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Review Article

Hossam Retrograde Mitochondrial-Nuclear Axis is the Hidden Secret for Rejuvenation: Granted US Patents Review

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Abstract: Mitochondria are the powerhouse of the cells. They are linked only to energy production and some very rare cases of maternal diseases. Recent studies at Harvard University show that there is a cross-talk between the mitochondria and nucleus that is responsible for longevity and rejuvenation. These studies postulate that the talk is mainly done via an antegrade pathway through 3 genes namely *Sirtuin, mTOR, and LINE-1*. Meanwhile, a group of granted US patents (US9,757,583), (US9,452,297), (US9,579,520), (US9,433,798), (US9,795,802) had issued and discussed different methods of stimulation of the mitochondria. They claimed that there is another retrograde axis of the cross-talk. This axis depends on a mild increase of the nitric oxide (NO) that enhances the mitochondrial enzymes. The above patents also claimed that the retrograde axis has the upper hand over that of the antegrade axis in controlling the cross-talk process. It is believed that fighting the aging process could be much easier and accessible by the stimulation of the 2-way axes together.

Keywords: MCU, VDAC, Autophagy, Apoptosis, mTOR, LINE-1 Gene, Sirtuin

1. Introduction

The mitochondria are of bacterial origin. They originate from Alphaproteobacteria. They are the only organelles that contain 2 membranes. The outer membrane is a host membrane and so, it is permeable. The inner membrane is not permeable and allows only certain materials to pass through. The inner membrane is more or less of a bacterial origin. They invaded the living cells in a process called symbiosis. This means that the living cells can not use oxygen for energy but they have food. On the other hand, the mitochondria can use oxygen as a source of energy but they do not have food. Therefore, mitochondria invaded the living cells and took them as shelters. Then, they receive food from their hosts and in return supply the hosts with the energy. Another important clue for mitochondria to be of bacterial origin is the mitochondrial chromosome. It is circular like that of bacteria. Thus, the new idea of the bacterial origin of the mitochondria has a solid basis. The process of symbiosis is considered the most fundamental step in life for a multi-cellular organism like a human. The cells without mitochondria could burn glucose incompletely which ends with pyruvate. This incomplete burning gives a very little amount of energy i.e (2 ATPs).

While complete burning of sugar through the mitochondria gives (36 ATPs) with end products of carbon dioxide and water. This process is called oxidative phosphorylation. The above concept links the mitochondria only with energy production. However, the mitochondria have many other functions and are linked with many other diseases of the human body [1-3]. Therefore, the cells that require a high amount of energy are full of mitochondria like the heart, neurons, the liver, the kidney, and so on. On the other hand, fat cells that do not need an excess amount of energy have very few mitochondria [44]. The mitochondrial function is not only energy production but most chronic diseases in the elderly are related to the mitochondria.

2. The Molecular Mechanic of the Structure of the Mitochondria

The mitochondria have 2 membranes. The outer is permeable like the host membrane. The inner is impermeable and only allows hydrogen ions or other very limited numbers of materials that can go through the transmembrane proteins or shuttles. The space between the inner & outer membrane is called intermembranous space which has a higher concentration of hydrogen atoms. The matrix is the internal space of the mitochondria. It contains circular chromosomes which are more or less similar to the bacterial chromosomes. The matrix is also full of *free radicals* known as reactive oxygen species (ROS) as this is the site of the burning of foods. The enzymes of burning namely the cytochrome oxidase complex are present on the inner membrane [4].

2.1. The Outer Membrane

As said earlier, it is permeable and from the host cell membrane. The most important transmembrane protein is called Voltage-Dependent Anion Channels (*VDAC*). This protein has great importance in communication with the nucleus. Recent studies show that all orders of the cells that come from the nucleus are supervised by the mitochondria. This means that mitochondria have the upper hand on the nucleus to control all the cell biological functions. The most important functions of (VDAC) are autophagy, apoptosis, and the regulation of insulin receptors of the cell membrane. These functions could be done via the recently discovered mitochondrial-nuclear axis. The studies also show the disturbance of this axis would lead to catastrophic diseases that range from aging problems to cancer transformation [5, 6].

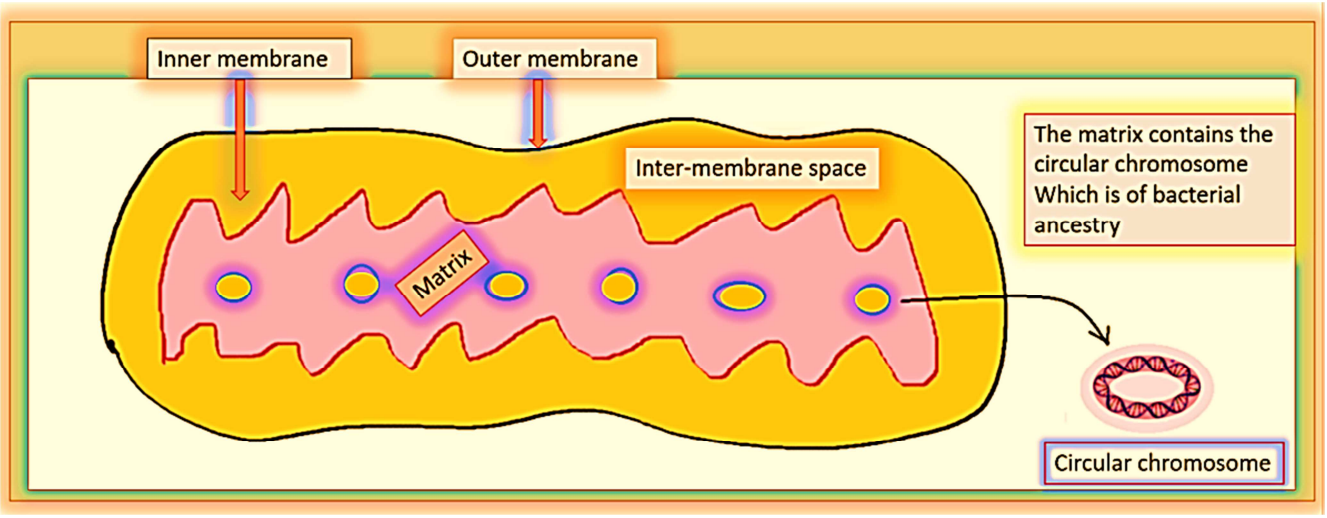

Figure 1. *The mitochondria have 2 membranes: inner and outer ones. The chromosomes are circular in shape like that of bacteria. This strengthens the theory that mitochondria are of a bacterial origin i.e alpha-proteobacteria.*

