UBIQUITINATION 17: GEARS OF THE "EYE CLOCK"

READERS SUMMARY:

1. WHY IS MELANOPSIN IS THE PHOTORECEPTOR OF THE EYE CLOCK?

2. DO ALL PHOTORECEPTORS NEED DHA TO OPERATE?

3. WHERE DID VISION COME FROM, LAND OR SEA?

4. WHAT DOES OPTIMAL SIGNALING PROVIDE TO A CELL?

5. WHAT CONTROL CELLS MOST, DHA, GENES, OR MITOCHONDRIA?

Today we start out with a lot of science but quickly we stop the deep science to explain to you how the eye clock gears work in your mitochondria. The summary offers you a simplified version of what optimal really is.

Do not die while you're still alive. An elevated ubiquitin rates allows that to happen. Oysters are a kiss from the sea that prevents the kiss of death from visiting you too early. Let us dive in and see why……

Several studies have established that the retina is the only tissue capable of visual and non-visual photoreception in mammals. Therefore, it appears the retina plays a vital role in circadian organization of the whole organism. Within the mammalian clade their is variability due to the levels of docosahexaenoic acid (DHA) that are used in the complexity of the eye's clock. The essential omega-3 fatty acid family member is avidly retained and uniquely concentrated in the nervous system, particularly in photoreceptors and synaptic

membranes in the CNS and PNS. DHA plays a key role in the eye clock, vision, neuroprotection, successful aging, memory, and other functions. In addition, DHA displays anti-inflammatory and inflammatory resolving properties in contrast to the proinflammatory actions of several members of the omega-6 PUFAs family. This is related to breakdown products called maresin, resolvins, and protectins. DHA has a unique cytosocial power over mammal membranes because DHA controls signalolipidomics in cell membranes. The term "**DHA signalolipidomics**" represents the cellular/tissue organization of DHA uptake, its distribution among molecular species of phospholipids, disposition among cellular compartments, the organization and function of membrane domains rich in DHA-containing phospholipids, and modulation of the synthesis of docosanoids, the DHA bioactive derivatives. Strictly speaking, docosanoids include NPD1, maresins , neuroprostanes, and related 22-Carbon derivatives. This makes DHA the key lipid in all eukaryotic cell membranes to determine signal function. This is why DHA presence is critical in the eye's clock timing mechanism.

EYE CLOCK

Retinal pigment epithelial (RPE) cells likely utilize a specific DHA-phospholipid pool as a precursor for neuroprotectin D1 (NPD1) synthesis. NPD1 is the key docosanoid of the eye clock. What do these resolving anti-inflammatory chemicals made from DHA do? NPD1 up-regulates anti-apoptotic proteins (Bcl-2 and Bcl-xL) and down-regulates pro-apoptotic proteins (Bax and Bad) in response to cellular oxidative stress and cytokine activation leading to an overall prosurvival transcriptome. This promotes cell survival in the retina. NPD1 protects cells from inflammation and it increases adiponectin. When adiponectin is raised leptin sensitivity is maintained because inflammation is kept in check. When NPD1 is lowered for any reason, Alzheimer's

disease is much more likely within the brain substance. This is why DHA levels in the eye and brain are critical in wellness states over the entire organism.
Biosynthesis of neuroprotectin D1 (NPD1) is complex but is worth a discussion. A membrane phospholipid containing a docosahexaenoyl chain at SN-2 position is hydrolyzed by phospholipase A2. This action generates free (unesterified) docosahexaenoic acid (DHA) in the blood plasma. DHA has 22 carbons separated by 6 double bonds (22:6). Phospholipid classes display a wide diversity of acyl chains in the SN-1 and SN-2 positions, encompassing a variety of molecular species. In most phospholipids, DHA is esterified to the SN-2 position to work optimally. This is also true in the case for arachidonic acid (AA). *Overall, DHA accounts for approximately 50% of the PUFAs of cell membranes in the CNS; the highest concentrations are in photoreceptor outer segments and synapses!!!*

The significance of DHA in CNS function and homeostasis is underscored by the discovery of docosanoids and by the relevance of DHA's enrichment, physiological role, pathophysiological involvement, and avid retention in the CNS of all eukaryotes. Docosahexaenoyl-phospholipids in cellular membranes are of interest in neuroscience and medicine due to the *biophysical implications* of these molecular species of phospholipids for membrane protein organization as well as their role in rhodopsin function, neurotransmission in general and, more specifically, neurotransmitter vesicle release and endocytosis.
The retina of the eye is technically part of the brain. The brain is the key part of the CNS. The CNS contains very low levels of eicosapentaenoic acid (EPA) but very high levels of DHA. Therefore, EPA may compensate DHA roles outside the CNS. DHA-phospholipids support transmembrane receptor function in the CNS, thus resulting in impaired receptor function when DHA bioavailability is decreased. **These effects are likely biophysical and not just biochemical.** DHA seems to control

the lipids and proteins it works best with. This is why DHA signalolipidomics really is all about. Consider, phosphatidylserine (PS), a DHA-rich phospholipid. It modulates AKT signaling by recruiting cytosolic proteins, Raf-1, and protein kinase C to discrete membrane locations, **that promoting cell survival by lowering ubiquitin rates.** AKT1 signaling is massively important in slowing the recycling of proteins in cells. AKT1 is involved in cellular survival pathways by inhibiting apoptosis. Apoptosis is known as self suicide by the cell. This begins with mitochondrial destruction by releasing cytochrome C from one of our respiratory proteins. AKT1 is also able to induce protein synthesis pathways, and is therefore a key signaling protein in the cellular pathways that lead to skeletal muscle hypertrophy, and general tissue growth as well. Since ATK1 can block apoptosis, it can promote extend cell survival in certain environments. The DHA modulation of AKT1 has been implicated as a major optimizing factor in many types of human cancers. This is why DHA has shown health benefits in most studies where it is found.

WHERE DID HUMAN CAMERA VISION COME FROM?

Vision and the brain evolved in the sea. In all vertebrates so far studied, DHA is the major essential fatty acid constituent of the brain. Crawford has shown us that atomic difference between DHA and docosapentaenoic acid (DPA) *differs by one double bond.* DPA comes in a n-3 and n-6 atomic lattice. That difference turns out to be massive. It also turns our that both forms of DPA are thermodynamically easier to synthesize and less susceptible to peroxidation than DHA. Yet neither versions has replaced DHA even one time during 600 million years of eukaryotic evolution. Considering Darwin’s theory of natural selection and its bias toward change, this represents extreme conservation of DHA in mammals. The preservation of DHA in neural signaling systems for 500–600 million years

occurred despite enormous genomic changes in the genomic record since the beginning of animal evolution and eukaryotic cells genesis.

