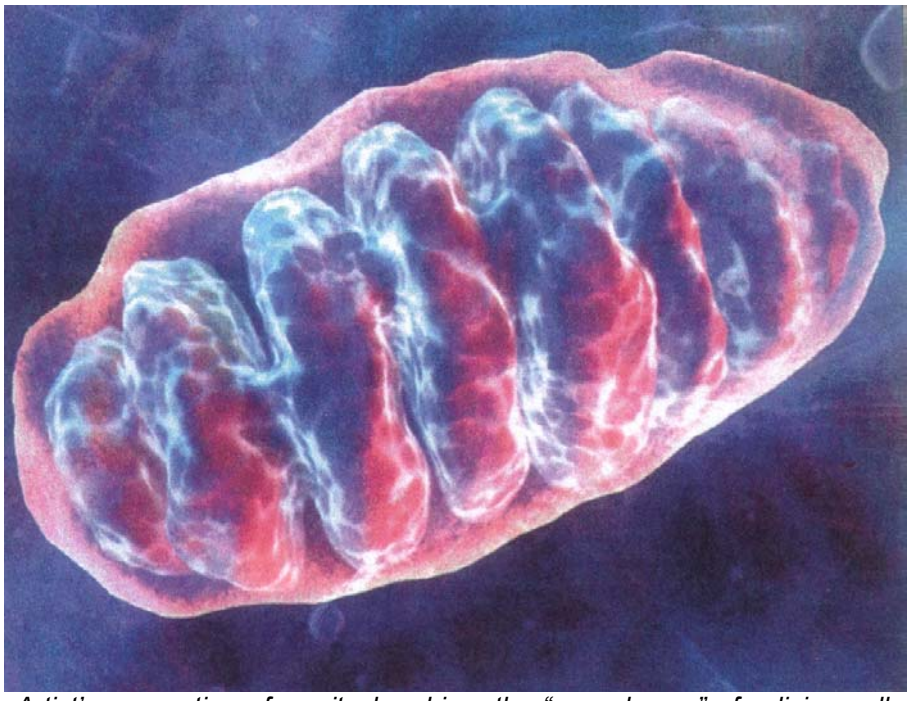


Artist's conception of a mitochondrion, the "powerhouse" of a living cell, where energy is generated.

Oxygen, Mitochondria and Cancer

By Serge Jurasunas

Lisbon - 2006

Introduction

Since the beginning of this new century new avenues in the field of cancer are immerging and after decades of failure in a perspective to understand and cure cancer the dogmatic theory of the functioning cell subordinate only to the DNA under decline. Biologists are not any more convince that cancer is only a question of cell's genes and of DNA that carry the instructions, but effectively doesn't necessarily control them. The genetic therapy has been now under severe defecit because of mortality and all the tests both in France and USA has been suspend. In 2003 about 4 new theories about cancer has been proposed (Scieces et Avenir Nov.2003) and one of them is the strong theory of mitochondria which I have introduced in TLDP in 1999.

In 2003 about 4 new theories on cellular DNA mutation and cancer has been proposed and one of them is firmily anchored to the theory of mitochondria that indeed regulate genomic activity.

In 1999 I introduced in TLDP some of my work linked with cancer therapy linked to the dysfunction of cellular respiration in mitochondria which was very well accepted. Since this day I have been constantly investigating about the relationship existing between mitochondria DNA mutation in cancer and experimented a number of protocols that could eventually restore damaged mitochondria stimulate the cellular respiration and thus normalize the tumor which today according to certain oncologists can be controlled instead being destroyed by chemotherapy.

Oxygen, Mitochondria and Cancer

Human physiology and our health status are greatly influenced by oxygen (O_2) which is an important modulator of cellular function in both normal physiology and disease states. Cells respond to oxygen over a wide range of concentration from anoxia to hyperoxia. Oxygen starvation of cells may trigger cancer promotion and tumor expansion via angiogenesis, while hyperoxic conditions often result in the generation of reactive oxygen species (ROS) that have been implicated in cellular and mitochondrial injury.

Oxygen is abundant in the geological evolution of our present 21% O_2 atmosphere and is essential for aerobic life. While O_2 is also present in the oceans, water, soil and vegetation, our bodies contain a large amount of oxygen for metabolism function and aerobic cellular respiration.

However it is useful to mention that atmospheric oxygen is today decreasing in most of the large polluted cities of North America and Europe, falling as low as 16%, which is dramatic for our health status and even our survival.

Every single second that passes, the body requires oxygen, particularly for the brain, and if we can tolerate being without food and water for several days, we can stand only a few minutes without oxygen before we simply die from brain collapse. Yet oxygen, which simply is essential for every corner of the body, both intra and extracellularly, is not considered an essential element for prevention or treatment of diseases.

The body is constructed in such way that somehow oxygen is the pillar of life. The oxygen we breath needs to be fixed and delivered by red cells to every single cell in the body.

Every day 3 trillion red cells produced by the bone marrow enter into the blood circulation to carry about 700-1000 liters of oxygen needed by our metabolism, energy making and detoxification.

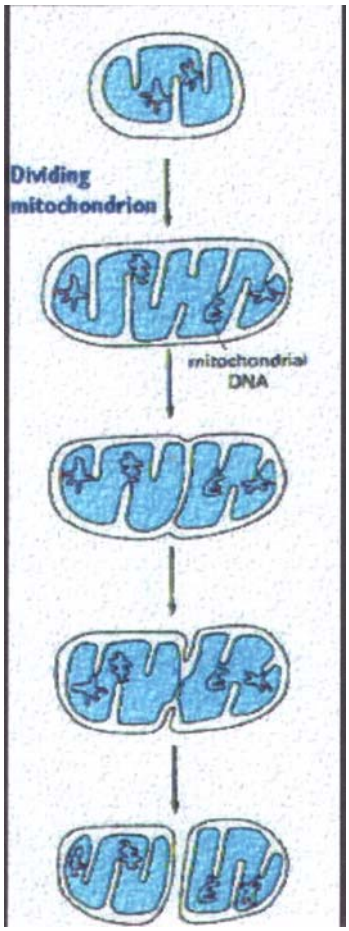
We simply need a constantly fresh oxygen supply and what we breath is mainly used by mitochondria which generate 80% of the required energy to sustain our health status.

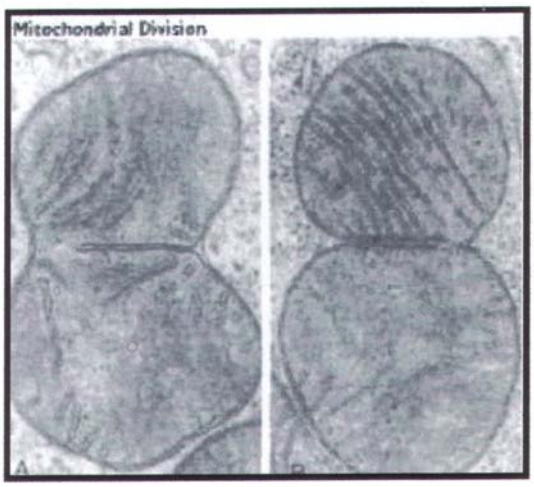
What are mitochondria?

The name mitochondria comes from the Greek mitos (filaments) and kondros (grain) and they are small tiny subcellular organelles of 0.5 – 20μ length either filamentous or oval, found in all aerobic (eukaryotic) mammalian cells (1).

Mitochondria are called the powerhouse of the body, since cells have a vital need for energy and depend on mitochondria that metabolize oxygen to generate high amounts of energy. In contrast, mitochondria of cancer cells are defective in their ability to metabolize oxygen (2).

However recent evidence and experimental studies have defined new and unexpected functions of mitochondria in the regulation of the genome.





This process is diagrammed in the cartoon. Mitochondria replicate much like bacterial cells. When they get too large, they undergo fission. This involves a furrowing of the inner and then the outer membrane as if someone was pinching the mitochondrian. Then the two daughter mitochondria split. Of course, the mitochondria must first replicate their micrograph depicting the furrowing process in shown in these figures. The figure on the right was taken from Fawcett, A Textbook of Histology, Chapman and Hall, 12th edition, 1994.

Mitochondria have been shown to play a crucial role in the regulation of apoptosis and maintaining cellular redox (3) that regulates cell growth in nonmalignant cells, typically characterized by growth factor activation at the cell surface of specific signal transduction pathways that activate crucial transcription factors to regulate genes essential for cell growth (4). Thus, a firm connection has been made between mitochondria and tumorigenesis. Orthodox medicine is strongly convinced by the scientific dogma that the cancer process has its roots only in changes in the controlling functions of the cell nucleus. According to this concept, tumors are irreversible and must be extirpated by surgery followed by radiation and chemotherapy. However we are going to realize that, on the contrary, the cell nucleus is not the only site responsible for cancer initiation and that cancer can be controlled and thus offer new perspectives in treating the disease without damaging side-effects.

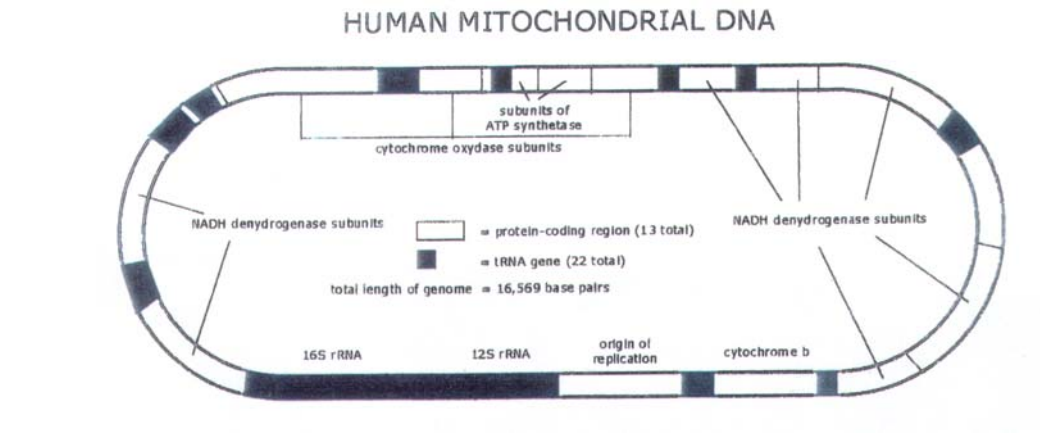
The origin of mitochondria

Mitochondria trace their origin to an ancestral protomitochondrial genome from prokaryotic (bacterial) derivatives that 2.5 billion years ago in an attempt to escape and become hidden from the new rich atmosphere on earth, penetrated

a primitive cell and became a host (5). Blue-Green algae and plankton from the ocean with the help of sunlight and the process of phosphosynthesis acquired the ability to split water (H_2O) into hydrogen (H) and Oxygen (O_2).