2.2. The Inner Membrane

It is impermeable except for hydrogen (H) which is essential for energy production in the process of electron transport chains or oxidative phosphorylation. It also has certain transmembrane proteins that allow only a very limited number of materials to pass through the inner membrane. The most important transmembrane proteins are the mitochondrial calcium uniports (MCU), carnitine shuttles, pyruvate-dehydrogenase enzymes, and cytochrome oxidase enzymes. The (MUC) is a recently discovered inner membrane protein that allows the entrance of calcium into the mitochondria from the endoplasmic reticulum. Calcium harms mitochondrial function because it causes damage to their enzymes. Recently discovered that the (taurine) supplement has a protective effect on the mitochondria via blocking of this port. The carnitine shuttles are needed for fat metabolism. The pyruvate dehydrogenase is needed for carbohydrate metabolism. The cytochrome oxidase is the enzyme that is used for the electron transport chain for energy production. The enzyme ATP synthase can add the respiratory oxygen into the hydrogen from the food to form water plus the release of a large amount of energy that could be stored in the form of ATPs [7, 8].

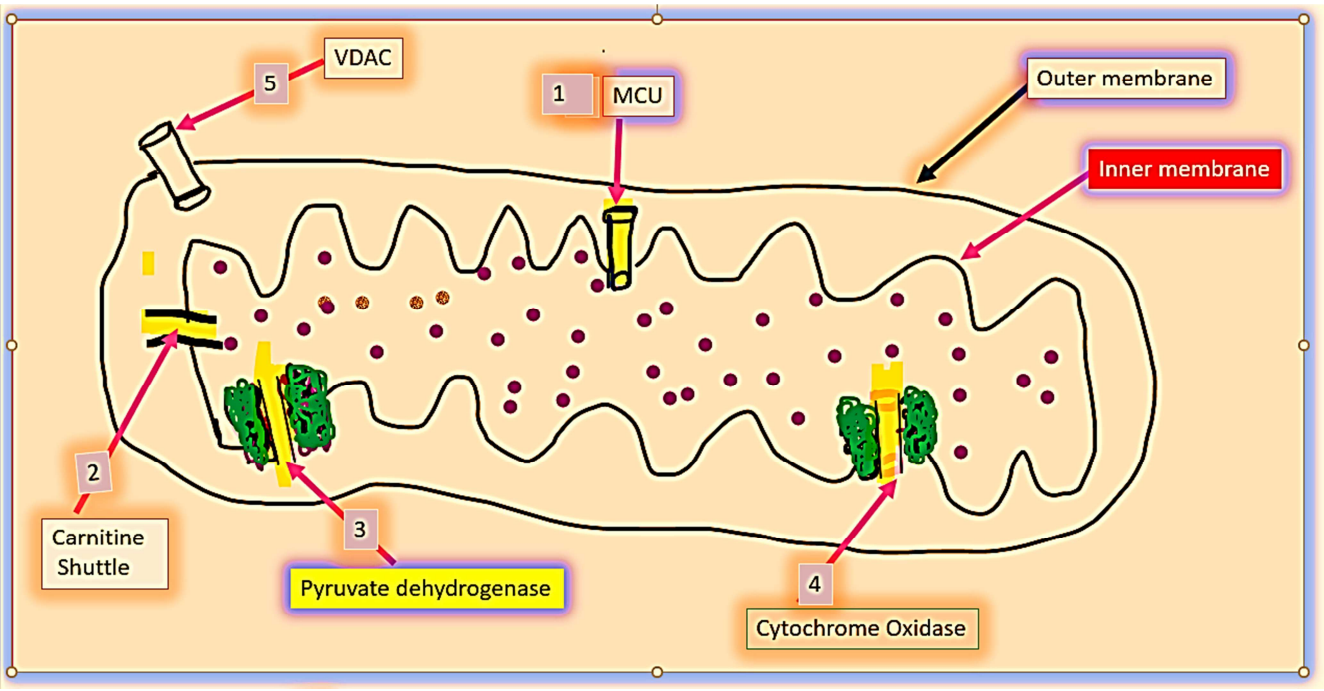

Figure 2. *The Inner membrane of the mitochondria contains 4 main types of proteins that allow only certain materials to enter. The outer membrane contains only VDAC. The space between the 2 membranes is called intermembrane space. The space inside the inner membrane is called the matrix.*

2.3. The Mechanism of Energy Production

The inner membrane has a complex system of enzymes that start with pumping hydrogen (H) atoms out from the matrix to the intermembrane space. As the inner membrane is impermeable, the hydrogen can not enter the matrix again except through an enzyme called ATP synthase. The Hydrogen atoms become concentrated in the intermembrane space leading to the rise of electrical gradient difference around the inner membrane. This stimulates the ATP synthase to work. While the (hydrogen atoms) are rushed from intermembrane space to the matrix, it causes a motor to rotate with the coupling of hydrogen and the respiratory oxygen to form water. This is associated with the release of energy stored in the form of ATPs that could be used for biological functions [9]. The ATPs act as the currency for energy. the surplus energy acts as an indicator for good health because the body can repair all the damaged tissues that could occur in the normal wear and tear process. on the other hand, lack of energy is an indicator of bad health because the damaged tissues could not be renewed. The accumulation of the damaged tissues is presented later as the aging process. This aging process differs according to the affected organ [42].

3. Step-down Theory of the Mitochondria

The link between the mitochondria and the diseases was only thought to be related to the mitochondrial chromosomes. This means that these diseases are transmitted from the mother and not from the father [45]. The mitochondria are also linked aging process and degenerative diseases in the elderly. It is believed that the main function of the mitochondria is just energy production, this is true in healthy normal conditions. In cases of degenerative diseases in the elderly, the mitochondria step- down from their main function of energy production and try to solve the problem of the disease process. In this situation, the mitochondria, do not produce energy enough for optimal biological function. This explains the debilitating condition that is almost always associated with long-standing chronic diseases. This is because his/her mitochondria are busy with another job. This is what is called a step-down theory [10]. *The main function other than energy production are*:

1) Calcium metabolism can be done through (MCU)
2) Fat metabolism can be done through carnitine shuttles
3) Carbohydrate metabolism through pyruvate dehydrogenase enzyme
4) An immune system including the autoimmunity and tumor
5) Autophagy is re-cycling of the misfolded proteins
6) Apoptosis (programmed cell death) is ordering the abnormal cells to commit suicide.