Recent experiments of neuro 2A cells cultured in a DHA- or (DPA)-enriched medium showed differential susceptibilities to apoptosis (cell suicide) as *an inverse function of phosphatidylserine (PS) membrane concentration.* The DPA-treated cells accumulated less than 80% of the PS measured in DHA-enriched cells and displayed increased apoptosis in response to serum starvation. Here you can see just DHA's presence in the cell membrane increases the assimilation of PS. When it is absent, apoptosis becomes more likely in the retina and brain. Apoptosis in the brain is not a good thing to have on a chronic basis because it leads to neuron loss. When it does occur disease like Alzheimer's and Parkinson's disease are the result. Some of our longest lived cells should be in our brain. In neurodegeneration, apoptosis is much more common than it should be because neurons develop "*mitonuclear coaptation*" errors. This means the mitochondrial respiratory proteins can no longer work optimally with our nuclear DNA. This leads to signaling errors and pseudohypoxia. DHA deficits in the retina and brain are magnified in neurodegenerative diseases. DHA deprivation or destruction by photooxidation (blue light) results in a concomitant *increase in DPA*, suggesting a *physiological compensatory need* for very-long-chain PUFA's. However, increased DPA in cell membranes is unable to reconstitute PS levels in the CNS. ***This dramatically affects how the "eye clock" can operate in blue light environment in mammals. This makes DHA the "Key cog" to optimal wellness.***

Today's humans have created a world and environment that is dominated by blue light emission night and day! Blue light destroys DHA presence in mammalian cell membranes everywhere in our tissues. **The destruction of the retina however is the most important, because the eye clock controls the flow of carbon in every cell of our body.** The flows of carbon are

directly tied to how well our mitochondrial respiratory proteins work in concert with nuclear DNA. As DHA levels decline, the inputs to the SCN from melanopsin photoreceptors also decline. This degrades the optics of the atomic lattice in the SCN that responds to 460-500 nm light. This is in the blue range. This causes cells to age faster by raising their ubiquitin rates. Simultaneously it lowers NAD^+ levels in cells.

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KEY POINT: *As NAD^+ lowers, so does the entire cell redox potential.* This selects for specific mitochondrial respiratory protein changes as they key factor in aging, heart disease, and oncogenesis. What are those changes? Normally the length of the respiratory chain in mitochondrial is **60 Angstroms.** When NAD^+ is lowered, the length increases. This alters how electrons can flow in electron chain transport and affect oxygen levels in cells.

DHA MEMBRANE DETAILS FOR THE GEEKS:

The membrane lipid terroir of photoreceptor membranes in which rhodopsin and other proteins perform their functions is determined mainly by phospholipids rich in DHA and in omega-3 FA derivatives longer than DHA's 22 carbons. Photoreceptor membranes contain phospholipids with two omega-3 FA's esterified at both the SN-1 and SN-2 positions of the same glycerol backbone. These atomic positions determine the supraenoic or supraene molecular species that can be generated by retinal metabolism. The early research findings from experiments, also identified di-docosahexaenoyl diacyl-glycerides in the retina. When these lipids are optimized for function they are loaded with DHA molecules. *These findings suggested that supraenoic molecular species of phospholipids are necessary to the eye clock's photoreceptor cell organization and function.* This is why DHA and the 460 nm frequency relationship are linked photoelectrically to melanopsin to tightly couple the eye clock in the human

retina. Melanopsin reacts to light in the 435-465 nm range. DHA is also found enriched in phosphatidic acid in the retina, and because of its active incorporation during phosphatidic acid biosynthesis. This prompted the idea and help create experiments that showed DHA may be introduced in phospholipids by this route rather than by acylation-reacylation. **My sense is both pathways are operational in humans in how tissues assimilate DHA**.

Supraenoic molecular species of phospholipids represent 31% of phosphatidylcholine, 52% of phosphatidylserine, 20% of phosphatidylethanolamine, and 9% of phosphatidylinositols in photoreceptor discs. The supraenoic phosphatidylcholines that contain DHA (at position SN-2) and the 24:6–36:6 elongation products of the omega-3 fatty acids (FA) family series at position SN-1 are tightly bound to rhodopsin proteins. They are found in outer segments of photoreceptors and not the inner retina with melanopsin is located. These very-long-chain FAs at SN-1 may " atomically curl" and restrict rhodopsin motion, likely conforming to a disk membrane domain not favoring the classical bilayer membrane organization. In fact, phospholipids containing DHA provide a favorable environment within which G-protein-coupled events can occur in all photoreceptors in humans. ***In fact, all circadian oscillators have been found to use G-protein coupled photo-protein events in all mammals.***

This is highly conserved and it **explains why DHA has not been replaced one time in 600 million years of eukaryotic evolution.** The van der Waals equation hints that DHA should have both **stereochemical and electromagnetic properties to pull off this physiologic task**. Guess what folks, DHA does indeed have those properties. Quantum mechanics can predict the existence of energy levels inside atomic lattices (the SCN is such a lattice), whereby, any electron in that energy level can be effectively spread across the whole structure. ***That is called coherent control of signaling.*** <u>This implies THAT the</u>

more DHA that is present within tissues, the better signaling will be in organism wide because it affords quantum control of signaling. **Optimal signaling builds optimal health because of the biophysical properties of DHA.**

MELANOPSIN

Currently, science believes the retina is the only source of photic input to the SCN and, hence, to the rest of the body. In humans, I am not so sure this is accurate, because blue light exposure on human skin has been shown to alter melatonin levels. I think *the skin and gut play* a major roll in the photo-circadian mechanism in higher mammals by suppressing melatonin because either an excess of blue lit environment *or from a lack of DHA in tissues*. The presence of an independent circadian clock system within the mammalian retina has been well established by a series of in vivo and in vitro studies. Circadian photoentrainment is the process by which the brain's internal clock becomes synchronized with the daily external cycle of light and dark. In mammals, this process is mediated exclusively by retinal ganglion cells (RGC's) that use melanopsin as their photopigment. These cells send axonal projections directly to the suprachiasmatic nucleus (SCN). Melanopsin forms a functional photopigment capable of catalyzing G-protein activation in a light-dependent manner. **This G-receptor needs DHA to function optimally.** It is the melanopsin iRGC's that generates melatonin rhythms in the pineal gland.

The experimental evidence also indicates that the retinal circadian clock network is hierarchically organized to control the entire organism and not just SCN. **THIS POINT IS THE KEY TO THE ENTIRE BLOG. HIERARCHICAL CONTROL MEANS IT CONTROLS THE ENTIRE ORGANISM.**

The cells responsive to blue light frequencies persist in the inner retina following destruction of the inner retina with kainic acid and in cultured photoreceptor layers (PRL's) in

lower mammals. Rods and cones in the outer retina are the predominant photoreceptor cells of the mammalian retina that allow for the "camera function" of the eye. Their high temporal and spatial sensitivity to light forms the basis of camera vision in the eye. For decades it has been known that many human patients and animal models with substantial rod/cone loss, could support some non-image forming (NIF) functions in the inner retina. Think macular degeneration. Within those "non camera" receptors, there was also found to be a lot of unique melanopsin's receptors. Implication alert: *Melanopsin controls the SCN's eye clock exclusively. That is called hierarchical control folks.* ***That means nothing is more important to a living thing. I'VE NOW SAID IT TWICE IN THIS BLOG.***

DOPAMINE AND THE EYE CLOCK

The outer layers of the retina form camera vision, while the inner layers from the eye clock. From the data it appears the RCG's associated with melanopsin are independent of retina's outer photoreceptors concerned with the eye's camera functions. Recent studies have also suggested that dopamine (DA) is another key player in the control of retinal circadian rhythmicity in mammals. Retinal DA neurons express all the core circadian clock genes. Those six core clock genes are Per1, Per2, Cry1, Cry2, Clock, Bmal1. In contrast, the circadian rhythm of dopamine metabolism in the retina and its release is dependent on the proper circadian rhythms of melatonin release in the CNS. Blue light exposure at night lowers melatonin release in the CNS. Lack of DHA in the eye also lowers melatonin release. Both cause lowering or the amplitude of the alpha wave on EEG's. Blue light exposure and lack of DHA also are associated with lowered dopamine in the retina and in the frontal lobes. This alters the reward tracts within the brain. **Dopamine release in the retina has also been tied to the retina's DHA level.** DHA is found at higher levels in the mammalian retina than in the brain. This means

dopamine function in the eye and the brain is also fundamentally tied to DHA levels in the retina. We do know that DHA is quite robust in the retina in healthy states and it is lacking in suboptimal states.

