Mitochondrial dysfunction – the key factor underlying chronic disease?

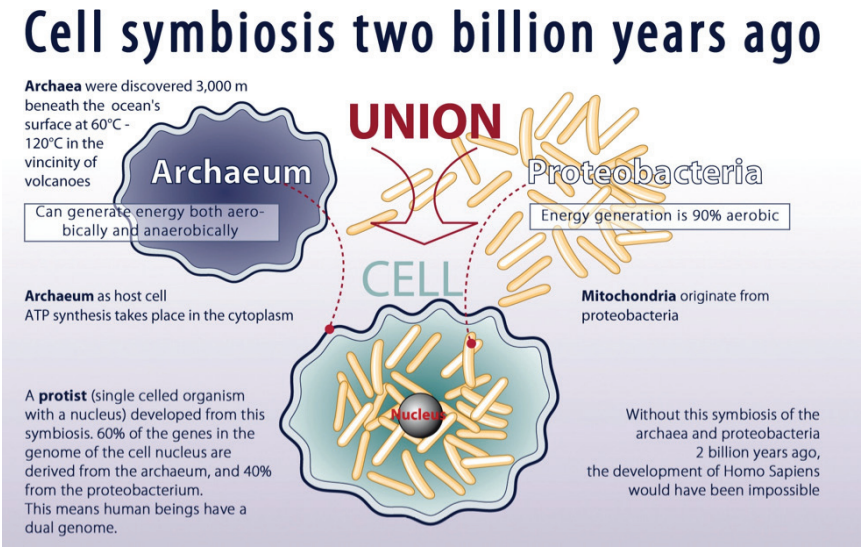
A new therapeutic approach from Germany focuses on understanding how our mitochondria are "programmed", helping to restore them (and patients) to health. Heilpraktiker **Jörg Hentschel**, an experienced Cell Symbiosis Therapy® practitioner and scientific advisor to the CST Academy in Germany, explains.

At the Third World Congress on Targeting Mitochondria in Berlin in November last year, 123 scientists from all over the world met to present the latest research on mitochondria. One of the central topics covered was mitochondrial dysfunction in chronic disease.

Except for mature erythrocytes, mitochondria are in every cell of our body. They are well-known as the power plants where most of a cell's ATP is produced. The average cell has approximately 1,500 of them, and neurons often have up to 4,500; mitochondria account for around 70% of the weight of our heart.

Prof Norman Booth from the University of Oxford was among those presenting in Berlin, previewing his new article (written with Dr Sarah Myhill and Dr John McLaren Howard), *"Targeting mitochondrial dysfunction in the treatment of Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome (ME/CFS) – a clinical audit"*, published on January 1 in the *International Journal of Clinical and Experimental Medicine*. ATP production in patients suffering from ME/CFS correlates with illness severity (measured in the form of neutrophils isolated from venous blood). Their paper concludes (as did their previous studies in January 2009 and June 2012), that all patients had measurable mitochondrial dysfunction, and that it was possible to elevate mitochondrial performance and ATP production via tailored therapy that included eating an evolutionarily correct Stone Age diet, taking specific nutritional supplements, and getting the right balance between work, rest and good-quality sleep.

Similarly, a 2012 book by Prof Enno Freye from the University of Dusseldorf entitled, *"Acquired Mitochondriopathy: A New Paradigm in Western Medicine Explaining Chronic Diseases"* elucidates the scientific connection between chronic disorders such as rheumatism, cancer, ME/CFS, cardiac disease and allergies, and mitochondrial performance as well as the NO/ONOO- cycle (nitrosative stress) from a biochemical perspective.



From: "*Cell Symbiosis Therapy®, a Revolutionary New Approach to Chronic Disease*" (eBook, R. Meyer).

(Nitrosative stress is oxidative stress derived from reactive nitrogen oxide species. It is mediated primarily by peroxynitrite (ONOO−) and nitroxyl (NO-).)