In case of disturbance of any above function, the mitochondria step-down from energy production and start to solve the above problem. This is the explanation of the lack of energy in case of debilitating conditions in the elderly. Not all the functions of the mitochondria are of equal importance. i.e. some are more important than others. Therefore the functions of stepped-down mitochondria would be arranged from their importance [11].

3.1. The Apoptosis

This is considered one of the most important functions of the mitochondria other than energy production. This means programmed cell death. If this function is not properly done,

the affected cell would be immortal and transformed into cancer. Therefore, this acts as the 1st line of defense against cancer. This means that any cell starts to get any mutation, the mitochondria give signals to the nucleus of that cell to commit suicide. The mechanism is done via (VDAC) to the nucleus which is the retrograde axis. Therefore, blocking of (VDAC) by any reason would block these signals and the mutated cell would proliferate and a tumor may arise [12].

3.2. The Autophagy

This is a very important function in repairing the damaging tissue. The misfolded proteins are accumulated inside the cells. These misfolded proteins have many side effects like trash in the kitchen. The proteins can not do their function except if they are properly folded. The gradual accumulation of these misfolded proteins causes the affected cell to be converted into *senescent cells*. These act as zombie cells that refuse to die and can not do their proper function as well. Furthermore, these cells would infect nearby healthy cells and transform them into new senescent cells. Fasting, if prolonged, activates the mitochondrial-associated protein ligase (MAPL). This collects the misfolded proteins in mitochondrial vesicles (MDVs) and sends them to the lysosomes for their destruction. The misfolded proteins are discarded and new amino acids would enter the amino acid pool. Therefore, the added new amino acids could be used for the manufacture of new properly folded proteins. The above consequent steps are simply the process of rejuvenation. For this critical function to occur, carbohydrates must be completely cut-off and to a lesser extent the proteins. Fats on the other hand do not inhibit autophagy. This theory was awarded a Nobel prize in 2016. The full explanation is via the effect of food on *mTOR* in the discussion [13, 14].

3.3. Mitochondrial Calcium Uniport (MCU)

This is a recently discovered opening in the inner membrane of the mitochondria. It exactly lies in the site of the mitochondria facing the endoplasmic reticulum. This pore (s) allow the calcium ions to enter from the endoplasmic reticulum to mitochondria. The recent discovery that calcium ions harm the mitochondria. This port could be closed by Taurine amino acid as in (figure 2). This is not true amino acid because the carboxyl group (COOH) is replaced by the sulphonyl group (SOOOH). Therefore, it is a sulfur-containing anti-oxidants. Because of its effect on the (MCU), it is considered one of the best cytoprotective agents. Taurine enhances the function of mitochondria through this mechanism. It is one of the anti-oxidants that activate the retrograde axis of the mitochondria which is the subject of this paper [15, 16].

3.4. Carnitine Shuttles

These act as fat-burning machinery. This means fatty acids would be used as a source of energy instead of carbohydrates. This is very fundamental in the prevention of obesity. Moreover, the utilization of fat is associated with a larger amount of energy. That is to say, 1gm of fat gives 9 calories while 1gm of carbohydrates gives 4 calories. This means a surplus amount of energy becomes available. This could be used for the repair and maintenance of the damaged tissues. It must be noted that the Lysine amino acid is essential for the manufacture of the carnitine. The surplus energy also activates the retrograde axis. Therefore, the Lysine amino acid would be one important amino acid that is very important for the mitochondrial function and the retrograde axis [17, 18].

3.5. Pyruvate Dehydrogenase

This is the port essential for the entrance of glucose for carbohydrate metabolism. Some antioxidants like alpha-lipoic acid (ALA) & N acetylcysteine (NAC) can activate this port. Thus, blood sugar and insulin sensitivity could be restored by certain anti-oxidants. Activation of this enzyme also could help in restoring the retrograde axis of the mitochondrial-nuclear axis [19].

4. The Mitochondrial-nuclear Axes

Recent studies show that as long as the mitochondria have cross-talk with the nucleus, the cells would have a perfect function. Moreover, the diseases of the aging process would not occur or be reduced to the minimum. However, the contact between the mitochondria and the nucleus occurs through the (VDAC) on the outer membrane, the inner membrane integrity is needed. This simply means that if the inner membrane is damaged or disrupted, the mitochondrial-nuclear axis would not properly work. Therefore, the recovery of this axis is essential for the reversal of the above step-down of the mitochondria. This depends on the integrity of the 2 membranes of the mitochondria but the actual message would be from the (VDAC) [20, 41].

4.1. The Cross-talk Between the Mitochondria and Nucleus

The mitochondria have more than 1200 proteins all are encoded by the nuclear DNA except 13 that are coded by mitochondrial genes [20]. Recent studies show that most of the aging process is just a reduction of the communication between the mitochondria & nucleus. It is sometimes called mitochondrial dysfunction. For the mitochondria to do their proper function, they must have good communication with the nucleus. Recently discovered that there are 2 ways in the communication between the mitochondria & the nucleus. These are the antegrade & the retrograde pathways which would be explained. This is just a simplification because the 2 pathways are interconnected and dependant on each other. Simply, there is no line of demarcation between the 2 ways. Furthermore, the retrograde pathway has the upper hand over the antegrade one and is the most important in the fighting of the aging process [21, 40].