In fact, our photoreceptors, the neuronal cells that make "camera vision" and the "eye clock" possible, *have more DHA than any other cells in our body.* We also know that healthy levels of DHA in photoreceptors maximize retinal function and protect against damage from bright light exposure and photo-oxidative stress. The latter is increased in people with age-related macular degeneration (AMD), retinitis pigmentosa (RP) and virtually all other retinal degenerative diseases. Cataracts form in the cornea to block harmful blue light in toxic environments to PROTECT THE DHA STORES IN THE RETINA. This loss of DHA can also occur when ubiquitin rates are raised for any reason. Ubiquination rates increase our requirement for DHA to maintain proper physiologic function. *When DHA is lacking in the retina, intraocular pressures can also rise and "camera blindness" can result.* In glaucoma, the "eye clock" continues to function under the direction of the "cytosocial" controlling arm of DHA remaining in the center of the retina by its actions on NAD^+ and sirtuins (SIRT 1) in the mitochondria of these photoreceptors. As a team they all act in concert to preserve accurate time keeping in the "eye clock". They can be thought of as "gears of the eye clock".

How do NAD+ and SIRT1 assist DHA in telling time?

SIRTUIN ENZYMES

Sirtuin enzymes exert their cell preserving function by removing acetyl groups from proteins saving massive amount of energy. Acetyl groups are a synonym for increased carbon flows to a protein. This links them to ubiquitin replacement rates. Protein turnover is a synonym for ubiquitin marking. Eukaryotes spend 80% of their total energy budget on protein synthesis. This is a huge amount of energy expenditure, and

points out why it must remain under strict metabolic control.

SIRT1 and NAD^+ provide that fine control via the biophysical prowess of DHA. This is why they are the key "gears in the eye clock" that allow proper atomic spacing and eventual timing within the respiratory proteins in the mitochondrial membranes that make up electron chain transport. Excessive blue light exposure, or a lack of DHA in these cells, increases energy expenditure of these cells by increasing the length of the electron chain. This directly affects the energy status in all cells, because it increases the signaling that controls protein turnover. Protein turnover is a synonym for ubiquitination rates. **This happens because the "eye clock" is hierarchically organized to control the entire organisms ability to turnover proteins by ubiquitin marking.**

SIRT 1 allows for deacetylation (carbon removal) to occur to inactivate the ubiquitin marking process in proteins in cells undergoing "carbon stress" from pro inflammatory or pro growth signaling. Acetylation is a synonym for additions of carbon to a protein to stabilize it or to eventually replace it. Acetylation of proteins in our cells means ubiquitin marking will continue to occur, and as a result, will continue to cost the cell a lot of energy. *Acetylation is one of the more ancient pathways used to move carbon in living things.* SIRT 1 is capable of altering the flow of carbon replacement in humans. SIRT 1 gains this control by being directly coupled to NAD+ function in cytochrome 1 of your mitochondria. This links the protein synthetic machinery directly to the respiratory complexes. NAD^+ function is highly dependent upon the sirtuin presence or absence. This directly links their enzymatic activity to the energy status of the cell via the cellular NAD^+/NADH ratio in a cell. **This is the key main redox sensor a cell has.**

Recently, it has been demonstrated that SIRT1 regulates the amplitude and the duration of circadian gene expression in the retina (via photooxidation signaling) through the interaction

and the deacetylation of key circadian clock regulators, such as BMAL1 and PER2. **This marks NAD+ and SIRT 1 as the key "eye clock gears" in humans.** Recent studies have discovered a novel circadian clock feedback loop in which both the rate-limiting enzyme in mammalian NAD^+ biosynthesis, nicotinamide phosphoribosyltransferase (NAMPT), and NAD^+ levels display circadian oscillation and control to modulate CLOCK:BMAL1-mediated circadian transcriptional regulation via SIRT1. Here again, you see regulatory control of the eye eye clock genes and peripheral circadian clock genes in other cells using the same two gears yet again. **Without adequate NAD^+ levels in the nucleus, SIRT1 cannot function properly.** Why? *NAD^+ is a mandatory co-factor for all of the sirtuins.*

I have mention David Sinclair name many times on my blogs. What David Sinclair and colleagues from both Harvard and Australia showed in a recent publication late in 2013, that supplementation with a NAD^+ precursor could reverse this mitochondrial dysfunction and it's associated "Warburg" metabolic state in mice in one week. That shocked many in the science world, but not me. I suspected all along, that alteration of the respiratory proteins in mitochondria where the key to biology because of how they light on the backs of electrons and how they separate protons across their thin membrane's. I mentioned this long ago in the quantum time blog. Darwin used "big time"to discover and describe evolutionary processes, and I am using "quantum time" to figure out the riddle of how epigenetics really operates.

Ketosis is a "natural way" to increase NAD^+ levels, but it must be linked by natural light to similar SIRT 1 levels to function to control how the mitochondria DNA and nuclear DNA communicate. **SIRT 1 and auxins have a lot in common physiologically.** You might want to remember that last statement as the series rolls on. A sirtuin is a very

conserved group of proteins, from an evolutionary perspective, found in all living things that can increase the life span. Auxins have similar function in plants. When proteins are undergoing "carbon stress", acetyl groups are added to proteins to stabilize them from conformational bending changes induced by inflammation and oxidation. Sirtuins remove these groups to keep the protein in service longer than usual, while simultaneously stabilizing the charge state of the carbon backbone in protein to resist any further changes their atomic shape. Sirtuins can offer fine tune control of the shape and charge in "stressed proteins" by altering carbon flows by using an ancient pathway called Acetyl CoA pathway. This is why they have their own special spot in my Quilt document.

NAD+/SIRT 1 CLOCK GEARS

These findings demonstrated a new function for NAD^+ as a "metabolic oscillator" of the "eye clock" in the retina. NAD^+ is a "gear" in your eye clock and in cytochrome 1 of your mitochondria. Cytochrome one has 45 proteins and is the site where most free radical leak occurs in humans. That leak is what gives us superoxide pulses used in mitochondrial signaling. SIRT 1 is a NAD^+-dependent deacetylase. This means that SIRT 1 is also a "gear" in your eye clock. SIRT 1 is also a master regulator of nucleosome positioning and chromatin structure in DNA. The nucleosome is where all protein synthesis machinery begins in the nucleus. In, eukaryotes, all completed proteins are made outside the nucleus. The mitochondria and the nucleus are in separate compartments in a eukaryotic cells but they are connected by the endoplasmic reticulum which is a membrane rich in DHA and eicansanoids. They must have precise mitonuclear signaling to make proteins correctly. SIRT 1 with NAD^+ function together to optimize mitonuclear coaptation. Their proper alignment in function *allows for reprogramming of gene expression. Light signaling from the melanopsin receptors in our eye clock, control these gears in our cells. If these gears become*

unyoked for any reason, we develop a mitonuclear mismatch.

