Endogenous UV in Warburg's Theory on the Origin of Cancer

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Abstract: The Warburg theory on the origin of cancer proposed cancer cells undergo rapid growth by glucose fermentation upon the lack of oxygen for respiration. Once Watson and Crick discovered the DNA structure, Warburg' theory fell by the wayside to genetic explanations of cancer. But almost 70 years later, genetic theory has failed to locate the genes that explain the origin of cancer. In this paper, the Warburg theory is extended to include endogenous UV created by simple QED in peroxisomes as the cellular organelle fermenting glucose. Simple QED is a nanoscale heat transfer theory based on the Planck law that requires atoms in the nanoscale regions of the peroxisomes to conserve metabolic heat by creating endogenous UV radiation instead of increasing in temperature. Hence, high metabolic heat during rapid cancer growth produces intense endogenous UV that mutates DNA, a finding that Warburg lacking a source of UV could not explain. Geneticist argue the DNA mutations occur before rapid growth, but the mechanism is still not known. Moreover, endogenous UV in peroxisomes during fermentation allows ATP synthesis to proceed by UV enhanced dehydration instead of oxidation by chemiosmosis. Further, UV enhances glucose consumption and lactate production, but if blocked by metformin used in diabetes treatment lowers glucose consumption. Endogenous UV also activates the AKT pathway proposed for metabolic genes to control the conversion from oxidative metabolism to fermentation.

I. Introduction

In 1956, Warburg proposed [1] cancer cells undergo glucose fermentation when oxygen is not available for respiration. Hence, cancer is caused as ATP is produced by non-oxidative breakdown of glucose by glycolysis. In contrast, healthy cells produce ATP from oxidative breakdown of pyruvate - the end-product of glycolysis. In effect, Warburg distinguished cancer cells from normal cells by the ratio of glycolysis to respiration.

Initially, Warburg's research showed sea-urchin eggs growth was fueled by oxygen consumption, but not for rat tumors that fueled their growth by consuming enormous amounts of glucose and breaking it down by fermentation. But Warburg tested human and other cancer tumors to find growth was also caused by fermentation during glucose consumption. How fermentation is initiated or how respiration is damaged leading to fermentation became the frontier of cancer research.

Given that cancer growth required energy, Warburg based subsequent research on how respiration and fermentation synthesized ATP, respiration measured by oxygen consumption and fermentation by the formation of lactic acid in the absence of oxygen. Since the respiration of all cancer cells is damaged, Warburg concluded whatever the cause it had to be gradual and irreversible as instant cell death would have stopped the cancer. Removal of oxygen causes cell damage and if then provided with oxygen, the damage is irreversible, allowing Warburg to conclude cells need respiratory energy to preserve structure, and if inhibited, both structure and respiration disappear. Even so, cancer growth not only includes irreversible damage of the respiration, but also an increase in the fermentation, the increase in fermentation compensating for the loss of respiration. But how does this increase of fermentation occur?

Warburg argued there is no physical or chemical agent with which the fermentation of cells can instantly initiate fermentation. Instead, a long time and many generations are necessary. The latency period to produce cancer is the time at which fermentation increases after a damaging of the respiration. For humans, the time is several decades. Indeed, the increase in fermentation takes a long time and only with many cell divisions. Because of this, there would be no cancers if there were no fermentation, and therefore it would be of great importance to know how fermentation occurs in the cell.

On structure and energy, Warburg thought respiration takes place in the structure of the mitochondria. Fermentation occurred in the protoplasm, but an organelle was not specified. The ATP synthesized by respiration in mitochondria involves more structure than that synthesized by fermentation. However, ATP is known synthesized in homogeneous solutions with crystallized fermentation enzymes. Like lower organisms, the structure of enzyme crystals is far less complex than mitochondria, i.e., respiration is connected to structure and fermentation with lack of structure. In this paper, fermentation takes place in peroxisomes having a far simpler structure than mitochondria.