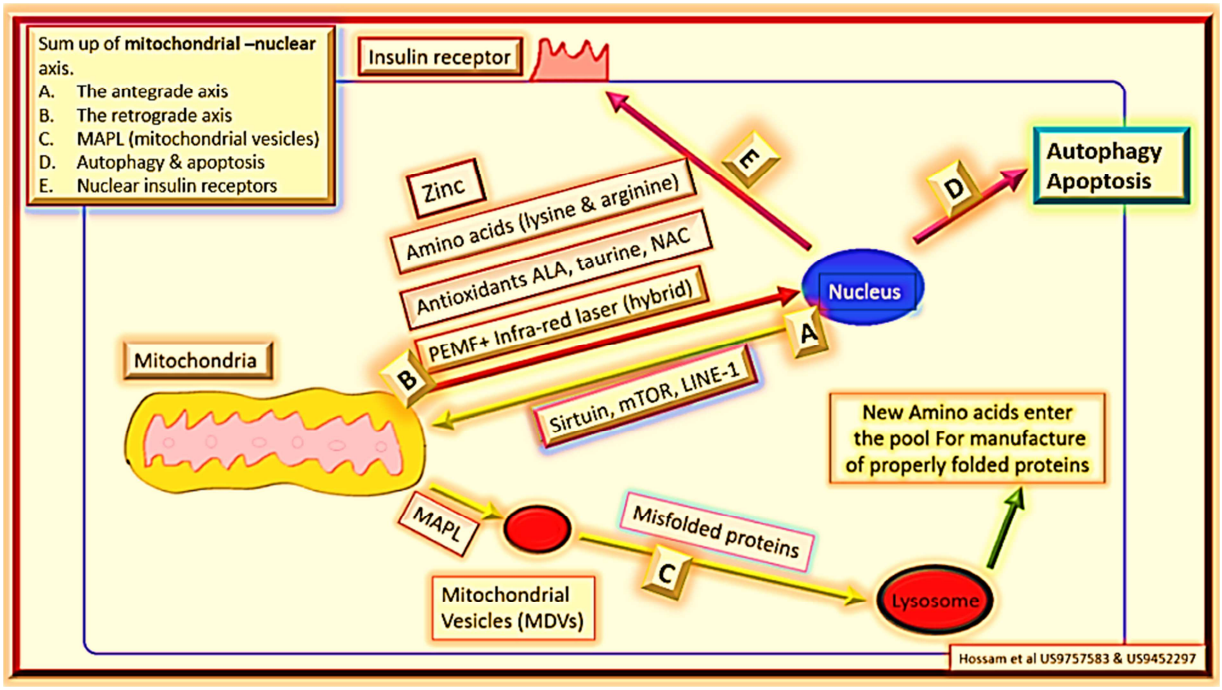

Figure 3. *The mitochondria have an integral central role to control all the biological functions of the cells. A& B are the 2 axes for the crosstalk between the mitochondria and the nucleus. (C) is discarding of misfolded proteins. (D) is the autophagy & apoptosis. (E) is the regulation of insulin receptors.*

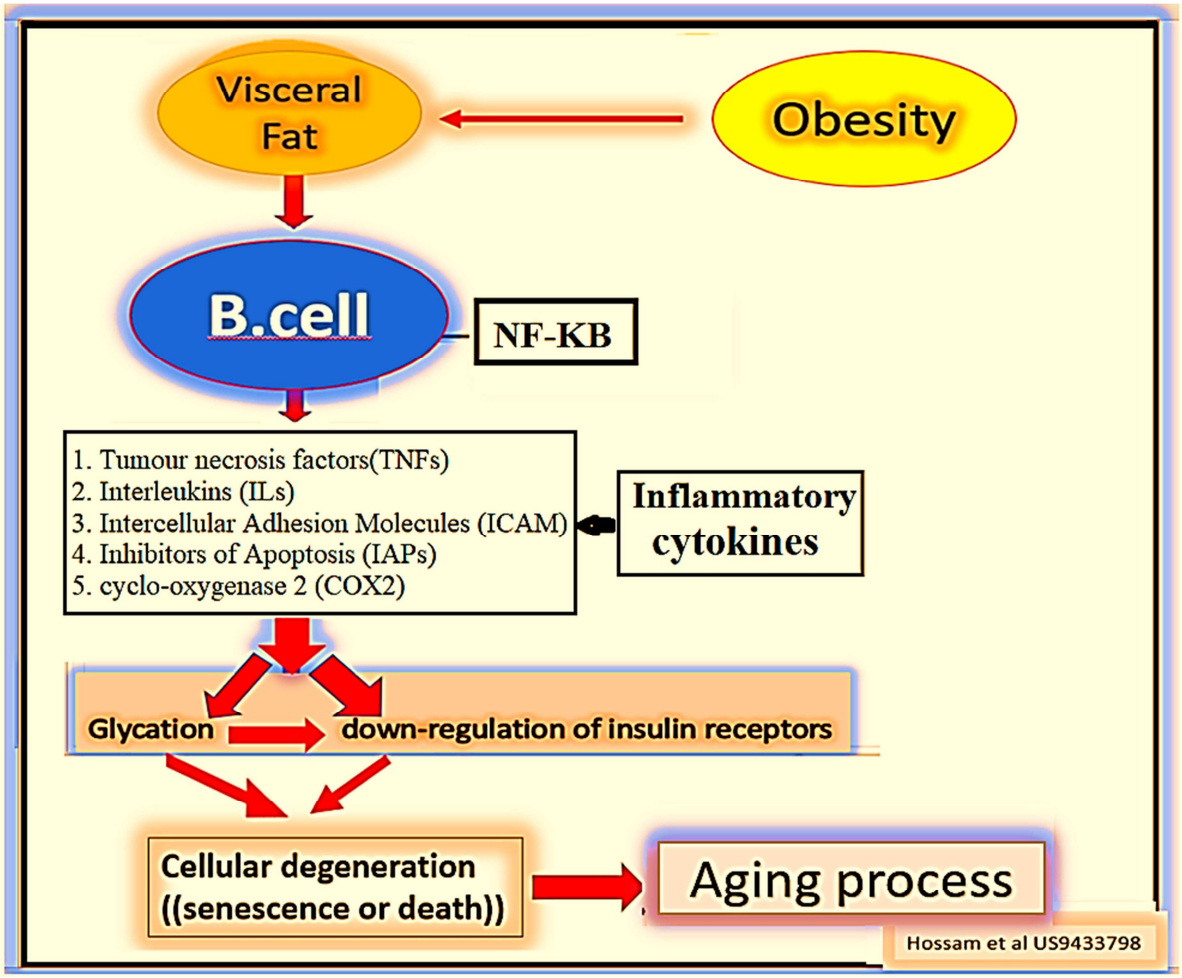

Figure 4. *The effect of obesity, hyperinsulinemia, and glycation on the mitochondrial function. the mechanism and sequence by which obesity can induce the aging process.*

4.2. The Antegrade Axis (Nuclear-Mitochondrial Direction)

This pathway is from the nucleus to the mitochondria. This pathway is responsible for most of the mitochondrial proteins as most of them are coded by genes in the nucleus except 13 of them of a total of 2000 proteins. This pathway is multifactorial and most of these factors are general or even distant factors like visceral fat, lifestyle, body weight, blood sugar, the presence of hyperinsulinemia, or not. Therefore, the antegrade axis is difficult to be controlled as it depends on a change in the lifestyle and/or the body weight of the patient which is sometimes difficult. The most important genes of the antegrade system are Sirtuin, mTOR, and LINE-1 genes. These would be discussed in detail in the discussion section. *Paradoxically, the most fundamental point for the antegrade axis to work properly is the integrity of the upper hand retrograde axis*. This is because all orders of the nucleus are supervised by the mitochondria [22].

