Vitamin C, Mitochondria, and Cellular Energy

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Reduction/Oxidation (Redox) Chemistry Basics

The essence of life is directly related to the maintenance of optimal electron exchange between redox biomolecules, along with the maintenance of an overall optimal electron flow through the cells, such that normal transmembrane potentials (voltages) across the cell walls can exist.

As such, electron dynamics produce the life force itself, and it is the inhibition or impairment of this state of electron exchange and flow that is the essence of all diseases.

Reduction/Oxidation (Redox) Chemistry Basics

Furthermore, at least functionally, the maintenance of optimal electron exchange and flow is just another way of referring to the maintenance of optimal ***energy production*** and ***dissemination***.

Therefore, anything that promotes electron exchange and flow promotes biomolecular, cellular, tissue, and organism health, and anything that blocks or impairs that exchange and flow promotes a spectrum ranging from just a lessened state of health to overt disease.

Reduction/Oxidation (Redox) Chemistry Basics

When biomolecules are replete [sated or filled] with electrons (REDUCED), they function normally.

When biomolecules are depleted of electrons (OXIDIZED), they are dysfunctional or afunctional.

While increased biomolecule oxidation is felt by many to ***cause*** disease, it is more technically correct to state that the presence of increased biomolecule oxidation (increased oxidative stress) **IS DISEASE ITSELF**. For a single biomolecule, health is the reduced state, and disease is the oxidized state.

Reduction/Oxidation (Redox) Chemistry Basics

The essence of redox chemistry-based clinical medicine is really the ***essence of vitamin C-based biochemistry***.

Pro-oxidant (aka “toxin”)

Takes, or causes to be taken, electrons away from biomolecules (OXIDATION)

Antioxidant (vitamin C is the prototype)

Gives (or restores) electrons back to oxidized biomolecules (REDUCTION)

Reduction/Oxidation (Redox) Chemistry Basics

All disease, then, results from the relative ***presence of*** and the ***interactions among and between***:

Pro-Oxidants (Toxic Molecules)

Pathogens (Toxic Molecule *Providers*)

Antioxidants (Nutrient Molecules)

Reduction/Oxidation (Redox) Chemistry Basics

This means that all disease exists because more ongoing **excess** oxidation is occurring on a daily basis relative to the degree of ongoing new antioxidant presence in the body (as is derived from a well-digested, optimal diet, along with good supplementation).

All disease-causing agents are toxins (pro-oxidants). There are no other ways, at the biochemical level, for disease (excess oxidation) to be initiated and sustained. If there is not an excess presence of oxidized biomolecules present, there is no disease, of any kind.

Reduction/Oxidation (Redox) Chemistry Basics

Whether biomolecules, cells, tissues, and organs are healthy is **simple**: are they oxidized or not? The nature and degree of the disease depends on:

1. **Which** biomolecules are oxidized?
2. **Where** are they located?
3. **Degree**: Is the percent of oxidized biomolecules minimal or advanced?
4. **Duration**: How long have those biomolecules been oxidized?

On the other hand, the many ways that pro-oxidants (toxins) are introduced into the body, along with the biochemical pathways and reactions that are impaired or blocked in the course of increasing the numbers of oxidized biomolecules, is almost incomprehensibly **complex**.

Reduction/Oxidation (Redox) Chemistry Basics

If there is no increased oxidative stress (increased numbers of oxidized biomolecules), **there is no disease**. Aging occurs over time due to the inevitable cumulative effect of ***physiological*** degrees of increased oxidative stress involved in the processing of oxygen, but the lifespan is normal in length and largely devoid of any chronic disease until the end of life is near.

Without the presence of non-physiological toxins, most of a normal life should be disease-free, as long as genetic defects (e.g., missing enzymes) are not present, and hormone levels (sex, thyroid, cortisol) are maintained in an optimal range.

Reduction/Oxidation (Redox) Chemistry Basics

Vitamin C is the **prototypical antioxidant**, as it:

1. Has a small molecular size
2. Has a structure similar to glucose, the primary energy substrate in the body
3. Has the ability to penetrate all cells and tissues, including ease in passing the blood-brain barrier (100-fold more concentrated in many neurons than in the plasma)
4. Has the ability to donate 2 electrons per molecule rather than one
5. Has the ability, directly or indirectly, to regenerate (reduce) all significant oxidized antioxidants

Because of these properties, vitamin C is arguably the **primary fuel on which the body runs**. The presence of physiological oxidative stress, along with the presence of old toxins and new daily toxin exposures, requires a high intake of vitamin C to maintain the redox balance throughout the body's organs and tissues in the favor of reduction. Even the best of diets will fall far short of the amount of daily vitamin C needed by the body.