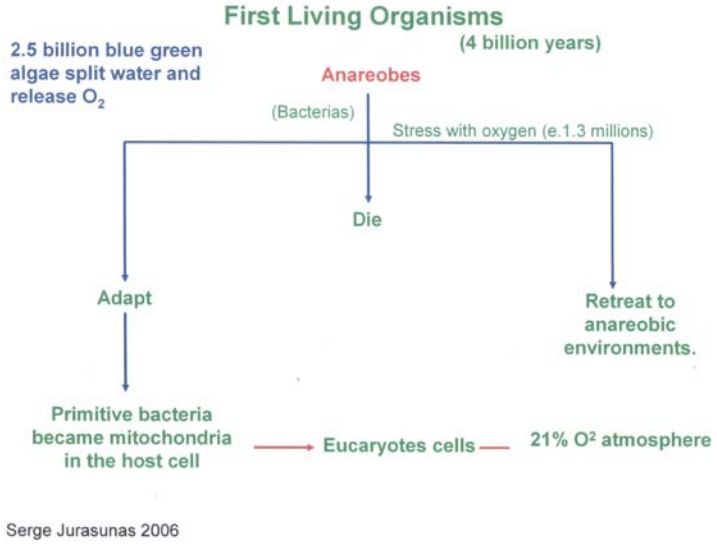
This chemical reaction initiated the release of billions of tons of oxygen into the atmosphere that led to the extinction of many anaerobic organisms, since oxygen combined with sunlight became a mortally dangerous mixture to primitive microorganisms.

Through anaerobic fermentation, resistant bacteria when penetrating primitive cells, became the host and developed a new form of genetic adaptation, necessary to a new way of life and energy making.



This evolutionary pathway led to the adaptation to channel and use the reactivity of oxygen as the main fuel energy promotor. The new cell host, mitochondria developed at the same time multienzyme defence genes against oxygen radicals produced in the form of toxic by-products from oxygen generated within the cells during the process of energy production.

Oxygen becomes toxic because it reacts with organic materials such as proteins, lipids and enzymes causing oxidation.



Many independent lines of evidence demonstrate that stress through oxygen began about 1.3 million years ago.

As hosts or intruders in the cell, mitochondria maintain a total independency as they possess some specific particularity. If cells have a DNA that contains our genetic programme developed some 4 billion years ago and a specific division cycle, mitochondria contain their own circular DNA, different from nuclear DNA (indeed similar to many (6) microorganisms) with their own and different replication.

In contrast with most of the complicated reproduction mechanism of the cell, mitochondria replicate by pinching, by division into two at a different time from one mitochondrion to another and from the rest of the cell. And as will be explained, it shows that some specific cancerous organs are different from others, since replication, quantity and damaging mitochondria can be quite different from one cell to another and from one organ to another, and therefore require different approaches.

What is the connection between mitochondria and cancer?

Because of the failure of expected results in the treatment of cancer, science today is developing new theories in all possible directions and exploring some last frontiers to explain cancer. New avenues are now emerging and if there is reason to believe that our hereditary condition is controlled by genes, a major biological and unexpected discovery is the discovery that they can be influenced by other factors, such as the mitochondria that actually regulate the genome and not only furnish energy for cells.

In complete contrast to the nuclear DNA, one particuliarity about mitochondria is that they do not obey the rules of parity, since they come only from the mother (from the cytoplasm of the egg) which has misled science for many years because it has not been regarded as a carrier of inheritance. For this reason, disease is not always from father to son, but rather mother to son.

First of all mitochondria are the central energy providers of the body. In an adult human, there would most likely be around 10,000,000,000,000 cells, each having a need for active mitochondria, which makes it quite critical that mitochondria be highly active and functional. We all are aware that oxygen is critical for life, but mitochondria and only they and not the cells, can use and breathe oxygen. For this purpose, and being the host cells, they have their own DNA and genes that contain a well-ordered multienzyme system, and enzymes of the Krebs cycle and all the enzymes for biological oxidation.

Mitochondria, like any other cells or tissue, can be damaged and precisely by oxygen radicals since they contain 45% of the total cell protein, 85% of phosphate-containing lipids, 20% of fatty acids subject to oxidation and even environmental lipid-soluble chemicals.

Mitochondrial DNA mutation

We always believe that oxidative stress from free radicals can damage nuclear DNA, causing strand breaks, cellular defects, mutations and cancer, but the discovery that defects of the mitochondrial respiratory chain can result in human disease is relatively recent (Schapira and Di Mauro 1994 – Wallace 1992) and for many years scientists virtually ignored error accumulation in mitochondrial DNA, while mutation (mtDNA mutation) has been considered as useless and of no significance to the cell. Now biologists pay more attention to MT DNA mutations that can predict diseases more readily than nuclear DNA.

Such important structures and unique DNA should be well protected from oxidative insult. MTDNA, however, in contrast with molecular DNA, is not protected from free radical damage because having no histones and introns, proteins cover the surface and are essential for the structural and functional integrity of genes. Histones are remarkably important in DNA, since they are responsible for turning its expression on and off.

Mitochondrial repair mechanisms, in contrast to nuclear DNA, are limited (Tritschler) since none of the proteins made in mitochondria are designed for DNA repair. This is why mitochondrial DNA is very sensitive, being more exposed and more susceptible to oxidative damage than nuclear DNA. Since mitochondrial turnover is fast, e.g. 5-6 days, significant changes may occur in a large portion of the cell's MTDNA.

Unlike cells that possess a "cell cycle" with checkpoints and can generate signals to stop division in order to carry out some eventual repair and divide into two daughter cells, mitochondria replicate as they are, with damaged sequences or any other oxidative injury.

For instance, it has been estimated that in a normal rat liver one oxidized base occurs for every 130,000 nuclear bases, but one in every 8.000 mitochondrial DNA bases (7-8). This is about 16 times more sensitive to oxidation that nuclear DNA. This is why oxidative insults can lead easily to DNA strand breaks and promote deletions during replication.

It has been found that MTDNA shows anywhere from 2 to 15 times as much evidence of mutation compared to the DNA that is in the cell nucleus.

The human mitochondrial genome is very small and contains only 16,5 million base pairs compared to the chromosomal DNA which has in the order of 1,000 million base pairs. Only 7% of the nuclear DNA is ever expressed or exposed to the cellular environment at any one time and thus most of it is protected from free radical attack, whereas expression of the entire mitochondrial genome is needed for the maintenance, repair and manufacture of new enzymes for the ETC and the Oxphos system. In this perspective, MTDNA is extremely susceptible to damage by free radicals. Thus, chemical mutagens do not affect MTDNA and nuclear DNA equally and we have learned that mitochondrial malfunction can affect cellular growth more quickly by interrupting the synthesis

of the genetic material ribonucleic acid (RNA) and deoxyribonucleic acid (DNA). The body becomes less resistant to disease and infection and this even leads to severe impairment of cellular function including tumor formation.

Food and oxygen as energy promotors

Generally speaking, digested food that penetrates via the intestinal membrane into the blood circulation to furnish nutrients to the body is not the end of the journey. Indeed it is only the beginning of a very complex transformation of broken-down food molecules by mitochondria, using oxygen as fuel to generate ATP energy (adenosine triphosphate).

The whole idea behind this process is to get as much ATP from food as possible, which is absolutely necessary for physical strength, energy and the maintenance of life itself.

We have determined the health of an individual from different angles, although medical science practically has no way to really determine the health status of an individual, and we are now discovering that health and the quality of cells and organs are mostly determined by the number and quality of mitochondria which in a single somatic cell run to between 200 – 4000, each carrying two to ten copies of the mitochondrial genome, depending on the energy requirement of the respective organs (9-10). For instance brain, skeletal muscle, heart and liver possess the greatest number of mitochondria, compared to other organs.

Now if we consider the 10,000,000,000,000 cells that compose the body and multiply by an average of 1000 mitochondria per cell, we obtain the astronomic number of 10,000,000,000,000,000 mitochondria, each one constantly generating energy. This seems to surpass the number of stars in the galaxy and demonstrate that indeed our body is a perfect copy of the universe.

This quantity and quality of mitochondria is determined by various factors

1 – Hereditary status

2 – Nutritional status

3 – Stress status

4 – Environment

Nutritional status and daily intake of food are most important determinants to ensure a good mitochondrial quality and function. Under stress conditions, mitochondria increase their number that cells need in order to generate more ATP energy to produce more hormones, proteins and energy balance. Fewer mitochondria in a cell would affect the resistance during a stress condition and lead quickly to psychosomatic disorders and physical dysfunction.

Environment is also a determinant, and while pollution penetrates all the lipid soluble membranes of the body's cells including mitochondria and generates free radicals with damaging effects, an environment rich in oxygen keeps mitochondria intact and in the highest quantity.

Pigeons enjoy a strong muscular system and their oxidation – reduction system and generation of erythrocytes seem remarkable. Pigeons can fly up to 600 km without stoppping because of the high number of mitochondria in the wing muscles controlled by their high redox potential.

The Dutch physician C. Moerman (11) spent forty years on animal experimentation related to food and cancer and proved that cancer cells can be inoculated into many animals except healthy pigeons. However when he fed pigeons only on white bread and white rice, their energy capacity decreased including that of the immune system and soon they were unable to fly long distances. After injecting cancer cells into the wings of sick pigeons, they died after several weeks, proving that cancer could not be induced in a healthy pigeon with intact mitochondria and a strong redox potential.