4.3. The Retrograde Axis (Mitochondrial-nuclear Direction)

This is the most important axis. Its direction is from the mitochondrial to the nucleus. Its main drive is the nitric oxide (NO) that activates the mitochondrial function. Thus, it can be affected by an infrared laser, PEMF, and more perfectly the hybrid system that contains both [23, 24]. It also can be modified by certain supplements and anti-oxidants. It is known that the mitochondria as the powerhouse of the cells are full of free radicals or reactive oxygen species (ROS). Thus, the anti-oxidants have a very good benefit for enhancing the performance of the mitochondrial enzymes. Some elements are also important like the zinc that activates nitric oxide synthetase. Other amino acids that may be very beneficial to the mitochondria include lysine and arginine. Lysine is needed for the carnitine shuttle & Arginine as a source of nitric oxide [25].

4.4. Hyperinsulinemia & Visceral Fat on Mitochondrial Function

Obesity is a catastrophic disease and it is the origin of all metabolic syndrome (X). It depends on the body weight and length in the form of body mass index (BMI). The Guideline of (BMI) is below 18 is considered underweight. From 18-25 is normal weight. 25-29.9 is overweight. Over 30 is the start of obesity. Obesity is almost always associated with excess visceral fat, glycation, and hyperinsulinemia. These are called metabolic triads. Visceral fat secrets tumor necrosis factors (TNFs) that increase glycation. Hyperinsulinemia causes down-regulation of insulin receptors by the simple feedback mechanism. This may be of a protective function in the early stages but later the affected cells suffer from starvation up to death. Thus, Hyperinsulinemia may be considered the worst to damage the tissue. It is more prevalent than DM II. It is considered more dangerous than DM II and it is about 3 times more common than it. In The US, DM II is about 11% of 36 million while hyperinsulinemia is 31% of about 86 million. Recent studies show that hyperinsulinemia is the cause of all the metabolic syndrome (X) of Alzheimer's, coronary artery diseases, osteoporosis, osteoarthritis, tendonitis, hypertension, and others. It has a false sense of security because the patient feels that he/she is not a diabetic yet and it is not needed to cut carbohydrates. The pancrease can compensate to increase the insulin and forcibly makes an entrance of sugar into the tissues. It is well-known that high blood sugar is dangerous but glycation and forcible admission of glucose into the tissues is more dangerous. It must be noted that obesity & hyperinsulinemia are generalized conditions, they affect mainly the antegrade axis [26].

5. The Externally Applied Energy for the Activation of the Retrograde Axis of the Mitochondria

5.1. Infrared Laser Therapy

Infrared laser has a stimulatory effect on the production of *nitric oxide (NO)*. The mechanism is via the stimulation of nitric oxide synthase. This necessitates the presence of zinc *(Zn)* & arginine or better citrulline amino acids. The zinc connects 2 subunits of nitric oxide synthase. Moreover, it can fix oxygen to the 2 subunits of the enzyme. Arginine or citrulline would be the source of nitrogen. The enzyme nitric oxide synthase can connect nitrogen and oxygen to form nitric oxide (*figure 5*). This material has a very stimulatory effect on the mitochondria to enhance its function more than 800 times [27]. The utilized laser differ according to the wavelength and intensity. According to the intensity, the best is low-level laser therapy (*LLLT*) which is in the range of 200-400m Watts. Paradoxically, the higher the intensity more than 500 mW may be associated with an inhibitory effect on the mitochondrial enzymes. According to the wavelength from 700-2500 nm is considered near infra-red laser (NIR) which has the highest penetration capacity 3-5 cm. The wavelength of 2500-4000 nm is considered a mid-infrared laser (MIR) which is a transitory field between the near and far-infrared laser. Lastly, a far-infrared laser is between 4000-1.000.000 nm. However, this is considered of least penetration power than near and mid-infrared laser, it is the only one that could stimulate (RUNX2) gene [28]. This discovery can change the career of modern medicine. RUNX2 was thought that it can help in osteoporosis because it converts stem cells to osteoblasts but now it can be used for the correction of many other diseases. Recent trials on RUNX2 can be used in the treatment of DM II, chronic renal failure, coronary artery diseases, Alzheimer's, and many others. Infrared laser therapy also has a very good healing capacity on most chronic diseases in the elderly via the vasodilator effect via nitric oxide (NO) production. The vasodilator effect increases oxygen and nutrition to the damaged area helping its recovery. Moreover, it also helps in the washing effect of the waste products that cause the pain. Thus, the pain would improve dramatically with tissue healing [29].

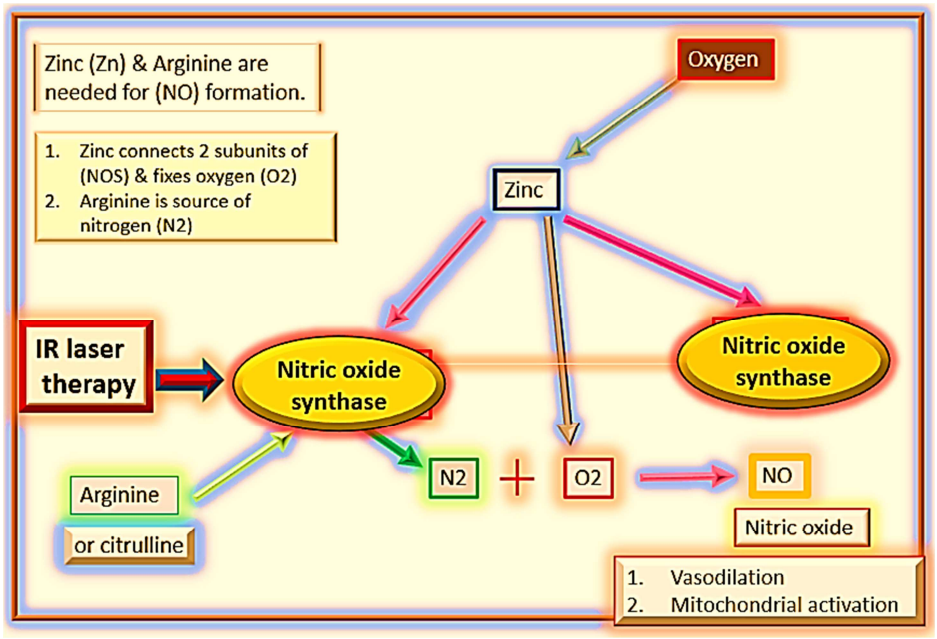

Figure 5. *The activation of the nitric oxide via zinc and arginine. The zinc connects between the 2 subunits of the nitric oxide synthase (NOS) and arginine is the source of nitrogen.*

5.2. PEMF (Pulsed Electromagnetic Field Therapy)

This new modality becomes well-evident after NASA granted its US patent in 2009 of a US patent No. (US 7,601,114). The mechanism of this line of treatment is ill-defined but the most probable is enhancing the nitric oxide (NO) of the mitochondrial enzyme like that of the infrared laser. Moreover, it increases the electrical gradient difference of the cell membrane of every cell exposed to its wave. This simply means saving the biological energy needed by the cells. The explanation is that about 2/3 of the biological energy is lost sodium/potassium pump mechanism (Na//K pump) to raise the action potential of the cell membrane. PEMF raises this potential for free without burning food. Thus, it saves about 2/3 of the ATPs that lost on this process. This means the biological energy is spent in the repair of the damaged tissues and rejuvenation. This device is excellent in the treatment of chronic and refractory and painful conditions. In some cases, this patented device may be more effective than medical and surgical intervention [30].