Reduction/Oxidation (Redox) Chemistry Basics

Biochemically, a toxin is pro-oxidant in nature, and oxidized vitamin C (DHAA) is also pro-oxidant in nature. Both molecules seek to gain electrons. But DHAA, unlike a clear-cut toxin, seeks to repeatedly ***take and give*** electrons in a relay-like fashion, over and over.

A toxin, however, ***takes and holds*** electrons. There is no relay effect, and electron "flow" hits a dead-end when a toxin takes on the electrons from the biomolecule it oxidizes. A toxin that has gained its electrons is in a state of greater biochemical stability and not looking to give them up again. Vitamin C, and other redox active antioxidants, have similar biochemical stabilities in either the reduced or oxidized state, readily facilitating the flow of electrons throughout the cells.

Mitochondria Basics: Facts and Figures

1. Found in all cells except for mature red blood cells
2. Depending on the cell type, one cell contains between 200 and 20,000 mitochondria; highest concentrations in cells with high metabolic activity, like heart, brain, liver, and kidneys
3. Physical mass of mitochondria in the body is substantial, as roughly 20% of the weight of the body is from mitochondria
4. Normally have a high turnover, as mitochondrial half-life is roughly between 5 and 12 days. The physiological function of mitochondria produces substantial (physiological) stress and reactive oxygen species, minimizing their lifespan.

Mitochondria Basics: Facts and Figures

5. Primary role of mitochondria is to synthesize ATP (aka**cellular energy**)
6. Additional physiological roles of mitochondria include the synthesis of heme, lipids, amino acids, and nucleotides.
7. Also play an important role in initiating cellular apoptosis (programmed cell death)

Mitochondria Basics: Facts and Figures

8. The inner mitochondrial membrane provides an additional barrier to outside molecules, existing in a state of many folds and twists (cristae) which provide a greater surface area for metabolic activity (similar to intestinal villae and microvillae). This inner membrane encloses an area of the mitochondria known as the **matrix**, while the area between the inner and outer membranes is known as the **intermembrane space**.

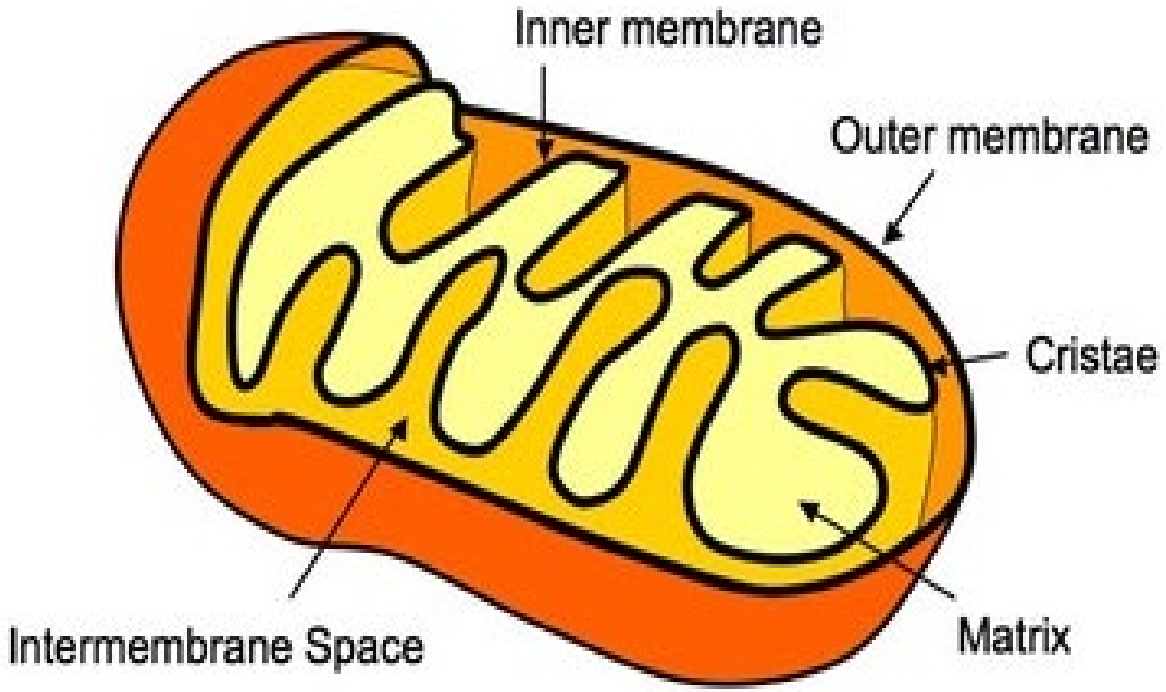
Mitochondria Basics: Facts and Figures

9. The only subcellular organelle with its own DNA, which is more susceptible to mutations due to proximity to the electron transport system and the lack of histone protection, which is a significant factor contributing to high mitochondria turnover