The "clock gears" become uncoupled when improper light signals persist in our environment and our processed by our retina.

HOW LIGHT CONTROLS YOUR GEARS

The frequencies of the light determines how the sirtuins can or cannot work with NAD^+ to slow ubiquitin rates to control aging via the redox potential in cells. This relationship is linked to amount of free radical leak in your mitochondria at cytochrome 1. Free radical leak is directly proportional to the amount of ELF- UV bio-photon release in your cells. The level of free radical leak and ELF-UV leak, is directly tied to your ubiquitination rate in proteins in ALL CELLS. This implies the bio-photon release in cells are also linked to ubiqutin marking. Russian data published for over 100 years has shown that ELF-UV bio-photons are what stimulates cells to undergo mitosis and grow. This process of photochemical light transduction ties ubiquitin rates directly to your metabolic rate. This is the phyical basis of how *abnormal* light frequencies can age us faster by altering circadian regulation of the entire organism by altering the optical signal from the retina. Excessive blue light is capable of releasing cytochrome c. Cytochrome c is another respiratory protein that tunnels electrons from foods. When it is released electron flow slows and the respiratory proteins cannot tunnel electrons fast, they become filled with electrons and this causes them to swell because they happen to be filled with transition metals. Red light causes tight binding to remain to cytochrome c in mitochondria and this allows electrons to continue to flow normally to oxygen. Blue light exposure lowers melatonin release in the pineal gland while red light increase melatonin release in the pineal gland. Blue light exposure slows electron flow in respiratory proteins while red light is capable of maintaining forward flow of electrons.

This implies any alteration of light passing into the eye has

some major affects in free radical leak and in mitochondrial capacity. Capacity is tied to the amount of energy a mitochondria can generate because of the speed of electron flow from cytochrome 1 to oxygen.

Chronic blue light exposure changes the ability of respiratory proteins to function well and this alone can change epigenetic expression in the nucleus by altering NAD^+/SIRT 1 coupling. Blue light has 435-465 nm wavelengths and this is the same specific frequency that melanopsin uses at night to alter mitonuclear coaptation during darkness. The respiratory proteins have different relationships between night and day.

Chronic blue light exposure leads to chronic lowering of NAD^+ and SIRT 1 levels. These actions age cells faster by raising ubiquitin marking. ***This is huge big deal that biology still ignores, but these relationships are well known but under utilized in clinical practice. Few researchers are even making sense of these connections because they are focused on the nuclear genome exclusively. It is time you realize why you must understand how your mitochondria link to your nuclear genome to get optimal.***

When you look at epidemiologic studies, however, the stamp of bad quantum time and rapid de-evolutionary evidence is present in every form of life today. It is seen in our oceans and our ecosystem. Its footprints are in just about every patient history in our clinics today. We have to look for that evidence. We will not find it if we don't know to look for it. If the brain can not sense it, it does not believe it can exist, much less affect the lives of our patients. This keeps it hidden from us all.

NICOTINE AND SIRTUINS FOR THE GEEKS:

In humans, SIRT1 regulates the amplitude and the duration of circadian gene expression through the interaction and the deacetylation of key circadian clock regulators, such as BMAL

1 and PER2. You heard me mention these redox couples in Ubiquitin 16. As mentioned above, sirtuins are nicotinamide adenine dinucleotide (NAD)-dependent protein deacetylases/ADP-ribosyltransferases that modulate many metabolic responses. The use of these nicotinamide based redox reactions provides versatility and reversibility. Under most cellular conditions, the free energy change is small and dehydrogenases catalyze both oxidative and reductive reactions. Many different types of substrates are used as partners for NAD and NADP such as carbohydrates, lipids, and amino acids. The coenzymes are diffusible and facilitate the shuttling of ***hydrogen atoms*** and *electrons* among different dehydrogenases that belong to "different carbon pathways". The different phosphorylation state of NAD and NADP provides a control mechanism to use the respective coenzymes for different classes of pathways.

Nicotinic acid, also known as *niacin*, is converted to nicotinamide in vivo. Nicotinamide is a NAD precursor, but use of this supplement *reduces* SIRT 1 production in cells. Therefore its supplementation, *lowers* the health building effects of NAD^+. *Nicotine seems to have the opposite effect by significantly increasing SIRT1.* This is why I often recommend nicotine gum during certain seasons to people with mitonuclear dysfunction. In other seasons, I may use vinegar to help mitonuclear functioning. Vinegar has major effects on the ancient Acetyl pathways to affect microbiome quorum sensing. Caffeine is capable of raising SIRT 1 but to a much lower degree. *On a per unit basis you get more "bulletproof" from nicotine gum than you do from any coffee.* **Vinegar is more powerful than coffee is in raising SIRT1.** Lowered SIRT 1 levels will act to age cells much faster by allowing higher ubiquitin rates in cells. This effect extends to serious neuro-degeneration diseases as well.

Many epidemiologic studies have show that smoking is "negatively correlated" with the incidence of Parkinson's

disease and Alzheimer's disease. This means smoking is some how protective. Shocking revelation, huh? Postmortem research and neuroimaging studies show that loss of *nicotinic binding sites* in the brain is the major feature of neurodegenerative diseases related to dementia and cognitive impairment. Acetylcholine (AChRs) has two receptors, muscarinic and nicotinic. When acetylcholine levels in the CNS drops we see lowered voltage on EEG's. This is also a sign of a loss of the DC current in cells. We lose the DC electric current when DHA is absent in the cell membranes of cells. It implies a serious loss of net negative charge in cells. It also correlates with low DHA levels in the retina and brain. Of the two, *nicotinic receptors* are more important in the brain physiology. The many types of neuronal nicotinic AChRs are located at synapses between neurons in the CNS where they are involved in cognitive function, learning and memory, arousal, reward, motor control and analgesia. The connections between neurons is called a synapse. Synapses are where DHA and iodine are found in their highest density in the CNS to protect it from oxidation because of its biophysical abilities.

Nicotine exposure also limits weight gain and maybe behind why smokers eat less, weigh less, and restrict food easier than non smokers. This helps explain why people who quit smoking often gain weight. Nicotine gum use can increase SIRT 1 to make calories restriction possible and easy because it increases the DC electric current while improving mitonuclear coaptation. Many athletes have tapped nicotine to improve performance. *You should be aware that use of exogenous nicotine will slightly increase your blood sugar.* This is not a bad sign even in diabetics, because, it is a very small measured signal that allows you to make small pulses of superoxide that are used to make new respiratory proteins from your mitochondrial DNA. This cannot hurt you, because the the small raise in glucose is used signal the fast replication machinery of the mitochondria. Your nuclear genome needs a

bio-photon release in order to activate its machinery. This is why AM dawning phenomena in diabetics exist. No one seems to understand this physiology because they do not understand how mitochondria work. The slight increase in blood glucose is all it takes to give you a superoxide burst to recycle your defective mitochondria without having to eat carbohydrates. When you use artificial sweeteners this superoxide pulse is often muted or lost. D-Ribose can occasionally provide that superoxide kick. This is why I often use it in my own bio-hacks in winter. Normally in diabetics there is a complete loss of superoxide pulse, and this leads to an inability to recycle mitochondria. This is called mitochondrial senescence. You can never reverse a disease until you get rid of poorly functioning mitochondria in a tissue. This is axiomatic. Poor mitochondria are a function of their altered respiratory proteins and nothing else. Using mitochondrial supplements is not a first line choice in my opinion.