Mitochondria and cellular respiration

Mitochondria basically accomplish their task of generating energy molecules using three major foodstuffs which are

Carbohydrates – Fatty acids – Proteins

The oxygen we breathe is used up to 95% by mitochondria to oxidize foodstuffs in the respiratory chain where food is burned employing a battery of enzymes encoded in their DNA.

The cell itself can break down glucose without an oxygen requirement, called glycolysis, and this occurs in the cytoplasm outside the mitochondria.

The process seems well organized and involves several steps as in a factory:

1 – A step of digestion (fuel breakdown)

2 – A step where fuel breakdown is oxidized completely (the Krebs cycle)

3 – A step that involves four enzyme complexes (or carriers) I II III IV known as the electron transport chain (ETC) or chemically called oxidative phosphorylation (oxphos) where electrons (hydrogen ions) extracted from food are transferred from one complex to another in a redox process to a final stage IV where energy is generated.

To begin, and this is the first stage of fuel breakdown, carbohydrates, fatty acids and proteins from food are broken down into their individual molecular components and harnessed for energy. Oxygen is used by mitochondria as fuel to oxidize foods in the oxphos chain, which is equivalent to burning, while food

which is completely broken down into small units containing carbon atoms are broken down further so that electrons are then released.

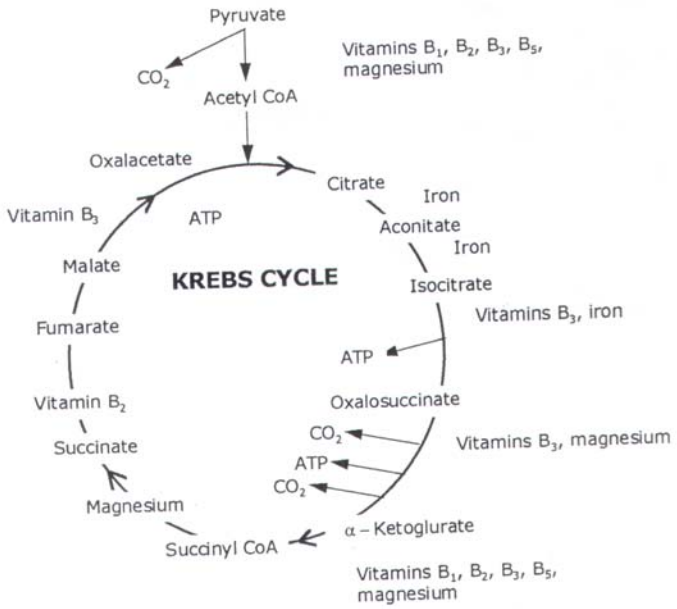
To run the Krebs cycle, several important molecules are needed in addition to all the enzymes. First required is pyruvate, which is made by glycolysis of glucose (from sugar) that enters the cell using special molecules in the membrane called “glucose transporters”. In addition, other foods like fats can also be broken down for use as fuel.

Pyruvate is then preferentially transported from the cytosol into the mitochondria and is converted into acetyl COA, by a soluble multienzyme, pyruvate dehydrogenase complex, and in this energy-rich form, the molecule is fully oxidized to CO_2 by reactions of the Krebs cycle.

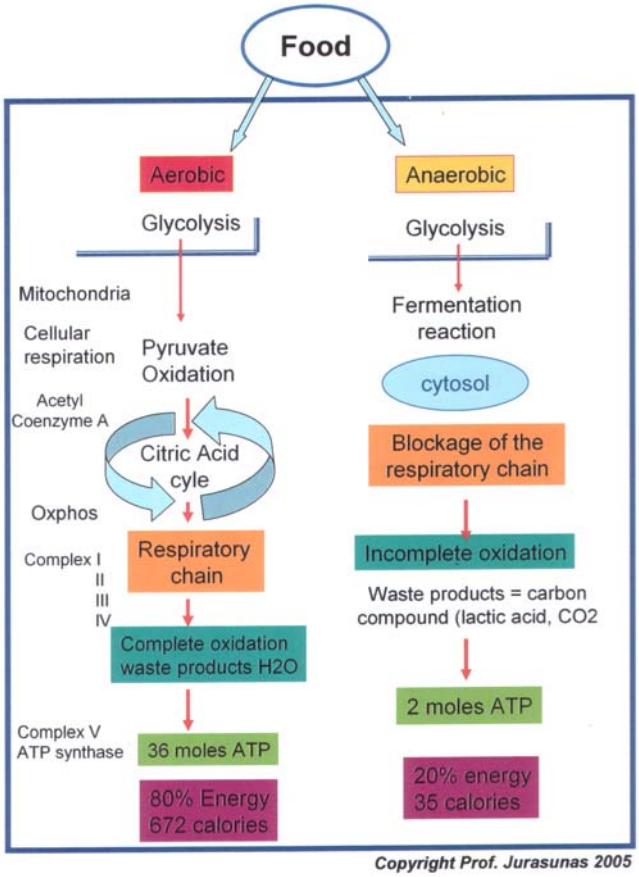
It is necessary to continue the breakdown process of the Krebs cycle inside the mitochondria – carbon and hydrogen, the best fuels, are released during this process. The carbon molecules are used to make more carbon dioxide that together with hydrogen ions is pick up by NAD and FAD. The carbon dioxide is a form of toxic waste which is quickly removed by red cells while hydrogen ions along with their partner electrons reach the terminal respiratory enzyme complex cytochrome oxidase to combine with oxygen to make water H_2O.

The electrons obtained in the oxidation of acetyl COA are joined to oxaloacetate to make citric acid. This gets oxidized to succinic acid, then to fumaric, then , L-malic and back to oxaloacetate. The electrons obtained during the oxidation are then channelled into the third stage, the “electron chain” with four major respiratory enzyme complexes:

Complex I	NADH dehydrogenase
Complex II	succinate dehydrogenase
Complex III	cytochrome C – reductase
Complex IV	Cytochrome oxidase a/a 3



The process is base on oxidation–reduction potential and electrons are transported across the inner mitochondrial membrane to the final cytochrome oxidase complex which passes them to molecular oxygen and combines with protons, producing a great deal of energy in the form of ATP. Then the synthesis of ATP is driven by complex V, the mitochondrial enzyme ATP synthase and energy stocked can be transported to where it is needed. ATP



must be constantly synthesized since the quantity is limited to only 3 ounces (75.05gr) which can sustain an effort of 5 to 8 seconds.

To make it more understandable, electrons are carriers and flow through the four respiratory complexes like electricity in a wire and can be likened to a battery to be charged. But the best comparison with mitochondria would be to an automobile that needs combustion to activate the motor.

A mechanism can understand both how it is working and know how to repair it and we should be able to do the same.

Gasoline ignites with oxygen, forming an explosion of heat and pressure: metal cylinders capture this energy and convert it into physical work and motion. This is a similar to the process that activates the whole body through energy generation and is necessary to movement, heat, osmosis, chemical function etc. Without ATP production life is impossible and this is a pre-condition for human life.

The efficiency of oxphos is measured by a P/O ratio which uses a polarographic measurement of oxygen concentration and when electrons pass to oxygen from NADH, the P/O ratio is 3.0, meaning that one molecule of NADH yields three molecules of ATP. When electrons pass from succinate or reduced FAD to oxygen, the P/O ratio is only 2.0. These ratios indicate that 3 molecules of ATP are synthesized for every pair of electrons transferred from NADH to oxygen whereas only 2 ATP are produced per electron pair passed from succinate dehydrogenase to oxygen. Indeed NADH is a great energy booster and seems to play a vital role in the prevention of diseases such as Parkinson's since it increases the level of dopamine.

If we have no oxygen, we only get a total of 4 molecules of ATP packets for each glucose molecule (in glycolysis). However, if we do have oxygen, then we get to run the Krebs cycle to produce many more hydrogen ions that can run those ATP pumps.

Therefore:

10 NADH per glucose lead to 30 ATP mole
3 ATP per NADH x 10 = 30 ATP mole
2 ATP from succinate dehydrogenase per glucose allows 4 ATP mole
2 ATP per FADH2 x 2 = 4 ATP

When we add 2 ATP from glycolysis to the 2 ATP from the Krebs cycle reactions, we have a total of 38 ATP mole conserved for each glucose fully oxidized in the cell to CO_2 and H_2O.

This is important to determine since only oxygen can synthesize a total of 38 mole of ATP while synthesis via the glycolytic pathway e.g. in cancer only generates 2 mole of ATP. When oxygen is limiting or absent, virtually all cells

are capable of extracting limited amounts of energy from glucose and other fuel by fermentation – a process used by probiotic cells that evolved for billions of years in an atmosphere poor in oxygen and have retained to the present these ancient capacities.

Basically, cancer cells do not use oxygen as their main fuel source because they have an altered metabolism that includes a higher rate of glycolysis, an increased rate of glucose transport, reduced pyruvate oxidation and increased gluconeogenesis, reduced fatty acid oxidation, and modified amino acid metabolism. The cancer cell generates its own energy from this phenotypic difference that ordinarily is unavailable for use by the cell.

In most major cancer hospitals around the world, oncologists use a new device called a PET scan (position emission tomography), which detects cancer by finding the spots of sugar-feeding cells in the body and indeed glycolysis in cancer is several fold higher that in healthy cells. Some researchers believe that if we can lower blood glucose we can slow cancer growth.

Here we have two mechanism for cellular energy production

1– cytoplasmic fermentation and

2 - mitochondrial oxidation

Usually both mechanisms are connected to synthesize the total sum of molecular energy.

Therefore, in mitochondria, the whole respiratory chain must activate electrons passing from one enzyme complex to another in order to generate ATP with a minimum of free radicals. Any complex that fails would stop the whole chain. For instance inhibition of one complex by mutation of the gene coding for the enzyme can have critical consequences on the cell and the organ itself.

It is similar to an assembly line in a car factory. Everyone at a certain position must do a particular part of the assembly and quickly pass on to another, otherwise the chain has to stop and something at the end is missing.

Cytochrome oxidase a/a 3 enzyme

We need to understand that the final electron acceptor in the respiratory chain is oxygen, but only if cytochrome oxidase a/a 3 of complex IV can do the transfer, otherwise oxygen is present but cannot accept electrons that start to accumulate, blocking the whole chain. As consequence, disorganized electrons act as free radicals caused by an overproduction that cannot be used. Hydrogen that can no longer be combusted accumulates since oxygen is no longer accepting it to be removed and soon hydrogen becomes toxic to cells. Disorganized and surplus production of electrons damages the inner membrane of mitochondria that start to swell and free radical escapes from mitochondria to attack DNA.