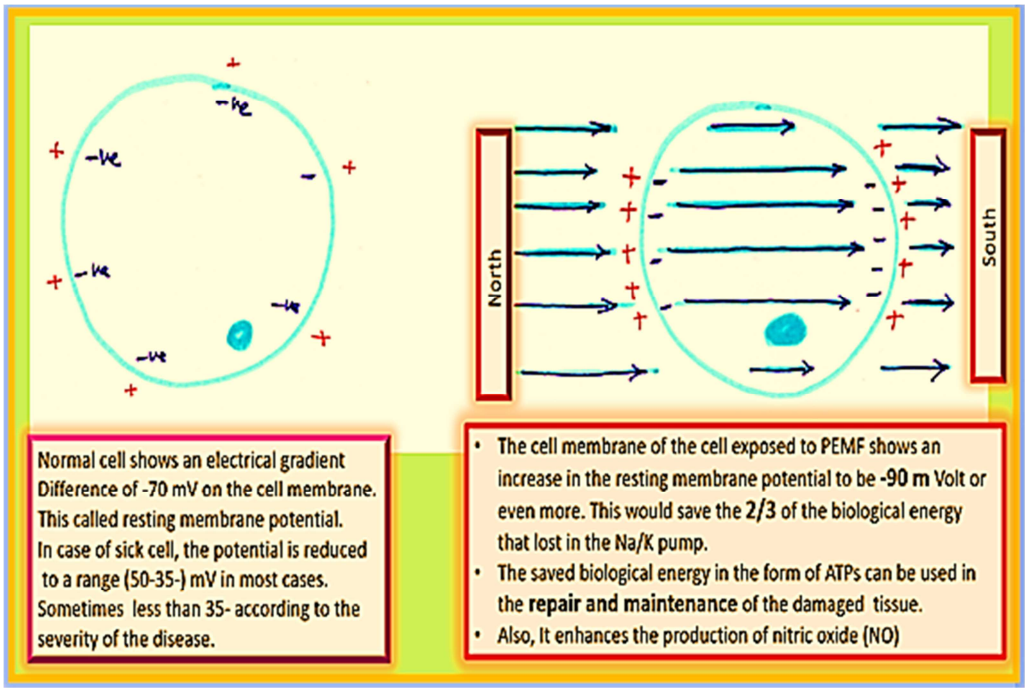

Figure 6. *The mechanism of action of PEMF according to the NASA patents (US7601114).*

5.3. The Hybrid System (IR Laser + PEMF)

This new modality is by far is the top in the stimulation of the retrograde mitochondrial nuclear axis. It has both infrared laser therapy plus the PEMF in the same device. Moreover, this is not just a summation of 2 types of energy but it is synergism at the same time. This means that each type of energy augments the other. Thus, the effect would be higher than the summation of both sources of energy. 2 US patents were issued for this line of treatment. These patents are (US 9,757,583) & (US9,452,297) [23, 24]. Moreover, the concept was proved in the Ottawa university laboratory [35]. These patents have the potential to correct most of the chronic degenerative diseases in the elderly via enhancing the retrograde mitochondrial-nuclear axis. As will be discussed later, this axis is the most important in the recovery for all chronic diseases in the elderly. Examples of that are Alzheimer's, coronary artery diseases, osteoporosis, osteoarthritis, and others.

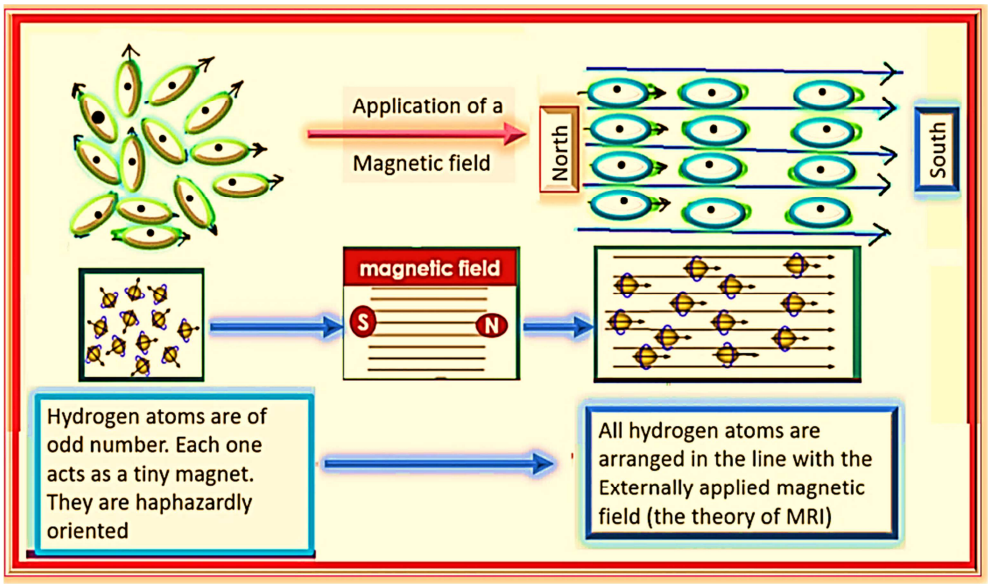

Figure 7. *The mechanism of action of the PEMF. This is done via the orientation of the hydrogen atoms under the effect of the externally applied magnetic field. i.e from North to South.*

6. Discussion

The mitochondria have the *central and key role* to control all other organelles of the cells including the nucleus. Mitochondria were thought to have only one main function which is *energy production*. The energy production via the mitochondria is called oxidative phosphorylation with the production of 36 ATPs i.e relatively large amount of energy than that produced in the cytoplasm through incomplete burning of glucose with only 2 ATPs. The end products of oxidative phosphorylation are carbon dioxide and water while in the case of incomplete burning is pyruvate. The mitochondria are of bacterial origin and this is evident by their circular DNA and which is related to alpha-proteobacteria [37].