With regard to Photodynamic Therapy (PDT), Warburg foretold the future of EM irradiation of tissue containing both normal and cancer cells. Normal cells survive PDT because of a higher residual respiration after irradiation. But descendants of the surviving normal cells may compensate the respiration decrease by fermentation increase and, thereby become cancer cells. Warburg concluded that radiation which kills cancer cells can also at the same time produce cancer - a lesson not yet learned by modern PDT research.

II. PURPOSE

Extend Warburg's theory on the origin of cancer by proposing peroxisomes having a crystalloid core are the source of fermentation in the cell that synthesizes ATP by UV induced dehydration instead of oxidative phosphorylation by chemiosmosis. Reduced ATP production in respiration by damaged mitochondria is compensated by an increase in ATP from peroxisomes that leads to runaway cell growth. The core converts metabolic heat to UV radiation by simple QED, a nanoscale heat transfer [2] process. ATP fermentation by UV induced dehydration is similar to ATP synthesis in homogeneous solutions with crystallized fermentation enzymes.

III. BACKGROUND

In the 1960's, the origin of life captivated biological research. Mitchell [3] proposed ATP synthesis in mitochondria followed hydrolysis given by chemiosmosis driven by the flow of H+ ions across the inner membrane. Chemiosmosis occurs by chain of complex redox reactions with electron transfer from donors to acceptors assisted by conveniently available enzymes. In contrast, Sagan et al. [4] proposed life on the early Earth began by a dehydration reaction under intense UV radiation and showed experimentally ATP was formed from ADP + Phosphate under UV. Nevertheless, ATP by hydrolysis and not UV dehydration was chosen the hallmark of modern molecular biology.

However, recent abiotic synthesis of nucleotides using UV radiation and phosphate to purify intermediates [5] supports polymerization of nucleotides into RNA, but requires high energy of which only UV radiation was indeed available on the early Earth. Nevertheless, the argument [6] is made that ionizing UV inherently destroys as much RNA as it creates and if UV was the primordial source of energy, why does no life today undergo ATP synthesis by UV radiation, thereby favoring chemiosmosis as an early bioenergetic process taking place alkaline hydrothermal vents.

Contrary to chemiosmosis, life on the early Earth recently was proposed [7] to have evolved from intense solar UV enhanced ATP synthesis by dehydration reactions as envisioned [4] by Sagan on the early Earth. UV does indeed destroy RNA, but not as much as it creates as the human species would not have populated the Earth. Indeed, survival drove mitochondria to evolve endogenous UV to replace solar UV upon ozone forming in the atmosphere. Today, the exogenous UV takes the form of EM waves standing between adjacent cristae as noted in Figure 2.