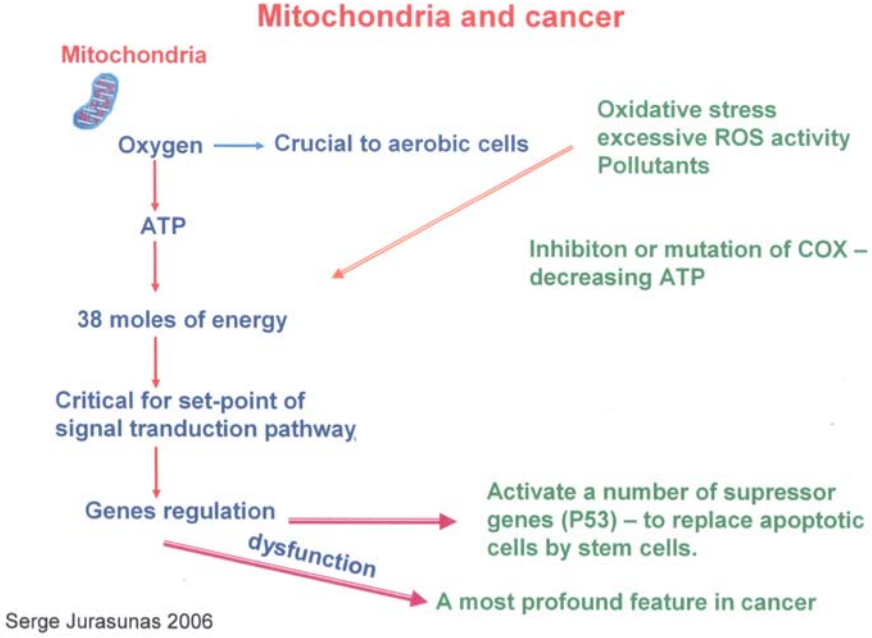
Therefore we have here a paradox, since first - and this is important to remember - normally about 700 liters of oxygen per day are fixed by haemoglobin for delivery to cells via the blood. In polluted cities haemoglobin binds more carbon monoxide and less oxygen. Warburg (12) was able to prove that e.g. exhaust gases not only paralyze the respiratory enzymes containing iron but also bind carbon monoxide analogously to haemoglobin with an affinity about 210 times greater than that of oxygen, which in many cases depending on the concentration of carbon monoxide can paralyse up to 50% of oxygen transport.

Secondly our blood must be clean, free from mucus, rigid lipid plaque formation, and red cells in rouleaux, meaning free to squeeze and enter blood vessels to deliver oxygen. Many other reasons can be responsible for oxygen starvation and impaired ATP production. Here we realise that even oxygen is not enough, since without cytochrome oxidase a/a 3 oxygen is present, bathing the cell, yet it asphixiates and all the electrons are blocked, depressing ATP production.

ATP – energy is critical for cell function

ATP energy is critical as a key determinant of the set-point of signal transduction pathways and therefore for gene regulation and the cell membrane in the regulation of embryonic cells. 30% of the energy produced is constantly use by the cell to activate membrane ion pumps, which maintain the balance between inside and outside such as Na^+ and K^+ in and out.

Depressed ATP output can affect the vitality of a specific organ, organs or even the body as a whole since less energy is stored. A decline in the entire chain involved in the production of energy in turn depletes the vitality of the organism, and can be linked with biological ageing.



More crucially ATP is required for the synthesis of more than 700 proteins and enzymes which are the basis of life.

Today, molecular biology has made some significant discoveries about what ATP does to activate and regulate all cell functions. ATP is necessary to activate cell division, enzyme repair mechanisms, apoptosis (13) and cell differentiation and again this is our missing link to cancer and should be our main treatment in attempts to reverse tumors.

Input of large amounts of ATP is needed to maintain a high degree of differentiation and, as I say again, to activate a definitive number of suppressor genes such as P53 and to create from originally pluripotent embryonic stem cells, lung cells, liver cells or colon cells with very specialised functions. Apoptotic cells must be replaced by stem cells which are located close to the basal membrane and have to differentiate into specific organ cells.

We have now more reasons to believe that mitochondrial dysfunction is one of the most profound features of cancer cells (14) and that the key to cancer is not solely the nuclear cell DNA but rather mitochondrial DNA mutations since they regulate a number of genes. Consequently mutations in MTDNA have been reported in a variety of cancer patients, including ovarian, thyroid, kidney, liver, lung, colon, bladder, head and neck, breast and leukaemia.

Most tumors contain homoplasmic (100% pure) mutant MTDNA because of the clonal nature of cancer.

Furthermore the many distinct differences in mitochondrial structure and function between normal cells and cancer cells offer a unique potential for the clinical use of mitochondria as markers for the early detection of cancer and to tailor adapted therapies (15).

Mitochondria, however, have developed protective antioxidant mechanisms to cope with superoxide load in particular. Superoxide dismutase (SOD) is our most important endogenous antioxidant (16) enzyme defence produced in the mitochondrial matrix to convert superoxide radicals into hydrogen peroxide, which in turn can be usually converted in most tissues by catalase or glutathione peroxidase in water. However, with the exception of the heart, mitochondria from most tissues do not have catalase; consequently they rely on glutathione peroxidase.

Glutathione peroxidase is not made in mitochondria, but is synthesized in the cytoplasm and then imported through the separate communicating membrane.

Therefore we understand that SOD found in mitochondria (manganese SOD) is a unique enzyme absolutely necessary for aerobic life and to protect the inner membrane from the damaging effects of ROS.

However manganese SOD (MnSOD) has more functions and now seems likely to affect the mitochondrial redox state, and in turn overall all cell behaviour (17).

Therefore SOD is both an antioxidant and an oxidant with physiological roles. ROS at high concentration is cytotoxic and damaging to most tissues, but ROS at low concentrations is involved in the regulation of cell physiological process.

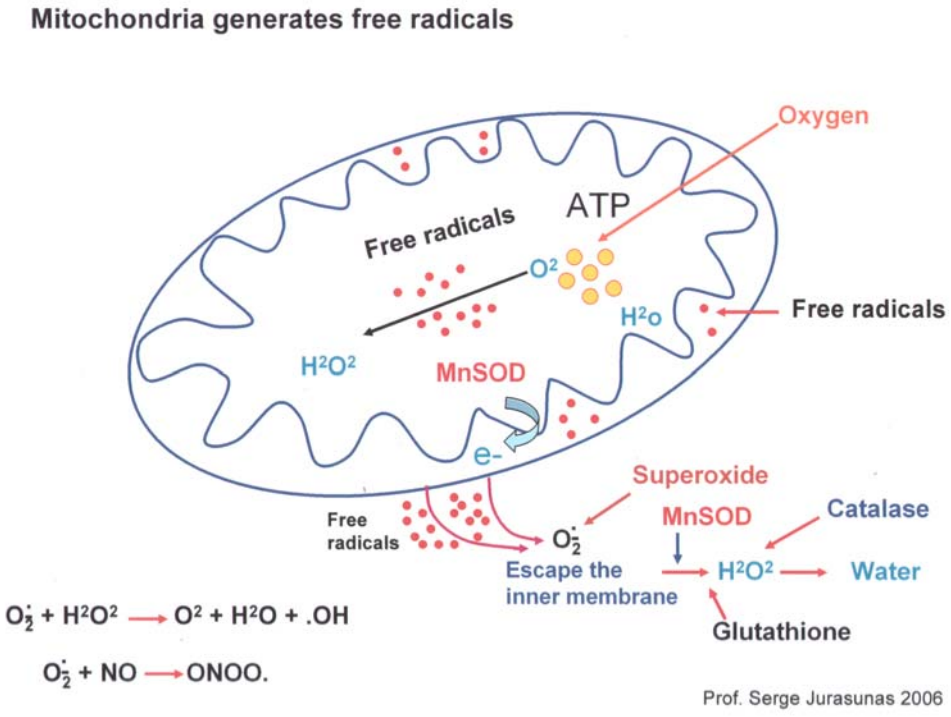
It seems that SOD plays a crucial role in maintaining the perfect balance in mitochondria to avoid any accumulation of ROS and at the same time regulates cell function. The depletion of MnSOD in mitochondria could be the death of an organ or the whole body.

Some studies demonstrate that MnSOD knockout mice die within 2 weeks after birth. Their mitochondria shown major injury and MTDNA exhibits increased oxidation. Superoxide radicals are most effective in striking critical targets in the respiratory chain and MnSOD inhibition could be dramatic, since mitochondria are a source of superoxide, basically complexes I, II and IV.

Complex I (NADH) and complex IV (cytochrome oxidase) are most vulnerable to ROS and particularly the hydroxyl radical (H_2O_2 + C- → OH- + OH.) a very toxic free radical that can cause extensive damage to membranes, as well as producing by products that are themselves mutagenic (Marnett et al 1985)

Accumulation of free radicals

Accumulation of free radicals by an unbalanced antioxidant enzyme level accelerates the oxidation of mitochondrial components such as proteins, lipids and DNA components.



MTDNA is located in the mitochondrial matrix, near the inner membrane, where both energy and free radicals are produced, which explains the crucial role of SOD.

These free radicals can damage MTDNA molecules or alter them, making it hard for mitochondrial polymerase to replicate them.

For instance, in the presence of inflammation–associated oxygen free radicals, nitric oxide (NO) a form of nitrogen reactive species, has a number of damaging effects on mitochondria that are thought to be of pathophysiological significance (18). NO can also form potentially genotoxic nitrating species such peroxinitrite (ONOO) involved in degenerative processes.

Hydrogen peroxide (H_2O_2) and nitric oxide (NO) react with SOD to produce strong oxidizing species which are damaging to mitochondria. For instance, NO inhibits the cytochrome oxidase a/a 3 enzyme by increasing H_2O_2 production, thus damaging the inner membrane and increasing leakage of electrons from the respiratory chain. Several lines of evidence demonstrate that nitric oxide and its derivative peroxinitrite are responsible for irreversible inhibition of the mitochondrial respiratory chain.