6.1. The Step-down Theory of the Mitochondria

The mitochondria have the main function of energy production. This is the situation of normal healthy conditions. But in certain other situations, the mitochondria step-down from this main function and become busy with other subsidiary functions. As the mitochondria become busy, the energy production is reduced accordingly to a variable degree. In longstanding and progressive diseases, the conditions become gradually worsen, and patients develop chronic debilitating conditions with very little or no energy production. The reversal of this mechanism could improve the patient's condition and he/she gradually feels more energetic. This is also reflected as better performance and well-being. This can be accomplished by the retrograde axis. Many patents issued that can stimulate the retrograde axis which depends mainly on activation of nitric oxide (NO) [38].

6.2. The Nuclear Mitochondrial Axes

There is no clear-cut demarcation between the above axes namely the antegrade & retrograde axes. This means that if any axis of them is disrupted, the other axis would also be affected. Moreover, it found that the retrograde axis (the mitochondrial-nuclear axis) has the upper hand. This means that if the retrograde axis is enhanced, the condition is greatly improved more than the antegrade axis alone. But the combination of both antegrade & retrograde would be better than any of them alone. Moreover, the antegrade axis is sometimes difficult to be controlled with because it depends on the general condition of the patient like obesity, visceral fat, lifestyle, feeding habit, and other factors that many patients find difficult to change. This is because all these general

conditions affect *mainly* 3 genes in the nucleus that controls the rejuvenation. While the retrograde mechanism as said earlier depends on the enhancing of the nitric oxide (NO) [39].

6.2.1. The Antegrade Mitochondrial Axis

1) The direction is from the nucleus to the mitochondria
2) It depends on the general condition of the patient
3) Sometimes it is difficult to be controlled with
4) It is executed via 3 main genes that affect longevity. These are *Sirtuin, mTOR, and LINE-1* gene.
   a. *Sirtuin* is a longevity gene. It helps in the repair of the damaged DNA. Daily there are 2 billion damages in the DNA. Accumulation of this damage without repair could stop the signal from the nucleus to the mitochondria. Thus, antegrade would be suppressed. These damages of DNA could occur spontaneously but is increased by free radicals, X-ray, exposure to poisonous like pesticides, and others [31].
   b. *mTOR* is called the mammalian target of rapamycin. It is activated by carbohydrate ingestion & to a lesser extent by amino acids, especially glutamine. Its activation may enhance cancer because it stops autophagy & apoptosis as in figure 3. It must be noted that fats in general have no or minimal effect on the mTOR. Furthermore, fasting inhibits the mTOR. Thus, This gene depends on the lifestyle and feeding of the patient and is sometimes difficult to be changed [32].
   c. LINE-1 gene is an abbreviation of *Long Interspersed Nuclear Element*. This gene is a hypomethylation gene. It destroys the DNA and prevents its repair. This would inhibit the antegrade axis. This gene could be inhibited by methylating agents like S. Adenomethyl methionine (SAM), Methyl sulphonyl methane (MSM), Choline, trimethylglycine (TMG) [33].

From the above, the antegrade axis is difficult to be controlled. Generally speaking, Fasting, cutting carbohydrates, increase exercise may enhance this axis.

6.2.2. The Retrograde Mitochondrial Axis

1) This axis is more effective.
2) Easily manipulated
3) It depends mainly on minimal increasing the nitric oxide (NO) which can enhance mitochondrial performance. Subsequently, it enhances the retrograde axis.
4) This can be accomplished by many methods but most of them are easy to be manipulated as said earlier:
   a. *Infrared laser therapy* (low-level laser therapy) LLLT.
   b. *The pulsed electromagnetic field* (PEMF)
   c. Hybrid system (discussed later)
   d. certain amino acids as *arginine, citrulline,* and/or *lysine*. Arginine or citrulline is a source of nitrogen for nitric oxide. *Lysine* is essential for the construction of the carnitine shuttle of the mitochondria.
   e. *Certain anti-oxidants* neutralize the free radicals. Thus, the mitochondrial function could be improved e.g Alpha lipoic (ALA), N. acetylcysteine (NAC), Taurine, and or others.
   f. *Zinc* as a metal has an integral role in nitric oxide production. Thus, it is used for the repair of the damage via activation of the retrograde axis. Zinc supports the 2 subunits of the nitric oxide synthetase and fixes the oxygen to the nitrogen to form nitric oxide (figure 5) [34].

6.3. The Hybrid System Is Most Effective on the Retrograde Axis

As said earlier, the infra-red laser has an enhancing effect on the retrograde axis via increasing nitric oxide (NO) production. Subsequently, it stimulates the enzymes of the mitochondria to make more energy production. The Pulsed electromagnetic field (PEMF) also enhances the mitochondrial enzymes to improve more energy production. This can be done also via enhanced nitric oxide (NO) production. The hybrid system is granted US patents (US9757583) & (US9452297). It is developed in the lab, of Ottawa University [35]. It is simply *a synergism* between the infra-red laser (IR laser) and pulsed electromagnetic field (PEMF). It must be stressed that is *not* just a summation of 2 types of energy but is a synergism. This means that infrared laser enhances the effect of (PEMF) and vise versa. The effect would be much better than any one of them alone. A Nobel prize was awarded in 1988 to a group of scientists who discovered the effect of nitric oxide (NO) in the rejuvenation process [36].

It must be noted that summation of 2 types of energy of different wavelengths was impossible according to the stimulated emission theory of Einstien. In the hybrid system, the hydrogen atoms (H) are the mediators that could link 2 types of energy of a different wavelength together [43]. The above patent exploited that (H) atoms are odd number atoms. This means that each one acts as a tiny magnet that could be arranged following the externally applied magnetic field (figure 8).