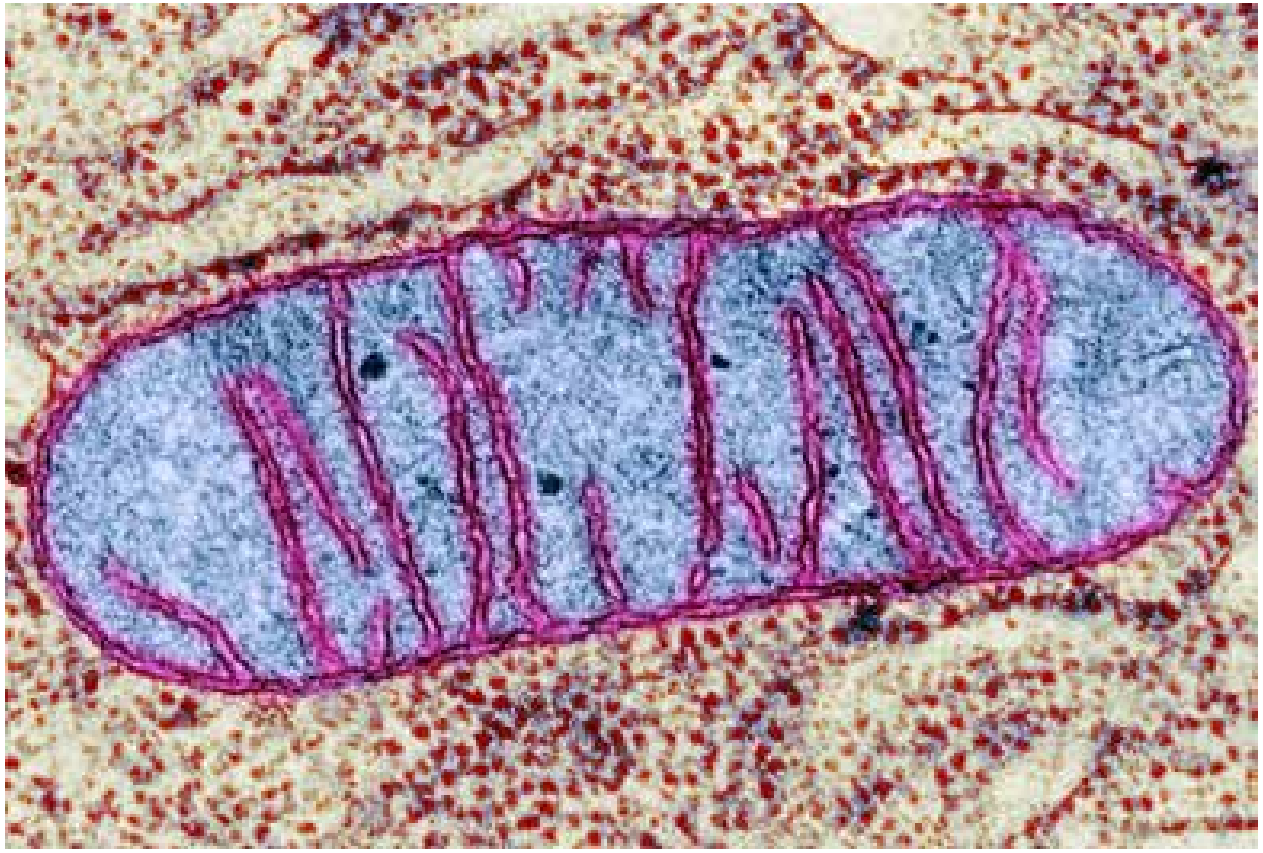
10. Have both an outer membrane and an inner membrane; each is comprised of **phospholipid bilayers** like the membrane enclosing the entire cell; nucleus also has two lipid bilayer membranes. Other organelles have one lipid bilayer membrane. The lipid bilayer facilitates intra- and extracellular communication, between cells and between organelles.