Both cases can lead to deletions, rearrangements and other mutations associated with specific cancers (19). DNA mutation affects the mitochondrial enzymes in such a way as to accelerate the failure of oxphos and thus electron transfer in the ETC.

In turn, mutation depresses ATP, producing more free radicals and inducing more mutations, which in turn lead to more free radicals leading to somatic mutations. MTDNA is particularly susceptible to damage by environmental carcinogens. Toxic substances and poisons including cyanide, malonic acid, aflotoxin and even some antibiotics inhibit the normal activity of the cytochrome system.

Cyanide, for instance, binds tightly to the iron in cytochrome a/a 3 (complex IV) (20) rendering it unable to transport electrons to oxygen, leading to halting of ATP production and accumulation of hydrogen.

The inactivation or destruction of cytochrome oxidase a/a 3 may be caused by free radicals but also environmental liposoluble chemicals that damage the cardiolipin (fatty acid) of the inner membrane where the cytochrome oxidase a/a 3 is firmly anchored.

We are simply submerged by over 60,000 chemicals from our environment (21) that are all toxic to the central system of cell respiration. This biological condition is registered in stem cells so that the following generation is affected by this condition. Children are particularly affected by pollution that has dramatically increased in Europe and childhood cancer rates continue to rise across Europe. 95% of the oxygen in the atmosphere we breathe is directly conveyed to the mitochondria and therefore polluted air is delivered to the

mitochondria of children (most probably with heteroplasmy) with serious consequences to their health status and cancer rate, while EC governments are at a loss to explain the increasing levels of cancer rates among children (International Scientific Conference – London 2004) and at the same time billions of dollars are spent on investigating new toxic drugs while prevention, nutrition and vitamin supplementation are subject to serious restrictions.

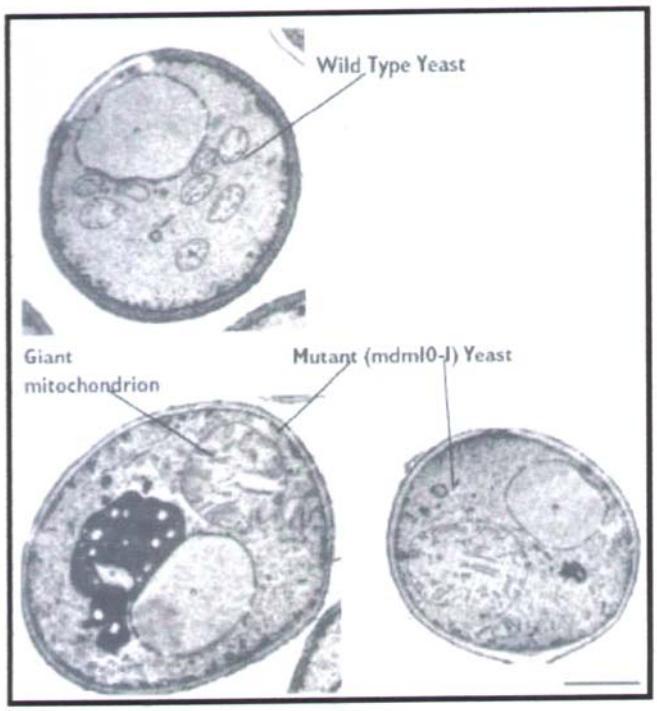
There should be a new approach in the way to understand what may cause cancer and a new approach for a biological standpoint to treat the disease by taking the cause with nontoxic therapy. A mitochondrial approach and diagnosis should be an important step since studies of MTDNA clearly show a difference between a normal healthy cell and a tumor cell. But more interesting is the fact that some tumors contain high numbers of MTDNA mutations that are not present in healthy tissues from the some individual (Lancet Oct 26.30.9342.13235) meaning that cancer organs are different from others, from damaged mitochondria, from ATP production and from cell behaviour and this is really a new door opening to finally understand why a normal differentiated cell can switch to a anarchic state of malignancy.

In cancer mitochondria are fewer and damaged

Interestingly the mitochondria of rapidly growing tumors tend to be fewer in number, small, and have fewer cristae than mitochondria in slowly growing tumors.

This may explain the resistance of some cancer cells to cytotoxic agents since a large input of ATP is required to activate the cell´s transduction signals and induce apoptosis. Mutations tend to decrease the quantity of mitochondria at each cell division because they need a certain protein made by the nucleus to undergo fission.

If this problem is not present, the mitochondria grow but do not divide and this leads to giant, inefficient mitochondria and in slow growing tumors but each time fewer in quantity (Josephine S. Modica – Napolitano and Keshav K. Singh 2002).



Fewer mitochondria is called hypomitochondrisis and is not specially related to cancer since it may only be inherited from the mother to child that in this situation cannot defend the body properly and progressively becomes sensitive to all infections and diseases since less ATP is generated in some organs, impairing good immune protection.

Vaccinations and antibiotics are just as disastrous as the disease itself since they have more damaging effects on mitochondria and favour more cancer in the future.

One other characteristic based on my iridology research, the central nervous system (CNS) and MTDNA mutation in cancer (22), is that the CNS appears to deteriorate in most cancer but seems neglected by most doctors of CAM. We have been working with hundreds of cases of juvenile cancer and observations of the brain center area in the iris seem to show the highest dysfunction of the collarete (ANS) compared to healthy subjects.

Base on my own observations, there is a definite link between MTDNA mutation, CNS and cancer such as brain, breast, ovary, and liver and in fact some new lines of research demonstrate that the CNS may control our genome as well.

Two interesting cases come to my mind and are worth recounting. First a young girl of 9 years with a chronic hepatitis that at 12 years of age degenerated to cirrhosis with the option of liver transplant.

Secondly, a 10 year old boy with liver cancer and metastases to both lungs. In both cases their iris showed a major implication of the nervous system

(collarete) and colon moving forward on the liver area. Both cases showed a poor physical constitution (poor iris density) which I have linked with heteroplasmy.

In both cases iris examination of the mother correlated in every particular with the iris of the children who in fact were considered healthy by the paediatrician and explained that the mother was asymptomatic from liver dysfunction or pathogen. The children inherited a degenerative disease.

According to Dr. Thomas Talberg, an immunologist, the central nervous system (CNS) in an adult person is still involved in inductional control and thus responsible for the “steady-state” control of the genome of our specialized organ cells. Up to Dr. Talberg the inductional control exerted by the CNS via the neurogenic lipid signals seemed to cause activation of certain heteroplastic mitochondria. The mitochondria seemed then to force the tumor cells back into normal transcription without apoptosis (23).

For the malignant cells, retransformation into normal structures also occurs according to the induction of the surrounding healthy tissue (24).

Since MTDNA are inherited solely and carry mutations passed on 100% of the time from the mother to all her offspring, we may understand why degenerative processes begin early in life.

What makes it difficult to define a status of the mother to the son is that the apparently healthy mother can carry MTDNA mutations but is asymptomatic. But their child as in the two examples above can develop quickly a degenerative disease, while an unborn child may suffer from oxidative damage as well to protein, lipids and DNA to contribute to the pathogenesis of inborn mitochondrial defects.

A new study indicates that in embryonic and foetal growth, induced oxidative stress may be detrimental (25) to the formation of the embryo which requires a large supply of energy in the form of ATP and oxygen is essential for the conversion of ADP to ATP (26).

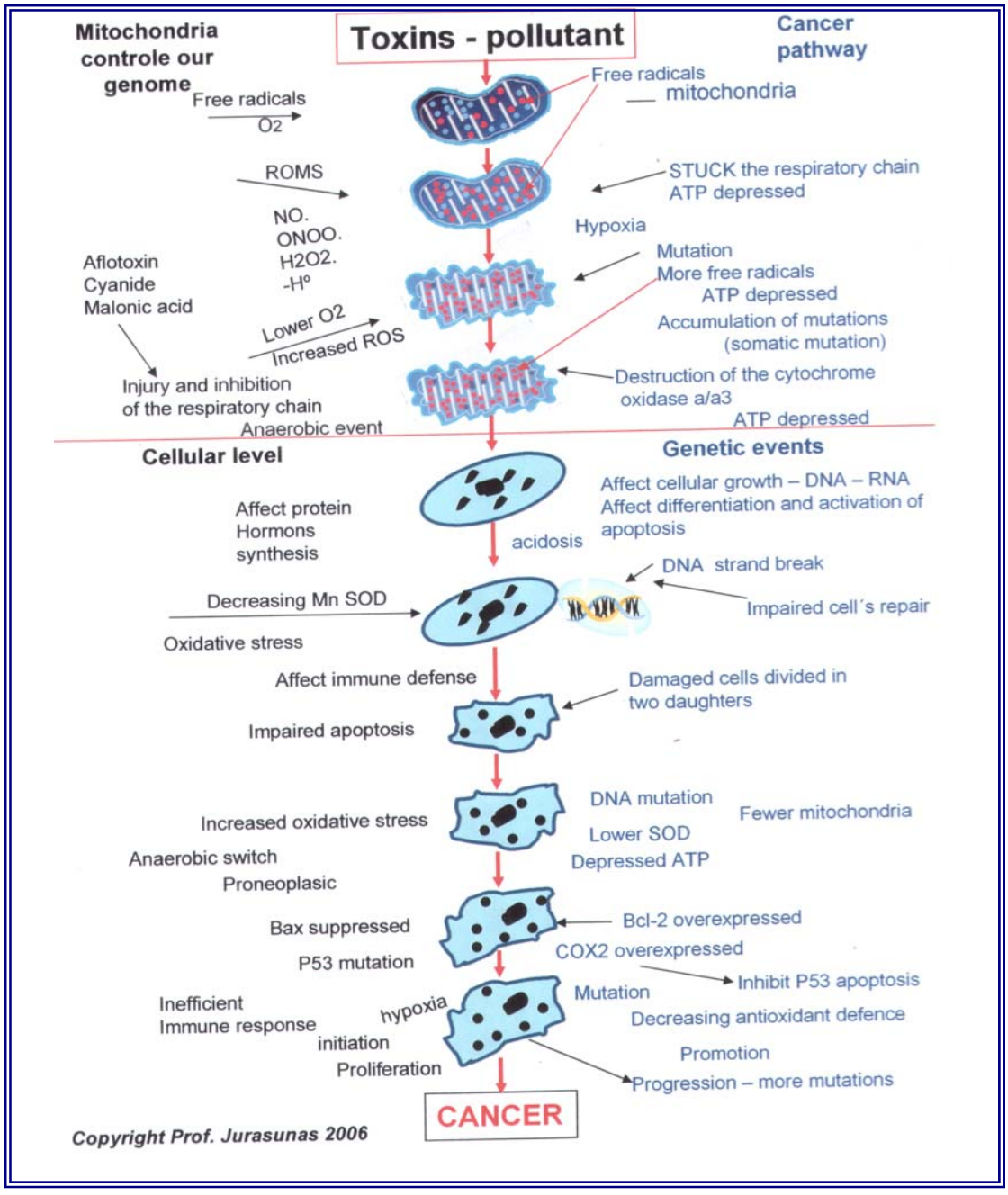
However, consumption of oxygen as an energy substrate also results in the production of reactive oxygen species (ROS), particularly the superoxide radical and the hydroxyl radical that need to be balanced by SOD that may be genetically low and thus damaging to mitochondria (28).