7. Conclusion

The mitochondria are organelles of a bacterial origin called alpha-proteobacteria. They enter the living cells in a *symbiosis*. They supply the body with energy and the body supplying them with food. It is believed for a long time that they are needed for only energy production and very rare maternal genetic diseases. *The step-down theory* of the mitochondria is a new theory that the mitochondria are involved in most of the *degenerative diseases* of the elderly. It must be concentrated on the role of the mitochondria in metabolic syndrome (X). The correction of step-down theory can be done via the understanding of the mitochondrial-nucleus axis or may be called the cross-talk. There are 2 pathways of this axis namely antegrade and retrograde. The retrograde pathway is from the mitochondria to the nucleus. It is more effective and is easier to be manipulated than the antegrade pathway. The retrograde pathway depends mainly on the enhancement of the mitochondrial enzymes via a minimal increase in the production of *nitric oxide (NO).* The antegrade pathway is multifactorial and depends on the change of lifestyles like

prolonged fasting, cut of carbohydrates, more exercise, and others. New US patents were issued to fix and repair the broken retrograde pathway. Therefore, they could help in the reversal of the degenerative diseases of the elderly that are caused by the step-down theory of the mitochondria. However, the subject of this paper is the retrograde axis, for optimal results, both axes have to be tried. Moreover, any future technologies that may help in the fighting of the aging process have to be tried.

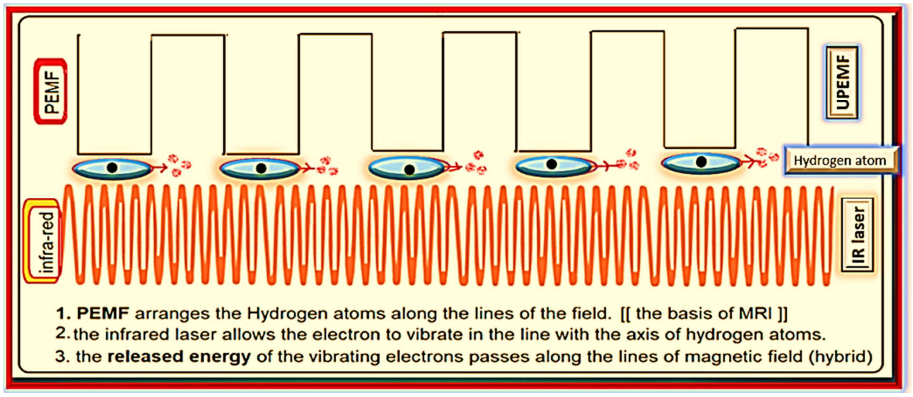

Figure 8. *The hybrid system is formed of 2 types of energy (infrared laser + P EMF). These are linked together via the hydrogen atoms that are arranged in line with the externally applied magnetic field.*

Table 1. *Comparison between the antegrade & retrograde axes of the mitochondrial-nuclear crosstalk.*

Comparison	The antegrade axis of crosstalk	The retrograde axis of the crosstalk
direction	From the nucleus to mitochondria	From the mitochondria to the nucleus
mechanism	The nuclear genes affect the mitochondria via the released messenger RNA (miRNA)	the activities of the mitochondrial enzymes send messages to the nuclear gene to modify their work
The most important players	Sirtuin (repair the fractured DNA) mTOR (block apoptosis & autophagy) LINE-1 gene (hypomethylation gene)	A). inner membrane: 1. MCU 2. Carnitine 3. pyruvate dehydrogenase 4. cytochrome oxidase B). outer membrane VDACs
activation	The general condition of the patients: 1. Cut carbohydrate 2. Exercise (HIIT) 3. Intermittent fasting 4. Reduce the bodyweight 5. Avoid exposure to toxins, pesticides, X-rays, UVR, processed foods, etc	Local activation of mitochondrial enzymes 1. Infrared laser (LLLT) 2. PEMF 3. Hybrid (infrared laser + PEMF) 4. Antioxidants (ALA, NAC, Taurine) 5. Certain amino acids (Lysine & arginine) 6. some supplements (Zinc & MSM)
Efficacy of the reversal of step down theory	Good	excellent
The manipulation	Sometimes difficult to be done like reduction of the body weight or reduce apatite	Easier to be handled i.e application of the device to the diseased site or receiving the supplement (s).

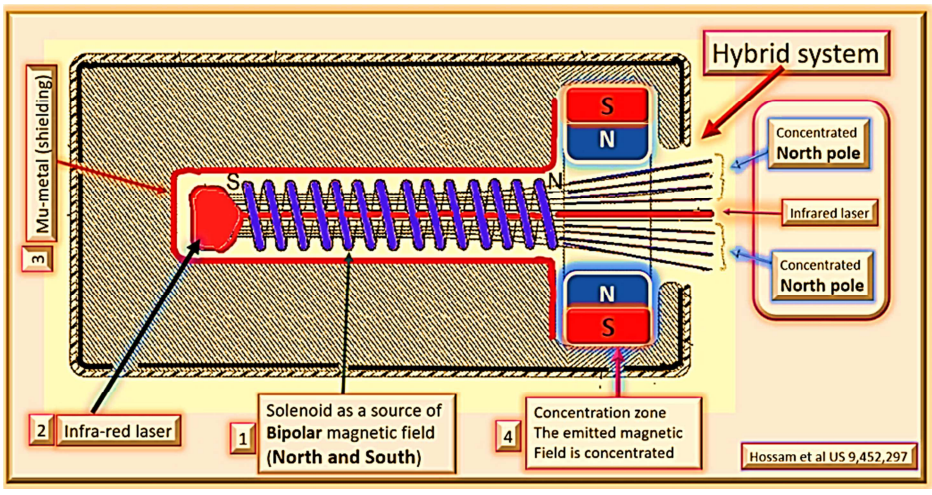

Figure 9. *Diagram of the Hybrid patent (infrared red laser +UPEMF). The acts as a breakthrough in the stimulation of the retrograde axis of the mitochondria also it can activate the dormant stem cells.*

8. Future Studies

A study between the retrograde pathway of the mitochondrial-nuclear axis & stem cells in the rejuvenation and healing of the chronic degenerative diseases in the elderly. Both the retrograde axis mitochondrial-nuclear pathway & stem cells are activated by the infrared laser & PEMF. Thus, both stem cells and the retrograde pathway could be stimulated by the hybrid system. Therefore, deeper studies have to be exerted on the relation between the stem cells, the hybrid system, and the retrograde pathway of the mitochondria.

1) The retrograde mitochondrial nuclear axis acts as the black hole of the cells. It has many secrets that could solve the problems of some chronic diseases in the elderly. Sometimes all the prior art methods of treatment either medical or even surgical may fail. The diseases that may respond to this new method of treatment include Alzheimer's, coronary artery diseases, osteoporosis, osteoarthritis, tendonitis, and so on. Therefore, a deeper study of this area is greatly recommended.
2) The step-down theory of the mitochondria needs to be deeply studied to discover further new techniques for the reversal of the step-down theory of the mitochondria.
3) As the mitochondria are of a bacterial origin, It is recommended, even at animal study, to inoculate bacterial genes into diseased mitochondria in the hope to find a solution.

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