11. Outer mitochondrial membrane has protein structures (porins) permitting a free passage of smaller molecules

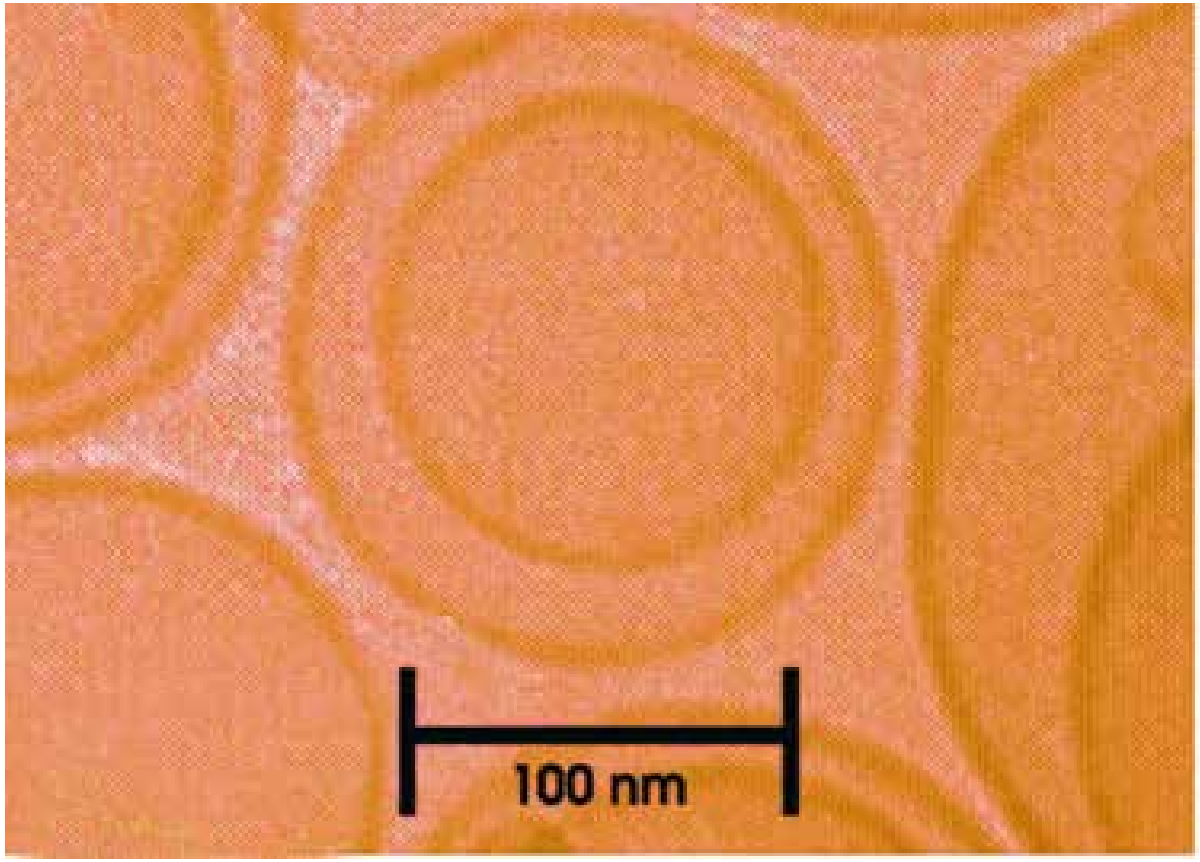
Mitochondria, Diagram



Mitochondria, Electron Microscopy



Liposome, with Lipid Bilayer, Electron Microscopy



Cellular Communication, Mechanisms

Extracellular Vesicles are important naturally-occurring players in intercellular communication [24265924, 23420871, 25392515], and they have been found in substantial quality in all of the body fluids tested [26978483]. These vesicles are spheres surrounded with **lipid bilayers**, housing variable contents derived from nearly all cells, with both ***physiological and pathological*** purposes [26001269]. The membrane structure is the ***same*** as the cell membrane or that of a subcellular organelle [24335232]. They are also known to help convey immune responses [19498381].

Cellular Communication, Mechanisms

Extracellular vesicles (membrane vesicles) consist mainly of:

1. Exosomes
2. Microvesicles
3. Apoptotic bodies
4. Liposomes

Cellular Communication, Mechanisms

Exosomes

Discovered about 30 years ago, but only seriously studied in the last 10 years; originally considered cellular “garbage cans,” now recognized as being critical in intercellular communication [21876726])

40 to 100 nm in diameter and homogeneous in shape, involved in protein storage, transport, and release. **Secreted** by many cell types, and present in sperm, urine, plasma, and bronchial lavage fluid [24141609]; also present in colostrum to modulate immune function [17641064, 23483481]

Cellular Communication, Mechanisms

Microvesicles

Secreted from cells as vehicles to transfer proteins, lipids, mRNA, and microRNA to distant cells. **Stem cells use microvesicles to repair damaged tissues as well**. [24231336]

100 to 1000 nm in diameter, with variable shapes, formed by the regulated, outward budding of the cell membrane [24141609]

Also allows for the dissemination of lysosomal components out of the cell [24288129]

Cellular Communication, Mechanisms

Apoptotic Bodies

Larger vesicles, distinct from exosomes, resulting from the process of programmed cell death (apoptosis).