These recent publications confirm the theses of Dr Heinrich Kremer, who in the 1990s had already postulated that the origins of chronic disease lay in mitochondrial imbalance. His book, *"The Silent Revolution in Cancer and AIDS Medicine"* was published in 2000 in German, and in 2008 in English (Xlibris Corporation).

Cell symbiosis

To understand the importance of these ubiquitous organelles, Dr Kremer explains that we have to start by looking at the symbiosis from which our cells evolved. Evolutionary biologists have established that around 2.1 billion years ago, unicellular organisms without nuclei from the realms of the archaea engulfed bacteria (most likely proteobacteria/ cyanobacteria) to create a new cell type called a protista, with the archaea serving as the host and forming a nucelus.The archaea had been able to produce energy (ATP) completely anaerobically, generating methane as a by-product. But after the first Ice Age, when the entire Earth was covered by ice, oxygen levels in the atmosphere began to rise exponentially, while methane and carbon dioxide levels fell: the archaea were at an evolutionary disadvantage. Proteobacteria had an electron transport chain that was capable of producing ATP from oxygen. The symbiosis served both of them.

The archaea were able to survive, while the proteobacteria (the predecessors of our mitochondria) most likely found they could take advantage of the archaea's non-respiratory mode of energy production to survive in atmospheres where the oxygen concentration was still too low. "All known eukaryotic cells contain mitochondria, or related organelles, which play central roles in energy conversion. These mitochondria retain common features with bacterial cells, including a small genome and a mitochondrial translation system, which reveal beyond a doubt that they originated from a specific bacterial group, the alpha-proteobacteria." (1)

Our dual genome

Our mitochondria still have their own genome

(mtDNA). Generally it is accepted that 60% of the genome of the human cell nucleus originates from the archaea, while around 40% stems from proteobacteria. (2) "Many features of mitochondria, including their shapes and overall structures, reflect their bacterial origin. Particularly convincing is the fact that they retain some of their original DNA. This mtDNA still exhibits clear bacterial features." (3)

The generation of ATP using oxygen produces a lot of oxygen radicals, and these would damage the DNA of the cell nucleus as it is not covered by a protective envelope during replication. The downregulation of aerobic energy production during mitosis was thus a perfect protective strategy, using the archaea's (albeit inefficient) alternative energy generation mechanism. This switching from one form of energy generation to the other is an ancient programme that our cells still carry within them: high-efficiency energy generation within the mitochondria, producing 36 ATP from one molecule of glucose (and a great deal more from fats), and the extra-mitochondrial "back-up system" (in the cytosol) using glycolysis during mitosis.

Evolutionary biolologists have hypothesised that all eukaryotes (cells with a nucleus), including human beings, owe their existence to this cell symbiosis, as DNA replication and thus cell division would not otherwise have been possible – nor the higher energy demands of more advanced organisms.

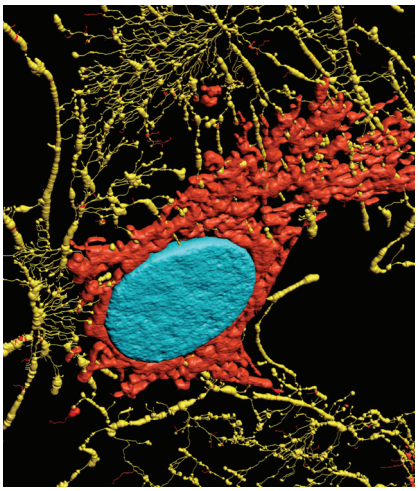
The "A genome" and "B genome"