The less one eats, the lower protein turnover is, because the body tries to recycle its usable proteins when substrates are unavailable. SIRT 1 has always been found to be higher in the plasma of animals in the CRON trials. Fasting increases ketosis on a short term basis acutely stimulates NAD^+ and SIRT 1 at the same time. This is why Intermittent fasting works for some people. If you are leptin resistant it likely will not work. ***If you are connected well to the solar cycle intermittent fasting works optimally.*** The return of a superoxide pulse is what is needed for mitochondrial regeneration in all humans. We can get this from nicotine, exercise, or from small amounts of morning carbohydrates. *Protein turnover is a synonym for elevated ubiquitin marking.* Recall, that eukaryotes spend 80% of their total energy budget on protein synthesis. High ubiquitin rates, lower the redox potential by lowering the net negative charge in a cell faster than any other process in biology. Consider the mitochondrial consequences of all these actions that are occurring at once.

Free radical leak at cytochrome 1 is designed to work with DHA in cell membranes to optimize the functioning of the respiratory proteins in mitochondria, while simultaneously eliminating dysfunctional mitochondria. **KEY POINT:** The mitochondria that leak the **MOST** free radicals, will leak the most light, because of a lack of DHA in the surrounding membranes. That light can be used to signal or turned into a DC electric current using DHA biophysical abilities to change electromagnetic signals. The more a mitochondria leaks free radicals, the more new copies of respiratory proteins a mitochondria is capable of making, to reverse the mitonuclear dysfunction. Any improvement in mitonuclear signaling increases health.

KETOSIS AND BARIATRIC SURGERY RISKS

This is why I made the prediction in Ubiquitination 6 that Mr. Moore would likely have *no superoxide pulses* from his mitochondria if someone looked for it. Without superoxide, you become incapable of making new mitochondria via mitophagy. In cases like this fusion and fission programs in mitochondria are also not working well. People who have had bariatric surgery also have low superoxide pulses. They also have low NAD+ and SIRT 1 levels in their cells chronically. Having this surgery does not reverse the process it institutionalizes the person to a life of ketosis and caloric restriction and horrible respiratory protein function. As a result, these people have to live with their bad respiratory proteins on their mitochondria while living the rest of their lives with defective mitochondria. This is why their weight loss plateau's and why they are often found to have higher rates of suicide post surgery. Ubiquitination 1 also showed you a link to higher suicide rates in people you would not have expected it in. Defective mitochondria on a long term basis, regardless of dietary choices, lead to serious disease of aging. Most bariatric patients are followed for a year and lost. My bet is that studies on them will show in the future

that they will suffer from a rebound affect of increased aging after their weight gain stops. Why? Both obesity and aging are associated with lower circulating adropin concentrations in humans. Bariatric surgery, on an acute basis raises adropin levels. If mitochondrial respiratory proteins are not repaired or recycled adropin levels will drop. This leads to rapid descent into diseases of aging.

When mitochondria leak MORE free radicals the signal is to CORRECT the respiratory deficit by increasing the mitochondrial capacity. Capacity, in this sense, refers to more new mitochondria being made from those 37 mitochondrial genes adjacent to cytochrome 1. Recall that mitochondrial respiratory proteins are clones made from your maternal germ cell line. They are designed to copy themselves much faster than your nuclear DNA because they only code for the respiratory proteins. When respiratory proteins wear out or fail, they do so by increasing their atomic size, get larger, and by losing their net negative charge. When their charge is lost this lowers the EZ of water in the MINOS that surrounds a mitochondria. This makes their inner mitochondrial membrane more permeable to protons and we lose our ability to concentrate H^+ in our mitochondrial matrix. This causes them to lose the ability to tunnel electrons and protons. This is how the entire process works in concerted fashion.

Consider this key point: When the respiratory proteins of cytochrome 1 increase the distance between the 45 subunits that make up this protein, there is a 10 fold loss in quantum tunneling of electrons. That causes massive losses in energy production in a cell and really lowers ATP production. This results in chronic pseudohypoxia. When ATP levels drop, proteins cannot fold or completely unfold properly to bind water to make an exclusion zone (EZ). A lower pH forms a smaller EZ and a higher pH increases the EZ in water. The lower the EZ the lower the net negative charge is in a cell. The lower an EZ is the lower the amount of DHA is found on

cell membranes. *Capacity can also relate to the amount of respiratory proteins capable of being made from our 13 mitochondrial genes.* The more mitochondria a tissue has, the better it tends to function bio-energenically. The more mitochondria a cell has, generally the CLOSER mitochondria come to approaching the nucleus, distance wise, to allow for maximal mitonuclear coadaptation. This affects and helped by the "sea of water" in your cells around your proteins. When water is abundant and the EZ is large, mitochondria are abundant and densely packed around the nucleus. Organ function is optimized in this state. **In the mitochondria a loss of water around it, allows the inner mitochondrial membrane to become more leaky to protons.** This has massive down stream effects on NUCLEAR epigenetic expression. All life uses protons separation on a thin semiconducting film to drive chemiosmosis of protons. This relationship was spoken about in Ubiquitin 5 blog and in Gerald Pollack's book on proton flows.

WHY IS OVERALL MITONUCLEAR CONTROL THE KEY FOR WELLNESS?

The initial coaptation of maternal mitochondrial DNA to nuclear DNA happens when an egg is fertilized by a sperm. At conception if there is a mismatch between maternal mitochondrial DNA and the nuclear genome infertile or spontaneous abortions. In humans, 40% of pregnancy's undergo early acute miscarriage. These pregnancies have no chromosomal abnormalities, so the defect clearly points to bio-energenic mismatch between your mitochondrial DNA and nuclear DNA in the zygote. *This is where leptin enters the equation.* I have told you leptin is fundamentally an electron accountant in humans. Leptin sensitivity or resistance is a good measure of a proper coadaptation of nuclear and mitochondrial DNA. Leptin resistance exists when they do not connect well or function well together. In a zygote, if there is a mismatch evolution makes the early choice for us. It won't allow an offspring to go onto completion if it cannot

hope to survive because of this mismatch. That is a waste of resources from Lady evolution's perspective.