1000 to 5000 nm in diameter, containing intact organelles, DNA, and histones [4561027, 12505355]. They form as the cell contracts and squeezes blebs in the cell membrane, which break off and contain the breakdown products of the dying cell. They work to minimize the surrounding inflammation that results from cell death via necrosis and rupture. The apoptotic bodies are engulfed by phagocytic cells [23787996].

Cellular Communication, Mechanisms

Liposomes

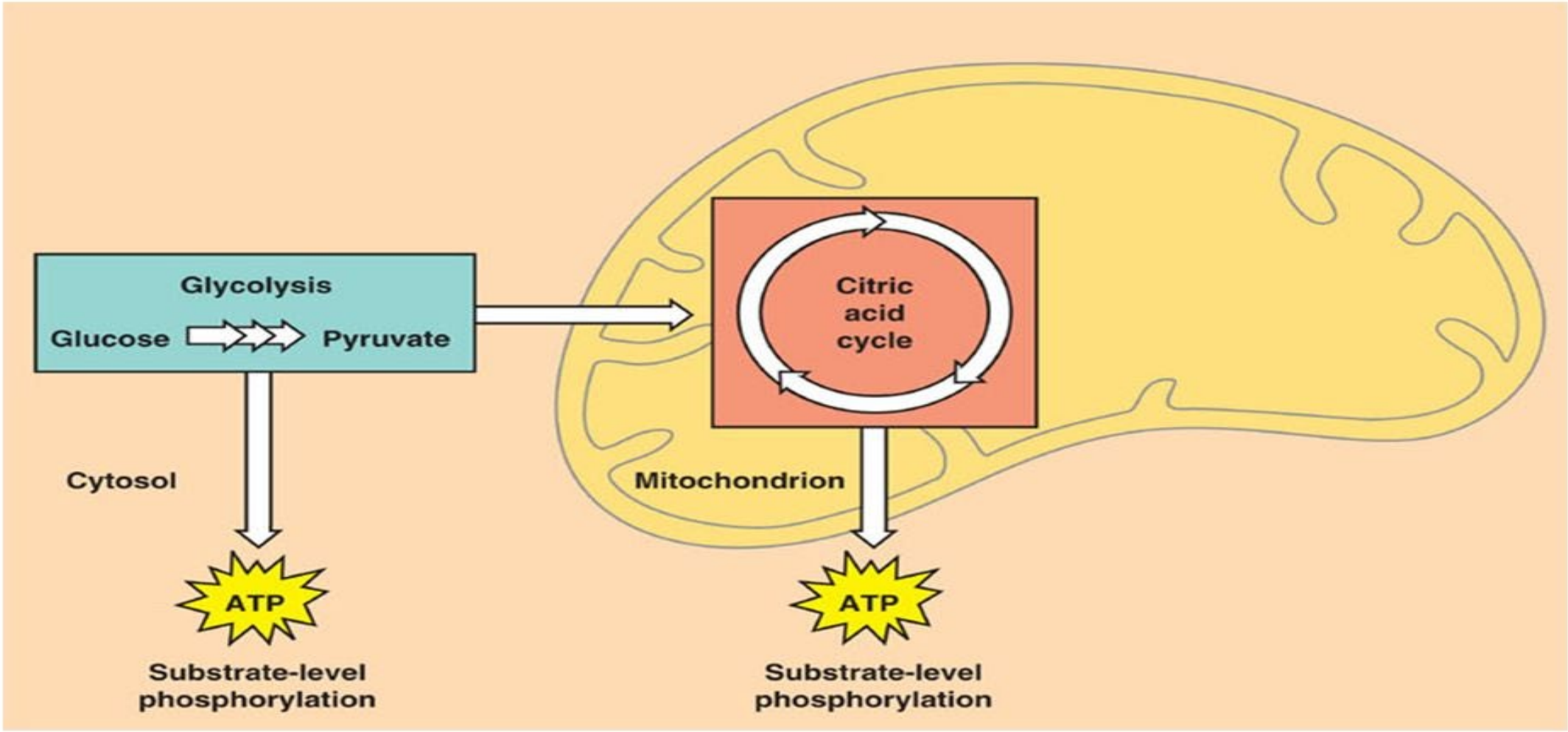
Able to be produced artificially, but **structurally very similar to the other extracellular vesicles** previously described; a liposome utilizes the properties of naturally-occurring extracellular vesicles to transport its payload into the cytoplasm of target cells. Due to the **lipid bilayer** membrane, delivery can also be made directly to other subcellular organelles, **including mitochondria and the nucleus**. There is some debate over whether liposomes are completely man-made extracellular vesicles or occurring naturally inside the body as well. Multiple sizes and modifications can be made to liposomes, with a wide variety of payloads, both in the core and in the membrane

