk of developing inflammatory diseases compared to the general population.³

- **Millions of Americans are affected by mitochondrial dysfunction** — In the U.S. alone, chronic inflammatory conditions affect close to 125 million adults,⁴ while cancer remains the second leading cause of death, accounting for more than

613,000 fatalities each year.⁵ Moreover, research indicates that mitochondrial dysfunction contributes to the resistance of cancer cells to conventional therapies, making treatment more challenging.⁶

- **Why mitochondrial health is drawing research attention** — These figures help explain why mitochondrial function has become an active area of investigation in inflammation and cancer research.

Beyond their direct effects, chronic inflammation and cancer are associated with a cascade of additional health problems. Persistent inflammation is associated with cardiovascular diseases, diabetes and neurodegenerative disorders, further compounding the burden on affected individuals.

- **Mitochondrial dysfunction is under investigation as a factor in cancer** — Cancer progression often results in debilitating symptoms such as pain, fatigue and loss of organ function, which drastically reduces life expectancy and quality of life. Understanding the role of mitochondrial dysfunction in inflammation and cancer not only illuminates possible therapeutic targets but also underscores why researchers are examining mitochondrial health across a wide range of conditions.
- **Mitochondrial dysfunction is a key player in the development of NLRP3-related conditions** — When mitochondria fail to produce adequate ATP, it sets off a cascade of cellular stress signals.

These signals activate the NLRP3 inflammasome, a protein complex that plays a significant role in the body's inflammatory response.⁷ The activation of this inflammasome is linked to various diseases, including chronic inflammation and cancer, as it is associated with uncontrolled cell death and tissue damage.

What the Study Found About Mitochondrial Function and Inflammation

A 2025 study investigated the intricate relationship between mitochondrial function and the activation of the NLRP3 inflammasome. The research focused on understanding how the inhibition of oxidative phosphorylation (OXPHOS), the process by which mitochondria produce ATP, affects cell death and inflammation.

The study employed various cell types, including myeloid cells, primary murine microglia, human monocyte-derived macrophages, HCT116 and HeLa cells, as well as conducted in vivo experiments using *Xenopus laevis* tadpoles.⁸ Note: This is laboratory and animal research that identifies a mechanism in cultured cells and amphibians; it does not measure outcomes in people, and the findings below should be read on those terms.

- **The NLRP3 inflammasome negatively impacts mitochondrial health** — The population studied encompassed a diverse range of cells to mimic different physiological conditions. The findings revealed that activators of NLRP3 significantly hinder mitochondrial ATP production, which in turn suppresses apoptosis, the process of programmed cell death.

This suppression allows damaged cells to survive longer than they should, which the authors describe as a plausible contributor to inflammation and, over time, to cancer development. The study demonstrated that when OXPHOS is inhibited, mitochondrial cristae — the inner folds of mitochondria — undergo structural changes that trap cytochrome c, a molecule essential for apoptosis.⁹

- **Other factors that diminish apoptosis** — The research also showed that various NLRP3 activators, such as nigericin, imiquimod and extracellular ATP, inhibit apoptosis not by activating the inflammasome directly, but through their disruptive effects on mitochondrial function. These compounds cause the closure of crista junctions, preventing cytochrome c from being released into the cytoplasm, which is a necessary step for apoptosis to proceed.

- **The impact of viral infections on mitochondrial function and apoptosis** — It was observed that infections like SARS-CoV-2 could strongly suppress apoptosis by inhibiting the cleavage of caspase-3, an enzyme involved in the execution of apoptosis. This suppression not only hinders the removal of infected cells but also facilitates the activation of the NLRP3 inflammasome, thereby promoting an inflammatory response.¹⁰

Why Mitochondrial Function Matters Across Chronic Disease

Biologically, the mechanism at play involves the inhibition of mitochondrial ATP production by NLRP3 activators. When OXPHOS is blocked, mitochondria cannot produce sufficient ATP, leading to the rearrangement of cristae and retention of cytochrome c within the mitochondria. This retention prevents apoptosis, allowing damaged cells to survive and multiply unchecked.