But what happens if this same situation develops way after the child is born? *That is called leptin resistance (LR). Fundamentally, LR is a defect in excessive light release from cells due to their "relative mitonuclear mismatch".* LR is results when any respiratory protein deficit causes improper signaling to the nuclear DNA. LR is the signal the hypothalamus gets when the proper redox shift is not made in reference to supply and demand between the mitochondria and nucleus. **What results instead, is an incompatibility between the mitochondrial respiratory protein functional capacity and your nuclear DNA**. This situation causes mitochondria to move away from your nucleus, distance wise, when researchers look at the relationship via electron microscopy. This effect is magnified in species (humans) who use oxygen as their terminal electron acceptor in their mitochondria. Oxygen has a very storng affinity for electrons, hence why it is able to provide a pull for electrons on our inner mitochondrial membrane. When the respiratory proteins are not properly aligned, not even the valence shell desire for those electrons can be met fast enough. This is why pseudohypoxia exists in these states. Humans, birds, and bats are a species who has a very high aerobic capacity because they have a large mitochondria capacity. They all use oxygen as their terminal electron acceptor. **This is why David Sinclair's paper, mentioned above, on pseudohypoxia, is incredibly important for you to understand completely, on your road to optimal.** For a human to survive this situation they would need *to retain the ability to alter how electrons flow* in their mitochondria to optimize function to their current environment.

When the respiratory proteins do a poor job of this, low NAD^+ and SIRT 1 ratio's are the result in cells. How does ketosis fit into this scenario? If you read my book, The Epi-Paleo Rx, you will see that ketosis is a *small critical part* of

reversing most diseases. If you don't understand this blog you will think I have just contradicted myself. I have not. **Ketosis can change the flow of electrons, but <u>it is the distance between the respiratory proteins</u> in the mitochondrial electron transport that ultimately determines the speed of flow of electrons**. Ketosis only augments the flow. It cannot recapitulate the quantum speed of TUNNELING electrons !!!!! This is why I you always here me say, you can never reverse a disease if you do not alter the environment you got ill within. Ketosis is only a tool in reversals.

<u>Fixing the respiratory proteins is the key sentinel event in any disease reversal.</u> This sentinel event needs the "eye clock" to be working perfectly to tell quantum time. Quantum time is reflective in the distance of the respiratory proteins. That "eye clock" works via specific light frequencies, to properly link to mitonuclear signaling to the SCN. When you're ill or suboptimal, your mitochondria tend to leak more free radicals, and that leak cause a lot more light release from bio-photons in our cells, Most people in medicine and biology are completely unaware that cells actually have been proven to release light in the extreme low frequency UV range (ELF-UV). If you don't believe it, please read Dr. Roeland van Wijk book if you think this hyperbole. You will likely learn a lot about things you never knew happen. It covers the last 100 years of this bio-photon research in detail. You need to understand how free radical leak and cellular light release are linked to really understand why your "eye clock" is the key cog in wellness.

<u>WHY HUMANS, BIRDS, BATS NEED PROPER SIGNALING BETWEEN THEIR MITOCHONDRIA AND NUCLEUS</u>

When a species aerobic threshold is high, they have a very low tolerance for a mismatch in *mitonuclear coaptation.* The reason is simple. Animals with high aerobic capacity and mildly dysfunctional mitochondria, signal apoptosis very early in the process. Apoptosis kills cells and removes them. If we

have stem cells to replace them all is well. If we don't we get organ failure because cells are replaced with scar tissue. This is how poorly selected eggs terminate so quickly in human miscarriages. The germ line eliminates mitonuclear mismatch before any energy is wasted. In an adult specimen, organ failure and shrinkage occurs, by apoptosis as a rule. *This is why neurodegeneration in adult humans causes brain shrinkage*. Tissue shrinkage in an adult with these diseases also has another positive thermodynamic effect. It makes energy distribution more stable and affective when one has damaged mitochondrial capacity to allow you to change the environment that person is in. If you don't brain shrinkage continues and the organ function declines quickly. Mass equivalence sets that relationship in stone. The real problem for neuro-degeneration and heart disease becomes magnified if you stay within the same environment you got ill, and you keep increasing the distance within your respiratory proteins to slow electron flow down. Eventually, you begin to deplete your stem cells as you quickly replace them due to elevated ubiquitin marking, and as a result you age way faster than your chronologic age. On your way to aging faster, you acquire more serious diseases of aging in tissues where the mitonuclear mismatches manifest.

So how do all these very complex things occurring in mitochondria link to circadian timing in your eye clock?
Time is a function of the amount of protons to electrons in a cell or a tissue. Here the balance of positive to negative charges can be seen to be fundamental in health. The more net negative charge a cell has the healthier it will be. DHA is critical to that underlying relationship. DHA collects and moves more electrons in eukaryotic cells than any other substance and this is why it has been extremely conserved for 600 million years. Your retinal DHA levels and cell membrane level of DHA are your KEY COGS in your optimal journey.

The timescale is a reflection of a gain in protons initially,

in acute inflammation. In chronic inflammation, there are more protons, with a simultaneous excessive loss of electrons, seriously lowering the overall net negative charge within a cell. DHA allows you to collect electrons from your environment. A loss of net negative charge in a cell means the positive charge rises in relative fashion. All inflammation carries a positive charge in a cell. SIRT 1 and NAD^+ levels decline when energy levels drop in the respiratory proteins. We can alter this relationship by improving the length or distance of the proteins that remain in service in our electron chain transporters. In retinal cell mitochondria with low SIRT 1 and NAD^+ levels, we should expect earlier cataract formation and glaucoma as early clinical findings. Both of these conditions are more common in environments the allow blue light exposure. It also occurs when we find low DHA tissue levels, or low redox potentials. This can occur alone in isolation or in combination. The more they occur together the bigger the stress response will be in the cell, and the more serious disease of aging will result. **The redox potential is the ultimate sensor for the genomic and mitochondrial response.** The key point you need to be aware of now, these conditions are always tied to ***retinal DHA depletion*** by some environmental mechanism that is present within the environment you allow.

SIRTUINS HANDLE ACUTE AND CHRONIC INFLAMMATION DIFFERENTLY

A lot of studies have looked at sirtuins made by our microbiome or by its presence in certain foods. Sirtuins expressed in those tissues and organs involved in systemic metabolism have been extensively studied. *However, the characteristics of sirtuins in the retina where our "eye clock" exists is largely under explored.* In the retina and SCN, local energy expenditure changes dynamically in response to light frequency stimuli. These changes signal the nucleus

in neurons of the SCN to control gene expression and protein synthesis of the ENTIRE ORGANISM. This is why I told youover 3 years ago about the metabolic trap door in Cold Thermogenesis 4 and in Cold Thermogenesis 6 , It was a big deal that most could not fathom.