Cellular Energy Production

A relative small amount of ATP is produced in the cytoplasm, where glucose molecules are metabolized to produce pyruvate and 2 ATP per molecule.

Upon entering the mitochondria, the pyruvate then fuels the electron transport chain (ETC) via four enzymes embedded across the inner membrane of the mitochondria in a sequence of chemical reactions known as the Krebs cycle (also known as citric acid cycle or tricarboxylic acid cycle), ultimately producing 36 more ATP molecules.

Krebs Cycle


Glycolysis
Glucose
Pyruvate
Citric acid cycle
Cytosol
Mitochondrion
ATP
ATP
Substrate-level phosphorylation
Substrate-level phosphorylation

Cellular Energy Production

The energy generated by the transfer/relay of electrons along the ETC is used to pump protons from the innermost matrix space out into the intermembrane space, causing the formation of a pH gradient across the inner membrane containing the cristae.

The final acceptor of the electrons being shuttled along the ETC is molecular oxygen. The biochemical nature of oxygen allows it to generate the most energy, in contrast in anaerobic (oxygen-deprived, glucose fueled) respiration that occurs in the cytoplasm and not the mitochondria. When oxygen is the final acceptor of the electrons, the end product is water, while an acidic environment (lactic acid) is produced in the oxygen-absent or oxygen-deprived microenvironment. And only 2 ATP versus 36 ATP is produced per glucose molecule under such circumstances.

Mitochondria and Increased Oxidative Stress

As everywhere else in the body, minimizing oxidative stress in the mitochondria is essential in maintaining optimal health of the cell and the entire organism.

The oxidative status of the mitochondria is **directly linked** to the oxidative status of the cytoplasm of the containing cell.

Mitochondrial glutathione arises from the cytoplasm. No glutathione synthesis occurs in the mitochondria [3860816, 7599223]

Glutathione deficiency leads to widespread mitochondrial damage.

Vitamin C spares and helps to regenerate glutathione.

Mitochondria and Increased Oxidative Stress

Conceptually, the cell and its cytoplasm, along with the subcellular organelles, can be considered as **basic support structures** for enabling mitochondria (and the nucleus) to optimally perform their functions as producers of energy and new biomolecules (lipids, amino acids, etc.). The nucleus permits cellular replication and genetic translation, and the mitochondria are the featured “performers” for the central role of cellular energy production.

Mitochondria and Increased Oxidative Stress

Except for genetic defect diseases [29465611, 29478218], mitochondrial “disease” does not really exist as an independent entity. Generally, an optimally healthy cytoplasm will result in optimally healthy mitochondria. On the other hand, any chronically increased oxidative stress in the cytoplasm will always negatively impact mitochondrial function to a greater or lesser degree.

Clinically, then, **optimizing the antioxidant status of the cytoplasm will permit optimal mitochondrial redox status and optimal function**.

Mitochondria and Vitamin C

Just as with the cell membrane, the mitochondria have uptake/transport mechanisms for vitamin C. There are sodium dependent vitamin C transporters that bring **reduced** vitamin C into the mitochondria (SVCT2) and GLUT1 transporters than bring **oxidized** vitamin C (DHAA) into the mitochondria [24907663]

SVCT2 involves active transport (energy consumption)

GLUT1 involves facilitated diffusion (no direct energy consumption)

Mitochondria and Vitamin C

Although intramitochondrial ascorbate dynamics are still not well delineated, it has been demonstrated that vitamin C administration increases mitochondrial vitamin C concentrations [7055553, 12915223].

Furthermore, relative to glutathione inside the mitochondria, vitamin C is more readily oxidized by pro-oxidants and reactive oxygen species, consistent with an immediate “glutathione-sparing” effect, although the later reduction of that oxidized vitamin C still depends mainly on glutathione [11368176].

Supporting Optimal Mitochondrial Function

Unless and until new interventions are discovered that can directly target the biomolecules and chemical pathways involved in a given intra-mitochondrial pathology, the best way to support and improve mitochondrial function is to **optimize the redox status of the cytoplasm**. A normal cytoplasm is the most reliable way to improve or normalize defective mitochondrial function, unless mitochondrial genetic deficiencies make that goal impossible.