- **The process of NLRP3 signaling and activation** — The suppression of ATP production provides a necessary signal for the activation of NLRP3. However, full activation of NLRP3 requires a second signal, highlighting the complexity of the inflammasome's regulation.¹¹

The study also compared the effects of different NLRP3 activators and OXPHOS inhibitors, revealing that while all these agents suppress apoptosis, only certain ones could activate NLRP3 without an additional signal.

- **What this may mean for future research** — This comparison highlights the intricate relationship between mitochondrial function and inflammasome activation, suggesting that modulating mitochondrial processes may warrant further study as an approach to influencing inflammation.¹²

The research provides mechanistic evidence that mitochondrial dysfunction, specifically through the inhibition of OXPHOS, plays a pivotal role in suppressing apoptosis and activating the NLRP3 inflammasome.

This dual action not only fosters a proinflammatory environment but also allows for the survival of malignant cells, thereby linking reduced mitochondrial function to the progression of inflammation and cancer.¹³ As noted on Georgi Dinkov's blog, the study demonstrates that mitochondrial dysfunction is a key player in both cancer and inflammation:¹⁴

"Yet another study, which demonstrates the inseparable link between metabolism and 'structural' problems such as cellular integrity and lifecycle (e.g. apoptosis), as well as mysterious processes of systemic inflammation, often occurring without any cause that medicine can identify.

Both of these processes are highly visible in cancer – i.e., lack of apoptosis in 'cancer' cells despite their wrecked genome and metabolic dysfunction, as well as their highly inflamed nature that 'recruits' nearby cells to the 'cancer' process through the cytokines the 'cancer' cells produce and releases in the blood.

In other words, all that takes for systemic inflammation and even cancer (i.e., lack of apoptosis in damaged cells) to form is reduced mitochondrial function, resulting in a prolonged drop of ATP levels.

Thus, chronic stress, inflammatory diet (PUFA anyone?), endocrine disruptors, and the 'modern' life characterized by never-ending soul-crushing routines are all direct causes of all our ailments as the one thing all those pathological processes have in common is their profoundly suppressive effects on mitochondria/OXPHOS."

How to Address Mitochondrial Dysfunction and Reduce Inflammation

Your mitochondria power every cell in your body. When they don't work properly, inflammation rises and damaged cells multiply instead of dying off naturally. The following are general dietary and lifestyle measures associated with mitochondrial and

metabolic health. They are not a treatment for any disease, and they are not a substitute for care from your healthcare provider:

- 1. Eliminate processed foods and vegetable oils** — The modern diet is rife with processed foods and vegetable oils rich in **linoleic acid** (LA) that damage your gut microbiome and promote harmful bacteria.

Though LA is an essential fatty acid required for normal mitochondrial function, when consumed in excess, it can compromise cellular energy production, so the goal is to bring intake back to historical levels, not to remove it entirely. Aim to keep your LA intake within 2 to 5 grams per day from all sources To help track your LA intake, enter your daily meals into the Food Buddy feature in the Pax health platform, and use its Seed-Oil Sleuth feature to check the LA content of individual foods.

In addition to processed foods, avoid nuts and seeds as well to reduce LA intake. It's also advisable to avoid dining out, since most restaurants use vegetable oils in their cooking, sauces and dressings.

Additionally, limit your consumption of chicken and pork, which are typically high in LA. Replace processed foods with whole, unprocessed foods and healthy fats such as grass fed butter, tallow, and ghee.

- 2. Optimize carbohydrate intake** — Carbohydrates play an important role in supporting mitochondrial function since glucose is the preferred fuel for energy production at the cellular level. Tailor your carbohydrate consumption to support cellular energy by aiming for at least 250 grams of targeted carbohydrates daily for most adults. Individuals with higher activity levels typically require more.