Dr Kremer has also deduced from over 20 years of literature research in the field that the "bacterial" (mitochondrial) genome is likely to be responsible for differentiated cellular activity, driven aerobically, while the archaeal genome is responsible for cell division and repair. Numerous studies have proven that the mitochondria are downregulated during cell division and repair to minimise oxidative stress: "It appears that progression through the [cell] cycle is supported by non-respiratory modes of energy generation. In fact, very recent findings in cells of mammals indicate that cyclin D1, which is involved in the phosphorylation and inactivation of the retinoblastoma protein, marking the entry of cells into the S phase of the cycle, inhibits mitochondrial function and represses the activity of NRF-1, a nuclear factor that masters the transcriptional expression of nuclear-encoded mitochondrial genes." (4) James Lake and Maria Rivera in their groundbreaking article "*The Ring of Life*" provide evidence for a genome fusion origin of eukaryotes that would appear to provide substantial evidence for this "division of labour" in cells, explaining that "informational genes … are most closely related to archaeal genes, whereas operational genes (... involved in cellular metabolic processes such as amino acid biosynthesis, cell envelope and lipid synthesis and so on), are most closely related to eubacterial genes." (5) For simplicity's sake Dr Kremer has termed the mitochondrial genome the "B genome" (for "bacteria"), and the archaeal genome "A genome" (for "archaeum").

When the "A genome" switch becomes locked in

But what does this have to do with health and disease? Why establish an entire therapy on this symbiosis?

The key is that the cell should normally switch back to dominance of the mitochondrial genome (the "B genome") immediately after mitosis: the "B genome" should be driving cell activity for the majority of the time. (6) However, numerous factors can cause the delicate mitochondria to dysfunction. They



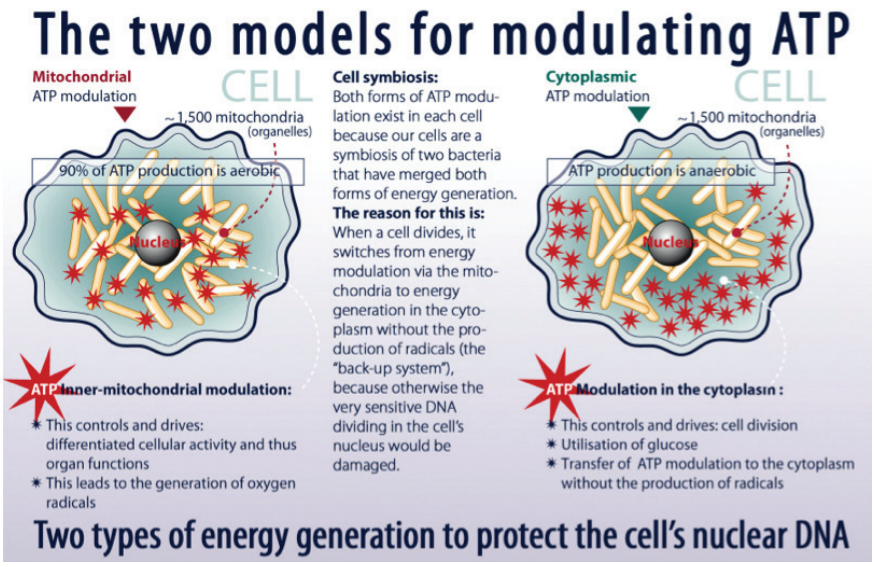
Microfilaments, mitochondria, and nuclei in fibroblast cells.

may lack sufficient co-factors along the electron transport chain (ETC), of which each mitochondrion has thousands, as electron microscope images have shown. Mitochondrial membranes may become blocked, so that the translocator proteins that cover a large share of their surface are unable to allow the correct nutrients in or ferry the products (and waste) out. (7) They may lack antioxidants to quench the reactive oxygen species (ROS) being generated during oxidative phosphorylation, glutathione being the most important.

For multiple reasons, the mitochondria may be downregulated to protect cellular components from being destroyed by ROS, or be disabled altogether. The "back-up system" will then take over: the ancient programme that is really only supposed to be activated during cell division and repair – energy production via glycolysis in the cytosol, driven by the archaeal genome (the "A genome"). This extra-mitochondrial pathway can only produce two molecules of ATP from one molecule of glucose, rather than the 36 that the electron transport chain within the mitochondria produces (together with the two – net – from glycolysis). It is programmed for cell repair and proliferation, and when our cell programmes are switched to this "A genome" long term, it will do exactly that – with consequences that can manifest themselves in many different kinds of chronic disease depending on genetic weaknesses and the exogenous (epigenetic) factors to which the individual is exposed.