Furthermore, calcium is readily transferred to the mitochondria from the cytoplasm, as it is well-established that the mitochondria have a substantial capacity to accumulate and store calcium, and they can serve as a buffer against at least minimal increases in intracellular calcium, effectively allowing calcium to perform its lower-concentration signaling activities more effectively [23224881].

Supporting Optimal Mitochondrial Function

Calcium concentrations in the extracellular spaces, in the cytoplasm (intracellular), and further inside the mitochondria, especially the matrix, are **primary regulators of oxidative stress** [22927718]. Whether cause or effect, increasing intracellular calcium concentrations are always seen with increased intracellular oxidative stress, just as cytoplasmic oxidative stress is always accompanied by increased calcium concentrations in the cells.

Just as increased extracellular calcium concentrations promote increased intracellular calcium concentrations, higher intracellular levels promote higher mitochondrial levels, initially in the intermembrane space just beyond the first lipid bilayer, and ultimately in the matrix, or innermost space of the mitochondria.

Supporting Optimal Mitochondrial Function

Specific toxins (all of which are pro-oxidant in nature) have been studied with regard to their impact on mitochondria, calcium, and toxic impact on the cells. Methylmercury cellular toxicity is associated with the loss of intracellular calcium homeostasis [22927718]. And even though calcium is a key element at lower concentrations in metabolic and intracellular signaling regulation, it is always highly toxic when present in supranormal concentrations [10229704].

Cell death secondary to toxicity is always associated with the highest of intracellular calcium levels [23595672]. The highest levels are seen with frank necrosis, while lower degrees of elevated levels are seen with apoptosis.

Mitochondria, Vitamin C, and Micronutrients

Because it alleviates oxidative stress, vitamin C supplementation, along with other key antioxidants (vitamin E and alpha lipoic acid) and other nutrient supplements (coenzyme Q10, riboflavin, creatine) are featured parts of treatment protocols for diagnosed mitochondrial diseases [17492503, 17486439].

Mitochondrial vitamin C serves to maintain healthy mitochondrial membrane potentials and prolong mitochondrial lifespans against eventual apoptosis [16195374, 17559880].

Mitochondria, Vitamin C, and Micronutrients

Sepsis is the prototype of a condition involving mitochondrial dysfunction early in its development. The early appearance of increased oxidative stress in the cells of septically-stressed and failing organs appears to be directly related to impairment of oxidative phosphorylation (ATP generation via Krebs cycle) [27501325].

Supplementation to optimize mitochondrial health and to reverse failing mitochondrial health always focuses on what will optimize antioxidant concentration and redox balance inside the cells.

Mitochondrial Support Agents

1. Vitamin C (good to utilize different forms—Multi-C Protocol); liposome form important for subcellular organelle uptake (both having lipid bilayer membranes)
2. Thiamine (vitamin B1), which is essential for helping to convert pyruvate into the acetyl coenzyme A required for entry into the Krebs cycle. A thiamine deficiency works to redirect pyruvate conversion into lactate, resulting in a vastly lower production of cellular energy (ATP).
3. Pantothenic acid (vitamin B5), required for coenzyme A synthesis (along with ATP and cysteine) [supplement as pantethine, not calcium pantothenate]; appears that B5 is not usually taken in sufficient amounts regularly, like vitamin C

Mitochondrial Support Agents

4. Riboflavin (vitamin B2); deficiency results in mitochondrial energy metabolism dysfunction [28475111]

5. Coenzyme Q10, which is a component of the ETC along the mitochondrial christae. Comes in the form of MitoQ (CoQ10 bound to a lipophilic TPP cation, which is taken up rapidly through the plasma and mitochondrial membranes into the matrix)

6. Idebenone, a supplement that is a synthetic derivative of CoQ10 and powerful antioxidant, and often effective when CoQ10 loses impact. Shown to be useful in inherited mitochondrial disorders [29133631, 28943110]

Mitochondrial Support Agents

7. L-carnitine (also available in liposome formulation); helps to transport long chain fatty acids across the mitochondrial inner membrane [20398344, 18646596, 15590999]

8. Creatine, which helps to produce of mitochondrial ATP and protects against mitochondrial DNA mutations [28069926, 16098029]