Introduce carbohydrates gradually to allow your gut to adapt, thereby minimizing digestive issues and endotoxin levels. Begin with white rice and whole fruits to nourish beneficial bacteria before considering vegetables, whole grains and starches. Avoiding high-fiber diets initially is important if your gut microbiome is compromised, as excessive fiber will increase endotoxin levels.

If your gut health is severely compromised, focus on easily digestible carbohydrates like dextrose water for the first week or two. Sip it slowly throughout the day to support gradual gut healing.

- 3. Reduce exposure to environmental toxins** — Exposure to synthetic **endocrine-disrupting chemicals** (EDCs), estrogen and pervasive **electromagnetic fields (EMFs)** further impairs your cells' ability to generate energy efficiently. Energy deficit makes it challenging to sustain the oxygen-free gut environment necessary for beneficial bacteria like Akkermansia to flourish.

Further, a lack of cellular energy creates an environment in your gut that favors endotoxin-producing bacteria, damaging mitochondria and creating a vicious cycle of worsening health. By tackling excess LA, estrogens (**xenoestrogens found in everyday items** like plastic), EDCs and EMFs, you help restore your cellular energy.

- 4. Support NAD⁺ levels** — Niacinamide is a precursor to NAD⁺, which supports mitochondrial energy production. NAD⁺ also enables proper cell death signaling and supports your immune system's ability to identify and remove damaged cells.
- 5. Get safe sun exposure** — Daily sun exposure is also important, for two reasons: its near-infrared wavelengths are absorbed by mitochondria to support cellular energy production^{15,16} and they also stimulate mitochondrial melatonin — a potent antioxidant that neutralizes reactive oxygen species right where they're generated.^{17,18}

One caveat: It's important to avoid direct sunlight during peak hours (from 10 a.m. to 4 p.m. in most U.S. regions) until you've eliminated vegetable oils from your diet for at least four to six months to reduce sunburn risk associated with stored linoleic acid.

Frequently Asked Questions About Mitochondrial Dysfunction and Inflammation

Q: What is the connection between mitochondrial dysfunction and chronic inflammation?

A: When mitochondria underproduce ATP, the body perceives this energy deficit as cellular stress. This stress triggers the NLRP3 inflammasome, a protein complex that amplifies inflammation. Over time, chronic inflammation damages tissues and has been associated with serious conditions including cancer.

Q: How does mitochondrial dysfunction contribute to cancer development?

A: Damaged mitochondria hinder the cell's ability to undergo apoptosis (programmed cell death). When apoptosis is suppressed, abnormal cells survive longer than they should, which in laboratory models allows mutations to accumulate. Researchers are investigating whether chronic inflammation associated with impaired mitochondrial function contributes to cancer progression.

Q: Why is linoleic acid problematic for mitochondrial health?

A: LA, found in most vegetable oils and many processed foods, is essential in small amounts but problematic in excess. Consuming high amounts has been associated with gut dysbiosis (an imbalance of gut bacteria) and increased inflammation. The recommended range is 2 to 5 grams per day — enough to meet the body's requirement, without the excess typical of a modern diet.

Q: Can improving carbohydrate intake help restore mitochondrial function?

A: Glucose is a key fuel for energy production (via oxidative phosphorylation) in the mitochondria. By incorporating adequate, easily digestible carbohydrates — such as white rice or whole fruits — you'll be able to support cellular energy and encourage

healthier gut bacteria. This approach is especially important if your gut microbiome is already compromised.

Q: What lifestyle strategies can support better mitochondrial function?

A: Key strategies include eliminating processed foods (especially those high in vegetable oils), optimizing carbohydrate intake, reducing exposure to toxins like endocrine disruptors and heavy electromagnetic fields, getting regular sun exposure, and supporting NAD⁺ levels. These measures are associated with lower inflammation and improved mitochondrial function markers. They are general wellness measures, not a treatment or preventive for any disease.

This article is for informational purposes only and does not constitute medical advice. Consult a qualified healthcare provider before making changes to your health regimen.

Sources and References

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