The over-generation of intracellular ROS during culture of mammalian embryos in vitro is generally though to be detrimental to embryo development (Johnson and NASR. Esfoliam 1994 – Guerin et al 2001).

We assume pregnant modern women with a stressful life and oxidative load. Monoxide carbon pollution and poor dietary status may reflect on her own health and can lead to a deficiency of oxygen in mitochondria to boost the require ATP energy for the normal embryonic and foetal growth.

A imbalance in the redox state of the developing embryo as a result of suboptimal culture conditions leads to altered gene expression and impaired adenosine triphosphate (ATP) generation, which can impair placental and embryo growth (29).

Mitochondrial DNA mutations in cancer have been studied (30) and more recently a table demonstrated point mutations, deletions or duplications of mitochondrial DNA in a wide range of cancer, such as prostate, breast, kidney, liver, etc…
www.expertreviews.org



The discovery of Paul Seeger M.D.

Visionary men are always ahead of their time and the understanding of science and colleagues. We have many such examples with Alex Carrel, Otto Warburg, J. McCord who discovered the metallic enzyme SOD and it took nearly 20 years before SOD emerged to be recognize as the most important endogenous antioxidant.

Paul Seeger that I made mention is one of them, having even been proposed twice for the Nobel Award.

Indeed 60 years ago Paul Seeger made a most significant discovery which is today recognized by science.

He found that in cancer the cytochrome oxidase a/a 3 is mutated with a failure of the respiratory chain, hydrogen accumulation and the cells deprived of oxygen switch to the phylogenetically older and less efficient option of fermentation.

He then demonstrated that the restoration of the electron respiratory chain of mitochondria is the only way to produce a new healthy cell free from cancer. In 1980 a German scientist, Khasa wrote a statement on cancer and Seeger. “Zur ursache von krebs” (On the cause of cancer) – “The teaching of Seeger concerning the dysfunction of metabolism in the initial stages of the generation of energy in the mitochondria due to inactivation and destruction of cytochrome oxidase has become more persuasive due to the failure of cancer therapy as well as the fact that despite the removal of tumors there are renewed relapses.

It cannot be more clear and hundreds of experiences from Seeger using specialized enzymes including base activators of the cell respiration and strong hydrogen acceptors demonstrate that a tumor cell can again become a healthy cell. This is what we call today a redifferentiation cell therapy.

The substances used by Seeger include flavonoids propolis, anthocyane, (red beet) black raddish, bromelain, blackberry, beta-carotene (which can accept 12 hydrogen atoms), kéfir, garlic and yeast cells.

The red pigment of the beetroot is also a very strong hydrogen acceptor and no wonder why since 1951, A Ferenczi in Hungary has considerably improved the condition of cancer patients and extended their lives by daily administration of 1 kg of beetroot.

Beetroot juice was also a favourite juice therapy of Max Gerson, the famous physician who cured so many cases of cancer (31) and become well known all over the world.

Seeger and Schacht (31) investigated the mechanism of action of beetroot on cancer cells in their electrochemical tests with anticancer substances. They found that the combination of beetroot with dextarotary lactic acid was capable

of activating the cellular respiration of highly virulent cancer cells by 500-1200% and the respiration of cancer cells was completely normalized, (Seeger1957). It is thus possible to arrest multiplication of cancer cells, to reduce the virulence via the normalization of cell respiration with suitable substances. Some nutrients such as vitamins B1, B2, B3, B5, iron, iodine, magnesium, coenzyme A and citric acid are also useful for activating the Krebs cycle to breakdown field components. By electrochemical measurements of the respiration of cancer cells in 100 animals within 1 to 12 days of inoculation, Seeger and Schacht (1957) discovered in the Charity Hospital that the proliferation rate, the virulence of cancer cells, is inversely proportional to their respiratory capacity (QO_2 levels). The electrochemical apparatus measured O_2 consumption in mg of tissue per hour. If cell respiration was lower, the virulence curve of the tumor increased since the reduction of cell respiration enhances proliferation due to the preponderance of glycolysis.

An Australian researcher, Professor Antony Linnane, a molecular biologist published a hypothesis in the March 25, 1989 issue of the Lancet (32) which proposed that certain substances including vitamins C and K, small molecules, zinc, copper, carotenoids, cysteine, redox enzymes including glutathione and coenzyme Q10 could be use to by-pass the breakdown in the cell energy chain. Several oxido-reduction carriers are routinely used in mitochondrial studies to bypass specific blocks in the respiratory chain in vitro, and some have already been used clinically for human mitochondrial disorders.

By increasing redox potential through specialized enzymes and activating enzymes of the respiratory acid, ATP regenerates and broken DNA chain can be repaired.

If oxygen becomes again fuel in the respiratory chain and electrons are accepted in the terminal IV, cytochrome oxidase, it means that cancer cells are consuming oxygen. Seeger and Schacht carried out some precise tests using their electrochemical oxygen measurements and demonstrated that the rate of multiplication of cancer cells is inversely proportional to the respiratory intensity of the cells. This was possible by replacement mechanisms of the enzyme chains in order to slow down tumor growth. Therefore there is also decreasing production of lactic acid as a by-product of glycolysis (fermentation) and gluconeogenesis decreases, and cancer cells become less dependent or glucose for energy production.

First, slowly but constantly increasing of ATP reactivate cell function, as it can be checked through the new computerized device, electromagnetic field test Vega-check. The donor cell RNA, DNA, mitochondria and enzymes are held to play a part in the rejuvenation of the body system including cell differentiation, cell division, cell repair and apoptosis, indeed impaired in most cancer patients. Exogenous nucleotides rich in RNA, DNA may trigger apoptosis but increasing ATP production may reactivate cell function and therefore decrease tumor growth.

We have to keep in mind that mitochondria actually regulate the genome and it seems to be possible to transform heteroplastic mitochondria that may reverse oncogene transcription and force a cancer cell to revert back to a normal cell (33).

If mitochondrial turnover is fast, such as 5-6 days, it is also logical to predict that this fast turnover would make it possible after several cycles to improve or regenerate their components via biological substances.

While some researchers believe that we cannot directly replace malfunctioning cells which contain damaged DNA, proteins, lipids or disordered enzymes, my belief is that first we can administer protective vitamins, minerals, trace elements and fatty acids and second, on the contrary, we can replace damaged mitochondria by new healthy mitochondria. New studies demonstrate that the import of nucleic acids into mitochondria in “vivo” may be necessary for therapy of nearly all mutations in MTDNA. Peptide nucleic acids (PNAS) have recently been tested as a potential antisense agent to inhibit the turnover of mutant MTDNA (34).

We can administer substrates and coenzyme of the Krebs cycle, nutrients such as the vitamin B complex, small molecules, beta carotene, oxidation – reduction carriers such as coenzyme Q10, cysteine, methionine, redox substances such glutathione, ascorbic acid and vitamin K. Antioxidant protection, SOD, catalase, lipoic acid, chromosomal mitochondria DNA sequences, cytochrome, enzymes, and nucleotides all from the enzyme yeast cell in a natural and active form (35).

Additionally germanium compound, a semiconductor which increases the transfer of electrons in the ETC, could be most useful to increase ATP production. Germanium compound is also a dehydrogenator and therefore a strong hydrogen acceptor and when used together with enzymes yeast cells, beetroot and germanium remove hydrogen accumulation and bypass blockage in the respiratory chain.

Another interesting biological preparation we have been using for the past two decades is the Regeneresan (RN13) formula (ampoule 5 ml i.m.) that contains ribonucleic acids from specific organs, i.e. cerebral cortex, heart, pituitary, hypothalamus, liver, spleen, adrenal cortex, kidney, ovary, placenta, testes, thalamus (from special cattle) and ribonucleic acids – sodium from yeast.

The ribonucleic acid (RNA) penetrates easily through the body’s mucous membranes and distributes quickly throughout the organism with highest uptake in liver and kidney. One of the effects of Regeneresan is involved with DNA – replication synthesis of RNA. In addition to its central function for protein synthesis, RNA has various other functions concerned with the regulation of DNA synthesis, cell differentiation and immune defence modulation.

Antioxidant compounds, and particularly SOD, are most important since one of the characteristics of the cancer cell is generally a significant diminution of the MnSOD activity when compared with normal cells from which they were derived

(36). However antioxidants such as SOD, catalase or glutathione should be used in low molecular weight form in order to be absorbed by the intestinal membrane. In contrast with most SOD and catalase available in tablets, new low molecular antioxidant compound (Anoxe) is immediately delivered to the target organ for quick healing (37).

Researchers like Oberley and Buettner (38, 39) demonstrated that MnSOD can regulate mitochondrial function. They also predicted that normalization of MnSOD activities in cancer would result in a more normal cell phenotype.

ROS at low concentrations are balanced by MnSOD and involved in the regulation of cell physiological processes, including cell differentiation (40, 41).