ACUTE INFLAMMATION = POSITIVE CHARGE = PROTONS CONCENTRATION IN CELL WATER

Time scales and aging are intimately tied to the relationship of NAD^+ and SIRT 1 levels in cells. They are critical in understanding acute and chronic inflammation in the eye and in tissues. All inflammation is positively charged. Chronic inflammation has a much lower pH and more sustained pseudohypoxia associated with it. Higher pH increase the charge separation in cell water to create an exclusion zone. The exclusion zone is able to exclude protons from it. This is incredibly important in mitochondria along the respiratory chains, because all life uses chemiosmosis to generate massive electric charges on cell membranes to drive biochemical flux and enzymatic abilities. Acute inflammation usually leads to neolithic diseases that do not kill. An example would be psoriasis or degenerative spine disease. Chronic inflammation can leads to chronic diseases like oncogenesis that extinguish life. These mitochondria have proteins in their cytochromes that have increased Angstrom differences in their subunits and this lowers the EZ in the MINOS around the respiratory chains to leak massive amounts of protons. This lowers electron flow and the ability to tunnel electrons to oxygen. This leads to highly reduced cytochromes. Highly reduced respiratory proteins stimulate autophagy. Autophagy occurs when inflammation is under decent control. That signal is what we use to replace bad mitochondria.
In acute inflammation, chromatin works as it is designed by evolution. This is why we do not see cancer in transient acute inflammatory conditions like wound healing. Chromatin should depart to and from equilibrium on strands of DNA in an orderly

sequence, in acute inflammation. This *temporal sequence* depends on proper circadian shifts in NAD^+ availability for SIRT1 activation and deacetylation of signaling proteins, which support orderly gene reprogramming during acute inflammation by switching between euchromatin and heterochromatin. In contrast, in chronic inflammation states where the redox potential is low, oncogenesis, heart disease, and neurodegeneration aremuch more likely. This is due to the limited availability of NAD^+, in concert with the reduced expression of SIRT1 in the retina. This also can happen simultaneously in the gut and many other tissues, so this becomes able to sustain aberrant chromatin structure and functions. SIRT1 also influences inflammation and cancer by directly de-acetylating targets like NFκB, p65, and p53 in the genome. Acute inflammation usually can be resolved by a cell, and if it cannot, it is killed by apoptosis and taken out of a tissue and replaced by a new stem cell that has brand new nuclear and mitochondrial DNA. This restores cellular function completely. This is how we reverse diseases thought unfixable. Higher levels of autophagy and ubiquitin marking are seen in acute inflammatory states. Self repair however, is present to fill the gaps that autophagy creates.

CHRONIC INFLAMMATION IS EXCESSIVE POSITIVE CHARGE WITH SUSTAINED LOSS OF ELECTRONS:

Chronic inflammation sustains pro-inflammatory chromatin. With chronic inflammation, several things occur connected with SIRT1 you need to be aware of. **A high fat diet forces the body or tissue to work with defective mitochondria, when inflammation is high.** Carbohydrates diets allow us to use fermentation pathways and give mitochondria a break. We can use certain wines, nicotine, and vinegar to do the same. It also allows for small elevations of free radical generation to make new respiratory proteins to reverse disease processes. I believe this situation was built into our seasonal pattern to as a control mechanism to sustain mitochondrial recycling.

Today we have lost seasonality because we live in a microwaved blue lit world. When you understand the nuance of this blog it becomes clear humans are designed to repair their respiratory proteins best in long light cycles, when carbohydrates are present in abundance by the sun's graces. This is why I follow a strict season approach to my own diet. I understand how mitonuclear physiology controls the respiratory protein recycling ability. **It is fundamentally tied to a quantum reason alone.**

Quantum tunneling in mitochondria have a strict distance allowable between their redox centers in our respiratory proteins. It must be below 14 Angstroms to work well with oxygen's pull. 1 angstrom = one ten-billionth of a meter = 10^{-9} nanometer. 14 Angstroms = 1.4 nanometers. Most of the redox cores in our respiratory chains are between 7-14 Angstroms by design. We have a few that go to 18 Angstroms. Oxygen as our terminal electron acceptor has the power to work within this atomic framework to draw electrons to it. The inner mitochondrial membrane is 60 Angstroms in length from cytochrome 1 to the ATPase. It is filled by megaliths of lipid rafts embedded in a membrane that is only 6 nanometers thick. The charge in this membrane is over 30 million volts because of these small sizes. You don't perceive them because you can't sense them but your cells relies on it to work. People have no idea how these tiny distances condition our modern beliefs that these changes have the effect they do. This gives many researchers the sense that small changes in the atomic lattice of our respiratory proteins can't possible matter too much because they do not understand how quantum mechanics really works in living things. My job is to chronically offend their senses, and your beliefs, of just how nature really works in us, until they do understand it. The consequences of these ridiculously small changes are seriously magnified by quantum tunneling. As your environment varies, so too do the angstroms vary between respiratory proteins. Your mitochondria pay attention to that variance. This allow

your mitochondria to sense, below your cognitive perception, of how electrons can radically slow down or speed up electron transfers. When the distance is off by just one Angstrom, electron flow suffers on orders of magnitude. This is how a small domino can created massive changes down stream in a cell. VIDEO SHOWING THIS EFFECT

Quantum mechanics works this way in our mitochondria, even if you can't fathom it. Atomic size matters a great deal as it interacts with different light frequencies that enter our eye and that energize electrons in foods we eat. The naked truth is that small wisdoms make big impacts in life. The things that really change the world or your health, are the smallest things we can't possible see, but happen daily, in every cell in us. This is why mitochondrial mutations and changes can be catastrophic for cells and tissues. I am of the opinion, that mitonuclear dysfunction are the key issues that occur in *autism and progeria in utero.* Few people perceive this untapped power in our mitochondria, as I do. That power is potential energy your body is capable of using, if you get out of nature's way. Your environment is what alters it. It is not your nuclear genome that is defective. Small changes in your energy, can lead to massive alterations in results.

SHOCKER DIETARY BOMB

Another key point that likely will shock people, is a high fat diet cleaves SIRT1 and there by lowers NAD^+ levels; this reduces SIRT1 synthesis in the "eye clock" and the gut. This is why chronic ketosis is no permanent answer for disease reversal. This is what will put me at odds with many current beliefs. But I am telling you why I see things different. No one else can tell you why they believe as they do with this level of precision. You must alter the environment that damaged the respiratory proteins to begin with before you do anything. Recall that all the respiratory proteins are filled with transition metals. Transition metals all enlarge

atomically when they absorb microwave, blue light, or nnEMF radiations. This increases the distance between the subunits of all the respiratory proteins to slow electron flow. If you do not alter the environment, while employing ketosis with DHA, the result is likely going to be a very serious disease that no clinician can fix. Why? The net result of a chronic high fat diet in this scenario, is a chronically lowered NAD^+ level with a simultaneous loss of SIRT1 production in a cell. Sinclair's 2013 paper tells us this is what happens in aging and diseases of aging. This seriously alters the way carbon flows in cells and the microbiome. This results in hyper-acetylation of the p65 subunit of NF-kB, which produces pro-inflammatory products. These pro-inflammatory mediators have a "positive feedback" on the formation of obesity, diabetes, and aging. With chronic inflammation, as time elapses, oncogenesis become much more likely.

What happens when a tissue and its mitochondria have faced decades of inflammation and doesn't die by apoptosis? If the cell is in a tissue and has a low metabolic requirement (fat), it can be serviced by poorly functioning mitochondria or by metabolism that produces lactic acid. This is why adipocytes swell to accept more fat in mitonuclear dysfunction. Obesity is actually protective in many cases. Pretty counterintuitive isn't it? This is why obesity is correlated with diseases of aging yet fat people tend to live longer. Now you may have a clue why this situation can occur. **Mitonuclear dysfunction (MD) = leptin resistance.** Can MD happen in the human heart or brain? No way. Why? These cells have huge aerobic metabolic requirements, unlike fat cells. This is the state I see many of the people in the LCHF community and post bariatric surgery communities in right now.