Mitochondrial ATP as an information carrier

This switch to long-term dominance of the "A genome" has even more deleterious consequences from another perspective on the function of ATP that Dr Kremer has spent many years researching. He has long held that cytosolic (glycolytically produced) ATP has a very different function to mitochondrial ATP. Why produce ATP along an electron transport chain (ETC) with five different complexes



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using an extremely convoluted method, if the outcome is exactly the same as the relatively simple enzymatic production of ATP in the cystosol? In glycolysis (in the cytosol), ATP is formed purely enzymatically, and the proton gradients built in the electron transport chain are not required to produce it. No connection has been found between the electron transport chain and higher enzyme production.

So what is its purpose? As Jeremy Berg et al write on the ETC in their definitive textbook "*Biochemistry*" under the heading "Electrons can be transferred between groups that are not in contact": "This question [of electron transfer] is intriguing because these groups are frequently buried in the interior of a protein in fixed positions and are therefore not directly in contact with one another. Electrons can move through space, even through a vacuum …." (8)

Dr Kremer has held for many years (and substantiation is accumulating fast, as will be discussed later), that mitochondrial ATP production is not based on chemical energy release, but instead rests on the absorption of photons. The proton gradient of ATP explains the thermodynamic development of heat, but not the function of mitochondrial ATP. His explanation is that when each pair of electrons is fed into the enzyme complexes in the inner mitochondrial membrane, the electrons are greatly accelerated by over 10^{14} (something backed by science, as in Berg's textbook). But why would this be happening? He believes it is to transfer information.

According to the basic laws of physics, a current of hugely accelerated electrons creates an electromagnetic field. The carriers of electromagnetic field energy are complex superimposed quantum states that can transfer information in the form of light quantum waves (photons) in accordance with the laws of quantum physics. In contrast to electrically charged electrons and protons, which have a mass, photons do not have a resting mass or a charge. In their coded quantum states, these photons can exchange quantum energy with electrons and protons. This takes place in the electron transfer chain, Dr Kremer posits, via the excitation of electrons in molecules that absorb photons: light-sensor molecules that are present in all single- and multicellular organisms, and that are present in the ETC in the form of adenine (and also other molecules). Mitochondrial ATP would, by this interpretation, be a very sophisticated information carrier.

The dual role of ATP

Studies are already discovering much about the dual role of ATP. Prof Geoffrey Burnstock, President of the Autonomic Neuroscience Centre at the Royal Free and University College Medical School, London, has been investigating ATP as a signalling molecule for many years. "The double life of ATP", published in *Scientific American* in 2009 with Professor Baljit Khakh, describes how "the molecule ATP, famous as an essential energy source inside cells, also carries critical messages between cells. That dual role is suggesting fresh ideas for fighting human diseases." (9)

Studies are also beginning to uncover the light induction of electron transfer within organisms (albeit small ones so far), for example: "Light- induced electron transfer and ATP synthesis in a carotene synthesizing insect". (10) It was mentioned above that adenine could well be functioning as one of the light-sensor molecules in mammals. What could the quality of adenine be that makes it capable of this?

When one looks at nature, the molecules of many key substances in food, our immune system and hormonal system are equipped with alternating double bonds. These can build up electromagnetic fields that can absorb and emit photons. Plant substances from the groups of the polyphenols and isoprenes have light-absorbing properties. Curcumin, for example, absorbs light in the violet spectral range of visible light (at 415 nm). The base adenine ring molecule in ATP is capable of absorbing light quanta at near to ultra-violet levels of 277 nm. (11) The adenine molecule is a very characteristic photon-absorbing ring molecule with typical alternating double bonds, and is the "A" in ATP – that molecule of which we produce our body's entire weight (on average) every day, with athletes sometimes generating up to a ton.