The new low molecular antioxidant compounds made from modified vegetables and seeds that contain vitamins ACE, polyphenols, flavonoids, beta carotene, glutathione, catalase, riboflavin, selenium, etc. with SOD-like activity demonstrate significant results against ROS activity (42). Anoxe also demonstrates strong oxidation – reduction properties, thus being efficient in activating the transfer of electrons as well.

I believe that this is a major rational approach to move more closer to the theory and work of pioneers such as Paul Seeger to restore the cellular respiration of damaged mitochondria.

While our own experience of over 30 years with cancer and cellular respiration using mainly the enzyme yeast cell, a strain of saccharomyces cerevisiae in liquid form, red beet juice, carrot juice, liquid chlorophyll, organic germanium, RN13 (Regeneresan) and lately the antioxidant compound Anoxe has demonstrated that cancer cells can be treated by stimulation of their cellular respiration and can be controlled via retransformation into normal structures.

Both redox and gene therapy using DNA and RNA molecules to bypass a number of nuclear gene defects has been encouraging (43, 44).

If damaged DNA strands can be repaired by nucleic acid therapy and through unblocking the cell respiration, stimulation of the enzymes of the redox, ATP energy increases and mitochondria use more oxygen. That in turn may activate signal transduction to induce cellular differentiation and/or apoptosis in a way that tumors become less aggressive and more sensitive to chemotherapy, while in many cases tumors can be controlled without cytotoxic therapy as we have shown on many occasions.

We remember that Seeger has demonstrated that a cancer cell can simply turn back to a healthy undifferentied cell which in fact has been lately demonstrated by a team of researchers from the University of Berkeley using in “vitro” cancer cells from breast cancers.

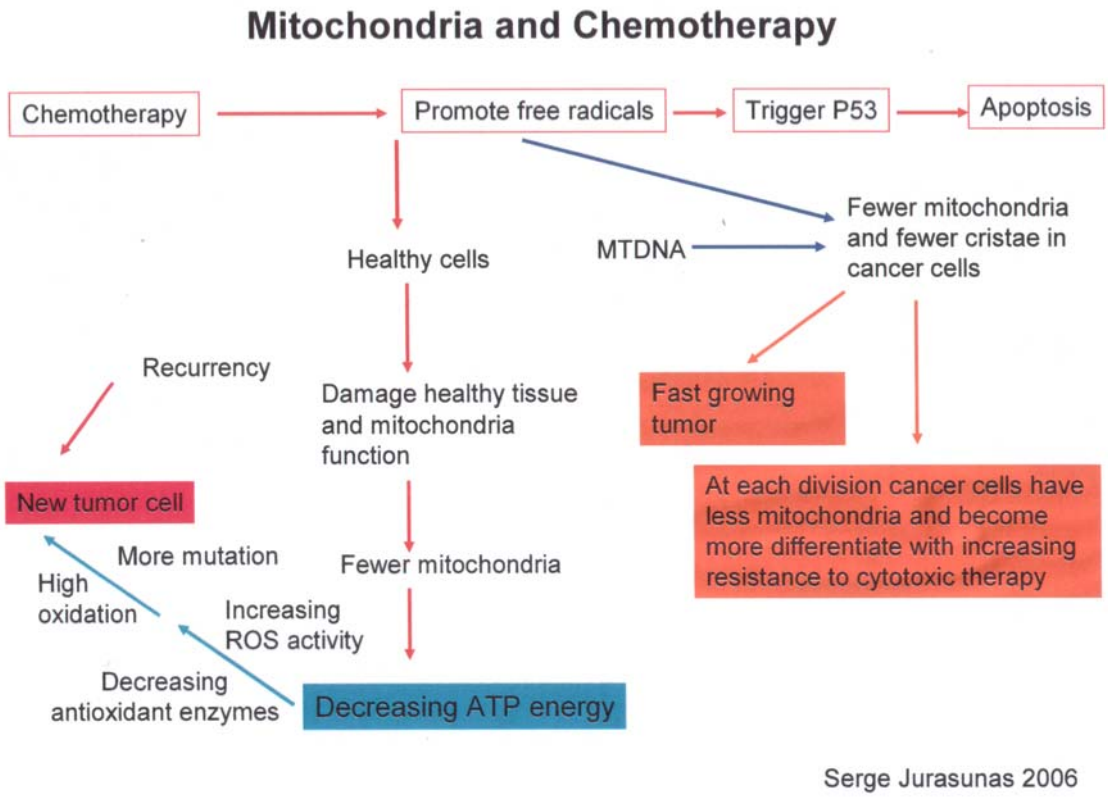
Generally speaking, an intact and functional mitochondrial cell respiration is a strong protection against severe metabolic diseases and cancer and this is my

deep belief since my interest in mitochondrial dysfunction began back in 1974 and my first research on mitochondria DNA in cancer was published over ten years ago.

Basically, we need to distinguish between a healthy body and a poor health status and based on my experience there is no cancer in a healthy body and probably a good mitochondrial status is the whole difference which is a key both to health and also cancer.

Mitochondria and chemotherapy

About 10 years ago I launched the hypothesis that chemotherapy may greatly affect mitochondria in cancer cells in order to induce more mutations and fewer mitochondria which in many cases could explain, after an initial response of the treatment, a period of resistance due to the lost of signals to activate the apoptosis pathway and the diminution of MnSOD which play a key role in maintaining cellular redox by eliminating cytosolic superoxide radicals.



In cancer cells and mitochondria, ROS increases while chemotherapy produces even more ROS that should affect the nuclear DNA of the cancer cell and thus activate the signals of apoptosis for self-destruction in which mitochondria play a essential role.

However cytotoxic therapy is not selective and may indeed kill many cancer cells while others start to create resistance, but also will affect somewhere else

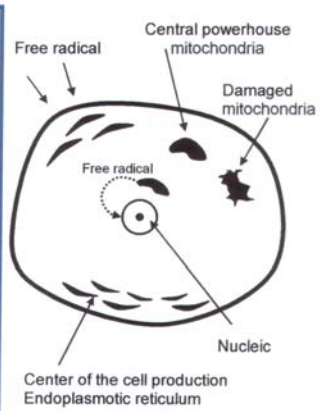
healthy mitochondria to induce mutations and after a few years developing a new cancer as demonstrated in so many cases. I have put forward this hypothesis since all chemical drugs may disturb the mitochondria membrane and attack its components. It is thus necessary not only to protect the body from the damaging effects of ROS from chemotherapy with some selected antioxidants, but also using as I propose some nucleic acids and further protection against mitochondrial injury in healthy tissue.

Based on my clinical practice and observation over a few decades, I am convinced that most cancer patients die from a general collapse of mitochondrial status and malnutrition, since patients are firstly under the wrong diet and eat less and secondly ATP is crucial to the synthesis of hormones, proteins, enzymes and energy in the form of calories. This is why we use large doses of enzyme yeast cells and even in debilitating conditions coupled with a nucleic acid base growth factor extract from the algae Chlorella known as Chlorella growth factor (Wakasa) which contains 10% DNA and precious nucleotide peptide complexes that are able to boost a quick regeneration of damaged cells and possibly reactivate mitochondrial function and thus may reverse the disease. I also believe that CGF is one of most important regenerative substances that we have at our disposal and taken together with enzyme yeast cells it has shown the most remarkable results.

Even the immune system activity is coupled with ATP production and one can perfectly understand that the failure of cellular respiration and mitochondrial dysfunction have a negative impact on immune defence.

The components of the vitamins-biological programe to catalize biochemical reactions and increase ATP production in each cell and mitochondria

The most important Biocatalysors are:
-Vitamin B1
-Vitamin B2
-Vitamin B3
-Vitamin B5
-Vitamin B6
-Vitamin B12
-Exogenous nucleotides
-Iodine
-Iron
-Zinc
-Coenzyme Q10
-Vitamin A, C
-SOD
-Gluthatione
-Methionine
-Magnesium
-L-cysteine



Professor Serge Jurasunas

The mitochondrial therapy of Dr. Serge Jurasunas

1- Increasing the level of oxygen supply in the body's (blood circulation, tissues, cells)

2- Activation of cellular respiration by restoration of mitochondrial components and bypass of the blockage in the RC to promote ATP production respiratory chain (RC)

3- Regeneration of the nervous system including the central nervous system (CNS) that controls most of the functions of the body, brain behaviour and our genome.

Zell-oxygen (enzyme yeast cells) has for the past 30 years been the bedrock of my method and more than 25.000 cancer patients have received this supplementation in our Institute. Enzyme yeast cells may not only restore damaged mitochondria but through their unique composition make it the perfect biological compound to regenerate the nervous system, one important step in cancer treatments.

Zell-oxygen contains 17 vitamins, 14 minerals, 16 amino acids, redox enzymes, NADH, nucleic acids, antioxidants, selected B complex, iodine, iron, citric acid, cytochrome, vitamin C to activate the Krebs cycle and oxphos.

Zell-oxygen contains the 8 main vital substances suggested by Dr. C. Moerman to protect the body against cancer. Detoxification of the blood circulation by the Zell-oxygen preparation essentially eliminates excess of mucous, blood fibers, lipid plaques and local inflammation in the ECM, increasing blood flow and favouring oxygen delivery to tissues and hypoxic cells. Hypoxia is one strong inducer of angiogenesis for new blood vessels that tumors need for growth expansion and invasion and therefore more oxygen delivery to cells is one way to prevent damaged cells becoming tumor cells or to decrease the ability of tumor cells to induce new blood vessels.

Enzyme yeast cells preparation (zell-oxygen)	*15ml 3 times per day*
Zell-oxygen Royal Jelly (to strength the body)	*1 ampoule per day*
Anoxe (sachets 3 gr)	*18-24gr per day*
Organic germanium	*300-400mg per day*
RN13 – Regeneresan	*3 i.m. per week*
Propolis liquid	*3 teaspoons per day*
Wakassa	*from 40 ml to 60/80 ml per day*

Vegetable juices

- 6 glasses per day of mixed organic fresh carrots, green juice and reed beet juice.

- 3 times per day mixed in one cup of spring water 2 tablespoons of enzyme yeast cells, 1 teaspoon of liquid propolis and 20 ml of CGF (Chlorella).