Their tissues are littered with mitochondrial mutations that slow electron flow in the ECT. They ahve trashed respiratory proteins. This is what they call "metabolic derangement" When I hear that term it tells me the person speaking has

ZERO clue how mitochondria really work. This gives them the false belief that ketosis is curative, yet they never get to optimal and they slowly decline with many medical problems. No matter what they do their health slowly worsens as they get fatter. Getting fatter helps them avoid more serious disease. They get better from their initial states of being, but they all stall. *Stalls are a clear sign to me of mitonuclear dysfunction.*

This is a sign to look to your environment to recycle your bad mitochondrial respiratory proteins. In these people on chronic LCHF templates, these mitochondria are called "**senescent".** This is why these people feel the need to gravitate to ketosis. Ketosis is capable of increasing electron flow through their defective respiratory proteins to a degree. *The degree is 100% tied to the distance between the subunits that make up their respiratory proteins.* The separation of the respiratory proteins will determine how long this set of circumstance will remain viable in them. **Recall, that 1 Angstrom increase distance in the mitochondrial ECT is equivalent to a ten fold reduction of the amount of ATP capable of being made in a mitochondria.** Senescent mitochondrial cause chronic activation of NF kappa beta, inflammation, and dysregulation of growth factors that all link to very high ubiquitin rates, low tissue and retinal DHA levels, low NAD^+, and low SIRT1 levels. In concert, sustained oncogenesis is likely in the tissue that this situation has been allowed to persist in.

*The direct downstream effects of a chronically reduced SIRT1 include an increase in adiponectin (*which is why many cancer patients are cachectic with no appetite*)*, a decrease in PPAR alpha, an increase in insulin secretion and a lowering of UCP 2, as well as an increase in telomerase expression, a decrease in UCP2 expression, and a decrease in FoxO1 and FoxO3 mediated pro-survival gene expression. *This is really bad news when you have a high grade tumor and it is where the Warburg metabolism*

manifests.

SUMMARY:

As life became more complex to form eukaryotic cells from prokaryotes, cells sustained more damage to both their soma's and their mitochondria simultaneously. Mitochondrial genes were deleted from the original prokaryote that formed our mitochondria so it could work properly with our more complex nuclear genome. This innovation continued until human mitochondria settled on 37 genes that make 1098 proteins, while simultaneously the nuclear genome expanded to 25,000 genes. The manner in which mitonuclear connections are selected for during adult life are directly controlled by light signaling in the SCN. Altered environments are the sentinal event that the SCN responds to and controls by altering NAD^+ and SIRT 1 levels in humans. **These are the eye clock's main gears.** Mitochondrial evolution kept its cell membranes distinct from the eukaryotic cell membranes around the entire cell and within the organelle in the cytosol.

DHA is critical in all these eukaryotic cell membranes for one specific quantum reason. In DHA, electrons in the pi cloud are at 6 Angstrom distance. **This allows DHA laden membranes to work even faster at tunneling electrons over membranes compared to the mitochondrial respiratory proteins.** This relative speed is incredibly important at maintaining the SCN eye clock working faster than the circadian clock genes in our tissues. Immortality is only maintained in our germ line. Leptin levels control human fecundity. Further sequestration of the mitochondrial machinery was necessary for mitochondrial genes to preserve their cloned copies from generations of previous maternal ancestors environments. Female fetus have 6 million eggs in utero. These eggs all clones optimized for specific environments our speciesh as experienced since we evolved. That number of eggs get thinned to 1 million by birth by apoptosis caused by the nuclear DNA that is formed in

the joining of 23 chromosomes by each parent. By puberty the number is thinned further to 600,000 by the environment the child senses in their first 6 years of life. A female only has 400 periods in her reproductive life where she releases one of those maternal cloned copies of mitochondrial DNA genes. The egg selected in that ovulatory cycle is specifically chosen by the mother's leptin protein that contains information about the relative amount of protons to electrons in the mother's fat mass. This is directly tied to quantum processes that allow the proper selection of an egg from her 600,000 left that best matches her current environment. That environment is tied to light signals from her SCN and leptin status. If there is no match between within her cache of eggs containing her mitochondrial clones, to her SCN/leptin signal, anovulation or infertility is the result. Humans sequester the mitochondrial clones from the nuclear genome so they can use the current environmental signals to provide the best current match of a germ cell to what the SCN senses. Mitochondrial DNA selects for specific respiratory proteins that relate to electron flow rates to the proper environmental signals. The eggs store in the maternal germ cell line and sequestered them to maintain their ability for immortality to avoid mutation. This is why most human children are born young and not afflicted with the early aging seen in progeria.

As cells became more complex in eukaryotes (humans), control between the soma and mitochondria become more problematic and regeneration ability was slowly lost. This occured because we stored most of our ability to generate our DC electric current in the CNS as humans. Humans overcame this ability by incorporating DHA into tissues at a higher rates than other primates. This ability to generate a DC electric signal slowly returned to the somatic line as more and more DHA became available to animals via the oxygenation of the sea after the Cambrian explosion to increase their tissue densities of this specific lipid. DHA is impossible to form

without oxygen in the sea. DHA content will make cell soma's *relatively* younger, than those without DHA in their cell membrane, because it increased the cell's ability to make the DC electric current from sunlight. This is why humans lost their hair. This benefit occurs in humans because of a more favorable distance the pi electron clouds DHA provide eukaryotes in cell membranes compared to mitochondrial membranes which have prokaryotic origins. This allows for exquisite GPS controls using Einstein's theories of General and Special relativity. The same ability is used in modern technology to control distance on Earth from orbit.

DHA slowly gave signaling control back to the cell soma because DHA altered the eukaryotic cell membranes everywhere in the cell, but specifically within the SCN of the eye clock. The eukaryotic cell membrane has the uncommon and uncanny ability to turn solar radiation into a DC electric current, because of the presence of DHA. The DC electric current is the biophysical manifestation that all living things on this planet use to regenerate their tissues. Plants and animals generate this current differently but the physiologic function remains identical. **DHA presence, at both levels of organization, the retina and cell membrane, allowed for complete quantum coherent control over evolutionary complex nano-machinery in all cell lines in eukaryotes for the first time in history.** This gave life more availability to tap energy sources from quantum coherent domains in cell membranes, water, and mitochondria, to build ultimate complexity. That complexity manifests best in the human brain today.

The more DHA your tissues have, the closer you will get to optimal because your mitochondrial capacity will match best your nuclear capacity. When you have excellent mitonuclear coaptation you lower ubiquitin marking on proteins. Protein synthesis cost eukaryotes the most energy. Recall that all protein synthesis in humans takes place outside the nuclear

DNA, and inside ribosomal DNA, that is always excluded from the nucleus by a distance. That distance is critical in mass equivalence. **DHA content always shortens that distance because its pi electrons work at 6 angstroms which are substantially smaller than the distances that the respiratory proteins works at in mitochondria. This means that signaling is faster over the cell membrane system to afford more control of cellular function. This gives membranes with DHA the ability to control all things in a cell with ease.** Alterations of light coming from the environment, to your retina cause mitonuclear dys-synchrony, and can lead to aging and disease.

The more you learn, the clearer it becomes that all the most interesting problems in physics are now in biology.

CITES:

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