9. D-ribose, which supports the production of mitochondrial ATP

10. NADH, which powers the electron transport chain in the mitochondrial membranes

Mitochondrial Support Agents

11. Tocopherols (vitamin E) are of benefit in lessening mitochondrial oxidative stress. Efficacy is improved when the tocopherol is bound to TPP, like CoQ10 in MitoQ, that concentrates in the matrix ("targeted") [20804578]. Regular vitamin E much less effective.
12. Dichloroacetate, a prescription medicine, works to maintain the decarboxylation of pyruvate to acetyl coenzyme A, critical in initiating and sustaining the energy production via the Krebs cycle [29059435, 28572638]
13. Alpha lipoic acid, which helps in the production of acetyl CoA, as well as playing an important role in recharging oxidized antioxidants [29191830]

Mitochondrial Support Agents

14. N-acetylcysteine (NAC), a source of cysteine, which is the rate-limiting amino acid in the synthesis of glutathione [28025489]
15. Omega-3 fatty acids improve cellular mitochondrial content and mitochondrial ATP production [24972878, 23107305]
16. Resveratrol preserves mitochondrial function and promotes mitochondrial biogenesis [25156660]
17. Magnesium promotes increased mitochondria numbers and workload capacity per mitochondria, and its deficiency lowers ATP production [29206066, 20388094]
18. PQQ (pyrroloquinoline quinone), an antioxidant that increases the efficiency of mitochondrial metabolism [24231099].

Supplements to Avoid

Iron, only to be taken when prescribed for an iron deficiency anemia is present, but never to be taken as a regular supplement

Copper, never to be supplemented

Calcium, never to be supplemented

All three are the **primary agents for increasing oxidative stress**, especially intracellularly. The mitochondria are always ultimately harmed by a cytoplasm that has increased oxidative stress.

Basic Supplementation

When you support and promote a healthy cytoplasm, you are also supporting and promoting healthy mitochondrial function.

The Big Four, all of which help to **normalize elevated intracellular calcium levels** and individually have been **shown to decrease all-cause mortality**:

1. Magnesium (to bowel tolerance, augment with transdermal)
2. Vitamin D3 (to a target blood level of approx. 50 to 80 ng/cc)
3. Vitamin C (many different ways to dose and supplement)
4. Vitamin K (including K2)

Basic Supplementation

5. Lysine
6. Proline
7. Omega-3
8. Mixed tocopherols (forms of vitamin E)
9. B-complex (some of which should be individually taken for a higher dosing)
10. Iodine/potassium iodide (Iodoral)

Additional Supplementation

There is no fixed protocol of optimal supplementation. Different people have different needs, along with varying abilities to afford paying for such supplementation.

Generally, however, taking the suggested “Basic Supplementation” is a good starting point (and **finishing** point, for some individuals).

Beyond the basics, however, it is difficult to “overdo” taking too great a variety of different nutrient/antioxidant supplements. When you can partner with your doctor and follow the interval changes in important bloodwork parameters, you can approach reaching the goal of optimal supplementation.

Vitamin C Supplementation

While magnesium and vitamin D are absolutely critical to good health, vitamin C is arguably the single most foundational of the important health-promoting agents/biomolecules.

All diseases are manifestations of increased oxidative stress, as discussed earlier. Vitamin C is, and remains, the most clinically important antioxidant to consume and to supplement. Physiological and toxin-induced oxidative stress continue to add to the oxidation side of the redox ratio, and new antioxidants, largely in the form of vitamin C, must be consumed on a daily basis to keep the redox balance in an optimally healthy range.

Vitamin C Supplementation

The goal of vitamin C supplementation is to reach and maintain as close as possible a state of body-wide **ascorbate saturation**. Furthermore, it is especially vital to achieve this goal as completely as possible in the **cytoplasm** and in the various **subcellular organelles**, especially the mitochondria.

Vitamin C Supplementation—Multi-C Protocol

1. Oral liposome-encapsulated vitamin C (for optimal ***intracellular*** access by ascorbate, as well as in subcellular organelles)

2. Multigram doses of sodium ascorbate powder, taken several times daily, up to or reaching bowel tolerance (in order to minimize gut toxicity & support ***extracellular*** access by ascorbate) [7321921, 4069036]

3. Oral administration of ascorbyl palmitate (for optimal ***fat-soluble*** access by ascorbate) [15209539, 12595755, 9890643]

4. Intermittent IV administration of ascorbate (to optimize ***extracellular*** access by ascorbate, as well as to further ***support*** intracellular pools of ascorbate); also **IV push applications**, sometimes with insulin and/or hydrocortisone

5. Intramuscular administration of ascorbate

Final Note

I appreciate very much the opportunity to present to this distinguished audience the concepts and information contained in this presentation.

Your comments, questions, or thoughts regarding what was presented are welcome. Please feel free to contact me at:

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