Food to increase cellular respiration

Kéfir or curdled milk (300gr per day)
Onions (cooked) – 200-300mg per day
Black radish – 100mg per day
Garlic (Raw) or capsules (1000mg) for patients who cannot tolerate raw garlic. One full head can be cooked, few minutes and mashed into a purée.
Blackberry (to mix with kéfir) 100gr per day
Red beet (cooked) and used in salad seasoned with olive oil parsley, cider vinegar.
Pineapple (bromelain) – 200gr per day.

Suggested vegetables for juices and cooked in the daily diet

Carrots, reed beets, onions, broccolis, Brussels sprouts, leeks, green turnip leaves, green kale, parsley, spinach.

All those vegetables are rich in iron, vitamin C, iodine, and magnesium but especially high in potassium.

A- They are suitable to activate the Krebs cycle and favour cellular differentiation, such combination potassium/iodine.
B- They interfere in the process of detoxification which is dependent on cytochrome P450 that impairs the bioactivation of carcinogens and may help damaging cells to induce apoptosis for self-destruction.
C- Carrot is very high in beta carotene (1.8 to 7.2mg %) a very strong hydrogen acceptor.
D- Dark green vegetables contain in their leaf more oxygen available to blood and tissue.

Other suggested vegetables include yellow corn, pumpkin and yellow pepper, tomatoes all rich in carotenoids and vitamin C.

Tomatoes are very rich in potassium 270mg and low in sodium which make them like other vegetables with this balance most indicated in the diet of cancer.

References :

1 – Annuals of the New York Academy of Sciences 503, 17 (1987) cavalier, Smith T « The origin of Eukaryotic and Archaebacterial cells.

2 – Warburg O. (1939) Metabolism of Tumors, Arnold Constable, London UK.

3 – Guidot DM, Refine JE, Kitlowski AD., Flores SC., Nelson SK., Wright RM., and Mc. Cord JM. Mitochondrial respiration scavenges extramitochondrial superoxide onion via a nonenzymatic mechanism J. Clin Invest 96: 1131 – 1136. 1995.

4 – Kim A., Zhong W. and Oberley TD – Reversible modulation of cell cycle kinetics in NIH/3T3 mouse fibroblast by inductibble overexpression of mitochondrial manganese superoxide dismutase. Antioxid redox. Signal, 6: 486-500-2004.

5 – The origin of Life on Earth – Miller SM et al 1974. Prentice Hall – Englewood Cliffs NJ.

6 – Annual revue of Cell Biology 4, 289 (1988) Attardi. G. et al – Biogenesis of Mitochondria.

7 – Mutation Research, 214 – 41 (1989) Ames BN, “Endogenous DNA damage as related to cancer and aging”

8 – Papa S. Mitochondrial oxidative phosphorylation changes in the lifespan. Molecular aspects and physiopathological implications. Biochemical et Biophysica. Acta – 1996 – 87 – 105.

9 – Wallace DC. Mitochondrial genetics – a paradigm for aging and degenerative disease. Science 256, 628, 632, 1992.

10 – Wallace DC – Mitochondrial diseases in man and mouse. Science 283: 1482 – 1488 – 1999.

11 – Dr. Cornelius Mormans. “Dr. Morman´s Anticancer diet. Avery Publishing Group inc. N.Y. 7 – 8 – 1990.

12 – Warburg Otto – “Cause for and preventon of cancer – 2 edition – K. Frilsch – Verlag – Wurzburg – 1967.

13 – Cellular ATP level is an important determinant for apoptic-cell death. Richter C et al (1996) FEBS, Lett 378 – 107 – 110.

14 – Chinnery PF. Samuels DC, Elson J., Turnbull DN – Mitochondria DNA mutation in cancer disease. Lancet 2002 Oct 26 – 360 – (9342:1323 – 5)

15 – Mitochondria as targets for detection and treatment of cancer. Josephine S. Modica – Napolitano and Keshov K. Singh. Reviews in Molecular Medicine. Cambridge University Press ISSN – 1462 – 3994.

16 – Tolmasoff JM,Ono Taud Cutler RG. (1980) Superoxide dismutase: Correlation with lifespan and specific metabolic rate in primate species: Proc. Natl.Acad.Sci. USA – 77 – 2781 – 2777.

17 – Kim A., Zhong W., and Oberley TD – Reversible modulation of cell cycle kinetics in NIH/3T3 mouse fibroblasts by inducible overexpression of mitochondrial manganese superoxide dismutase. Antioxid Redox Signal, 6: 489-500-2004.

18 – Mitochondria and cell Death – Guy C. Brown and Vilmate Borutaite – "Nitric Oxide, Cytochrome C. and mitochondria – Princetor University Press – N.J. 1998, 17 – 18.

19 – Cooke, M.S. Evans MD, Dizdaroghin, M. LUnec J. Oxidative DNA damage: Mechanisms, mutation and disease. Faseb. J. 2003: 17:1195-214.

20 – DAVID, s. Goodsell "Our Molecular Nature – The Body´s, Motors, Machines and Messages" – Spring Verlag Ed. – New York – 73, 74, 178 – 1996.

21 – Samuel S. Epstein MD, and David Steinmar – Breast Cancer – Poisons, profiles and Prevention – 1998 – TLDP – 24, 178.

22 – Jurasunas, Serge – Mitochondria DNA Mutations in cancer and degenerative diseases – iridology profile – American Biologic´s Conference – Malta 2004.

23 – Talberg Th "Cancer treatment, based on active nutritional biomodulation, hormonal therapy and specific antologous immunotherapy" – J. Austr. Coll – Nutr X – Env – Med. Vol. 15, Nº 1 – 1996 – 5 – 23.

24 – Weaver VM, Petersen OW, Wong F. et al., Reversion of the malignant phenotype of human breast cells in three dimentional culture and in vivo by integrin blocking antibodies – J. Cell Biol. 137 – 231 – 1997.

25 – Phyllis A. Dennery – Role of Redox in Fetal Development and Neonatal Diseases – Antioxidants x Redox Signaling – Feb.2004 – Vol.6, nº 1 – 147-153.

26 – Guerin P., EL Mouatassium, S. Menezo, Y. Oxidative stress and protection against reactive oxygen species in the pré-implatation embryo and its surrounding – Hum Reprod. Update 2001 – 7 – 175 – 89.

27 – Goto Y. Noda Y. Mori T. Nakano M. Increased generation of reactive oxygen species embryo cultures in vitro – Free Radic Biol. Med, 1993 – 15 – 69 – 75.

28 – Orsi N. and Less HJ (2001) protection against ROS during mouse pre-implantation embryo development. Role of EDTA, Oxygen tension, catalase, superoxide dismutase and pyruvate – Molecular reproduction and development 59 – 44 – 53.

29 – Harvey AJ Kind K4. Thompson J. Redox regulation of early embryo. Development – Reproduction – 2002 – 123 – 479 – 86.

30 – Fliss MS, Usadel H., caballero Ol, W4 Butta, Mr. Eleff SM., Jen J., and Sidransky D. – Facile detection of mitochondrial DNA mutations in tumors and bodily fluids, science 287 – 2017 – 2019 – 2000.

31 – Max Gerson MD. A Cancer therapy – Results of fifty cases and the cure of Advanced cancer by diet therapy – 5th edition – Publ. Gerson Institute – calif.USA.

32 – Linnane AW., Marzuki S., Ozawa T., Tanaka M. – Mitochondria DNA mutations as an important contributor to aging and degenerative diseases – lancet 1, 642 – 645 – 1989.

33 – Tallberg Th., Stenback H., Pabeck J., Palkama A., "Complete disappearance of human malignant histiocytoma cells following dietary biotherapy, leading to activation of inductional control mediated by mitochondria – J. Austr. Coll – Nutr. X Env. Med. Vol.15 No 2, 1996 – 5 – 10.

34 – Taylor RW., Chinnery PF., Turbull DM, and Lightowhers RN. Selective inhibiton of mutant human mitochondrial DNA replication in vitro by peptide nucleic acid – Nat Genet 15 – 212 – 215 – 1997.

35 – Jurasunas, Serge – The therapy of Enzyme Yeast cells in cancer disease, CFS and aging process. New theories on cancer growth and defence mechanisms – Natipress Ed – Portugal al 2001.

36 – Oberley TD and Oberley LW – Oxygen radicals and cancer in : Free radicals in Aging, edited by YU BP Boca raton, Fl. CRC Press., 1993 p.247.

37 – Jurasunas, Serge – Therapeutic application of a new molecular antioxidant compound (Anoxe) in ROS activity. Int. Symp. On ROS and Nitrogen Species. St. Petersburg – Russia – 2002.

38 – Oberley and Buetter G. R. – Role of superoxide dismutase in cancer a review . Cancer Res. 39 – 1141 – 1149 – 1979.

39 – Oberley TD – Mitochondria, Manganese Superoxide Dismutase in cancer – Antioxidants Redox Singnaling – Volume 6 – nº 3 – 483-487 – 2004.

Allen RG and Balin AK – Oxidative influence on development and differentiation: an overview of a free radical theory of development – Free radical – Biol. Med. 6 – 631 – 661 – 1989.

41 – Nemeto S., Takeda K., Yuz-x, Ferraus VJ and Funkel T., Role of mitochondrial oxidants as regulator of cellular metabolism – Mod. Cell. Biol 20 – 7311 – 7318 – 2000.

42 – Ionescu J. MD, Jurasunas, Serge ND and Dietmar Weber Ph.D. – Effects of natural SOD like compound on Redox potential and free radical generation in venous blood and plasmas – Research Dept – Spezialklinic Neukirchen – Germany 2002.

43 – Engelhardt JR., Redox – mediated gene therapies, for environmental injury, approaches and concepts, Antioxid. Redox Signal - 1 – 5 – 14 – 1999.

Serge Jurasunas is Europe's best known holistic naturopathic and integrative medicine doctor.

Over the past 3 decades he developed several innovative cancer protocols and he is well known for his wide experience in the field of cancer and cellular respiration using the therapy of enzymes yeast cells.

He is the director of a International clinic that today has gained a World reputation.

Serge Jurasunas is Board Certified Naturopathic Physician. (ANMCA) in USA member of ANMA, member A4, World Society of Anti-Aging medicine and member of the New York Academy of Sciences.

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