The adenine molecule – biochemically designated a base – is not just a component of the ATP nucleotide, but also of numerous coenzymes in the mitochondria, cytoplasm and cell nucleus. It is also one of the four nucleotides that form the huge DNA molecule in the cell nucleus, and thus all genes. The three other nucleotides, which have a similar structure, also have photon-absorbing properties, and differ in functional terms only in respect of their somewhat lower photon-absorption intensity with the identical wavelength of 260 nm in the near UV range. (11) The same applies to the large variety of RNA-nucleotide sequences within and outside the cell nucleus. It would therefore appear that the entire process of genetic expression and the metabolic processes dependent on it are photon-regulated.

What happens when this mitochondrial ATP is disabled?

But to return again to the significance of this in health and disease: if the ATP formed within the mitochondria is disabled when mitochondria become dysfunctional (for the myriad reasons touched on above), we are left with only cytosolic ATP. Firstly, this naturally leads to a huge energy deficit: we are only able to generate 1/18th of the energy of "high-performance" ATP production in the mitochondria, because this cytosolic pathway only generates two ATP from one glucose molecule instead of 36 (and even less if one makes the same calculation using fats). This explains fatigue, whether in CFS/ME or any of the multiple fatiguing conditions that arise in chronic illness. But secondly, derived from the key postulate of Dr Kremer's outlined above, one can imagine the devastation caused by long-term disablement of mitochondrial ATP in its function as a signal transmitter for differentiated cellular activity. And this is something that will inevitably happen in chronic inflammation, for example, because inflammation causes cell turnover: the need for cellular repair as a result means that the "A genome" is switched on. If this continues long-term, the natural concomitant (according to the CST concept) is downregulation of the "B genome", ie a shutdown of energy production along the ETC (because the mitochondria are disabled). This means that chronic inflammation is also eventually accompanied by the symptoms of fatigue (lower ATP production) and loss of differentiated cell function/"informed" cell signalling.

Switching off inflammation/the NO/ONOO- cycle

A key component of the therapeutic concept is preventing inflammation and reducing nitrosative stress. The oldest immune reaction of unicellular organisms is the elimination of pathogens via nitric oxide, which is produced naturally throughout the body via the various types of nitric oxide synthase – iNOS, nNOS and eNOS. (12, 13)

The mitochondria that originate from proteobacteria use this gas in their defence against intracellular pathogens (viruses, and certain types of bacteria and fungi), while at the same time activating Th1 immune cells (via cytokines). As this gas is highly diffusible, it can penetrate the membranes of cells and the mitochondria. It is a powerful radical, and has to be detoxified via the glutathione transferase system of the mitochondria just like exogenous toxins or the ROS emitted along the ETC.

If this system is overstretched, the nitric oxide (NO) binds with $O2^-$ to form peroxynitrite ($ONOO^-$), an extremely dangerous radical. Constant inflammation leads to breakdown of the detoxification system, meaning that a great deal of $ONOO^-$ and other radicals are formed.

The extracellular immune response – Th2 – is upregulated in response, explaining

many autoimmune reactions and allergies. (14) If the NO system is constantly activated, the upregulation of IL6, IL17 and TNF alpha (for example) leads to overload of the mitochondria, which become damaged/forced to downregulate their activity. This reduced activity of the mitochondria is reflected in every physiological activity of the body (whether our immune cells, endothelium, the epithelial cells of our villi, or our axons – every cell of the body except mature erythrocytes is powered by mitochondria), leading to a vicious cycle.

Food intolerances are one of the greatest sources of inflammation, particularly the formation of IgG 1 – 3, which can result in chronic inflammation if they continuously irritate the mucosal membranes, leading to histamine overproduction, dysbiosis and gut permeability. This in turn leads to the production of nitric oxide, overloads our detoxification systems, attacks healthy tissue – whether joints, connective tissue or mucosa – and results in nitrosative stress.

Disorders linked to mitochondrial dysfunction

Disorders that have been associated with mitochondrial dysfunction and treated successfully using the CST concept include (15):

■ Hypertension ■ Diabetes ■ Cancer ■ Virus and fungal infections ■ Orthopaedic disorders ■ Age-related diseases/premature ageing ■ Depression, psychoses ■ Allergies ■ Fatigue-related syndromes, burnout syndrome ■ Intestinal disorders ■ Circulatory disorders (heart attacks, strokes, arteriosclerosis) ■ Organ degeneration ■ Elevated cholesterol ■ Hormone disorders ■ Immune disorders ■ Autoimmune disorders ■ ADHD ■ Obesity

The therapeutic implications

Dr Kremer and a group of German doctors and complementary therapists have developed a diagnostic and therapeutic concept from these insights that incorporates both these evolutionary interpretations of cellular and mitochondrial metabolic processes as well as the light-absorbing emitting properties of nutrients and natural substances, termed Cell Symbiosis Therapy® (CST). Around 4,000 therapists are now working with CST across Europe.

CST considers it of prime importance in chronic disease to repair defects in mitochondrial function in order to restore inner-mitochondrial energy production as fast as possible, and to encourage mitogenesis (the production of new mitochondria). Assuming that our mitochondria are programmed to work with light-sensor molecules as indicated earlier, the most natural and efficient way of doing this is to feed them appropriate exogenous polyphenols, flavonoids and isoprenes that will serve this function, as well as removing barriers to uptake. This is very similar to the Institute for Functional Medicine's wonderfully apt message, "What should I add? What should I remove?" but tailored to the mitochondria as being (very often) the heart of the problem.

Diagnostics are key to establish exactly where the cause lies. Are heavy metals causing the blockage? Is an intestinal issue preventing uptake of nutrients and cofactors? Is heme synthesis disrupted by nitrosative stress, or is it downregulation of the mitochondria themselves that is causing the symptoms of anaemia? (Since four of the eight steps of heme synthesis take place in the mitochondria, including the very first, to α-aminolevulinic acid, it is an almost inevitable consequence of mitochondrial dysfunction that heme production will be disrupted).

In the event of severe chronic disease, CST also suggests the use of IV therapy with specific amino acids, vitamins and trace elements tailored to the patient's needs, to activate the generation of new mitochondria.

Tailored laboratory diagnostics

Specific laboratory diagnostics have been developed to establish whether the patient is suffering from mitochondrial dysfunction, and then to track their recovery. Markers include the lactate dehydrogenase (LDH) isoenzymes 1-5, and M2PK (in blood). Lactate dehydrogenase is a cytoplasmic enzyme present in almost all tissues that catalyses the oxidation of lactate to pyruvate. Isoenzymes 4-5 are active during foetal development, while the mitochondria are inactive (the oxygen radicals along the ETC would damage the foetus' genes during development); if LDH isoenzymes 4-5 are upregulated, this suggests a reversion to non-mitochondrial energy production using the glycolytic pathway. This will generally be accompanied by downregulation of some or all of the "adult" isoenzymes 1-3. M2PK (pyruvate kinase isoenzyme type M2) in serum shows the levels of pyruvate that are being released (this is the enzyme that breaks down glucose to pyruvate and lactate). The higher this is, the greater the switch to the "A-genome" (extra-mitochondrial ATP production via glycolysis). A 3-nitrotyrosine assay can be used to measure nitrosative stress (nitrotyrosine is an indicator of cell damage and inflammation as well as of the production of NO). Even mitogenesis can be measured (via PGC 1-α: an increase indicates elevated mitogenesis).

The largest laboratory-documented multi-practice study is currently ongoing in Germany among around 4,000 therapists practising CST. They are building a database of protocols for specific conditions, often with sworn affidavits from their patients as evidence, using verifiable and replicable test methods from specified laboratories.

Mitochondrial functionality is at the heart of CST therapy, whether case-taking, diagnostics or the therapeutic concept. Results of the case studies to date show that even cases considered hopeless have often responded. Viewing the mitochondria as the key target can open up entirely new horizons in the approach to chronic disease.

* The CST Academy is holding a free introductory seminar on Saturday February 16 at the Rembrandt Hotel in London, and a half-day workshop with case studies on February 17. It will also be running a Foundation Course in CST on April 27 and 28: www.cst-academy.co.uk

About the author

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