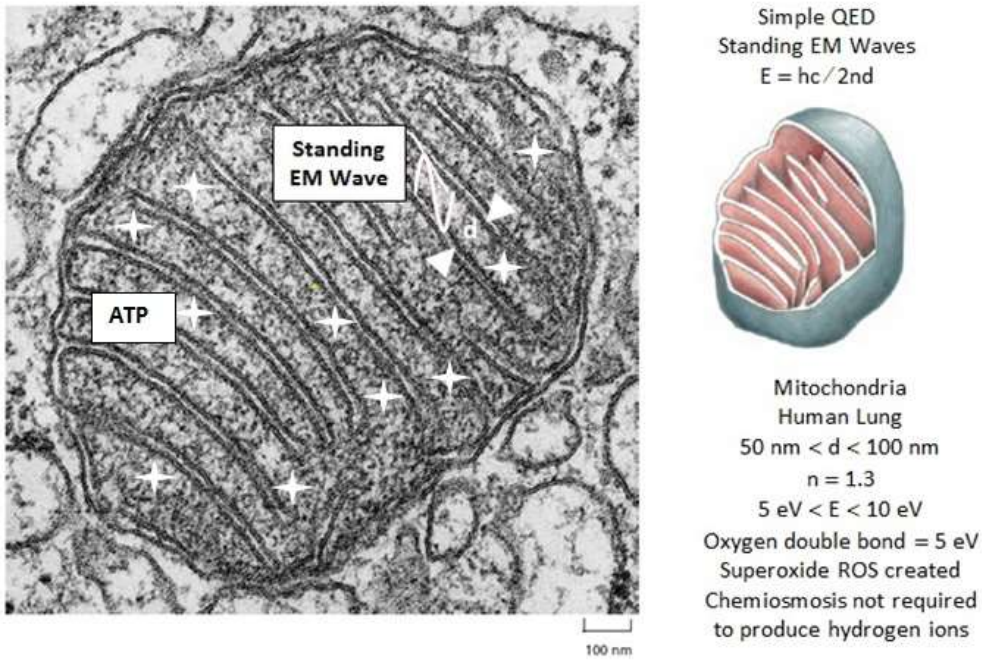

Figure 2. Human Lung Mitochondria
Showing ATP protecting DNA while providing heat source to EM standing wave

The EM wave standing in the mitochondria matrix [5] with a spacing d between adjacent cristae is defined by (50 < d < 100 nm). ATP molecules – white stars – are shown dispersed throughout the matrix. ATP binding is the likely heat source for simple QED to produce EM radiation. The Planck energy E of the standing EM waves based on a refractive index n ~ 1.4 is beyond the UV at 5 to 10 eV. The standing EM waves [3] are only shown between adjacent cristae with ATP synthase bound to lateral cristae surfaces in Figure 3.

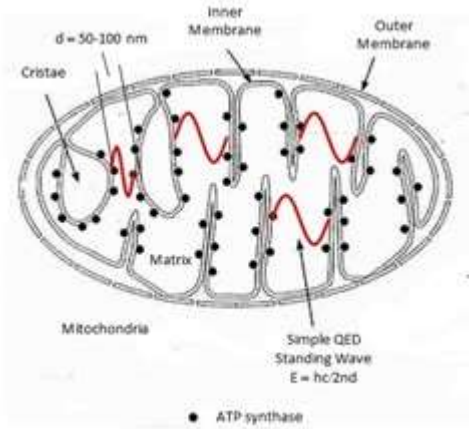

Figure 3. Standing EM waves between Cristae

Unlike exogenous UV from solar radiation, the UV radiation is endogenous to the mitochondria following the nanoscale heat transfer process of simple QED that converts [6] metabolic heat to EM radiation instead of temperature. Simple QED is based on the Planck law of quantum mechanics that denes atoms in nanostructures the heat capacity to conserve heat by a change in temperature. Hence, metabolic heat in human lung mitochondria having

nanoscopic spaces < 100 nm between adjacent cristae create EM radiation > 5 eV that produce ATP by the dehydration reaction,

$$ADP + Pi + UV \rightarrow ATP + H_2O$$

where, Pi is a phosphate group. However, Nature most likely did not choose chemiosmosis as the mechanism for ATP synthesis as a more direct path is UV enhanced dehydration, thereby avoiding complex sequential electron chain reactions that require specific enzymes to be instantly available at each step to create electrons that pass from one electron carrier to the next. Indeed, ATP synthesis is simply more direct by UV assisted dehydration reaction.

IV. Simple QED

Simple QED is a method of nanoscale heat transfer analysis that conserves heat with EM radiation instead of temperature. QED stands for quantum electrodynamics, a complex theory based on virtual photons advanced by Feynman [8] and others. In contrast, simple QED is a far simpler theory based on the Planck law that requires the heat capacity of the atoms in nanostructures to vanish allowing conservation to proceed by the creation of real photons comprising EM waves that stand within and across the nanostructure. Unlike electron level quantum states, simple QED quantum states are size dependent based on the dimension of the nanostructure over which the EM waves stand.

The Planck law at 300 K is illustrated in Fig. 4. By classical physics, the kT heat capacity of the atom is independent of the EM confinement wavelength λ, where k is the Boltzmann constant and T absolute temperature. QM differs as the heat capacity of the atom decreases under EM confinement λ < 100 microns, and at the nanoscale for λ < 100 nm, the heat capacity may be said to vanish.

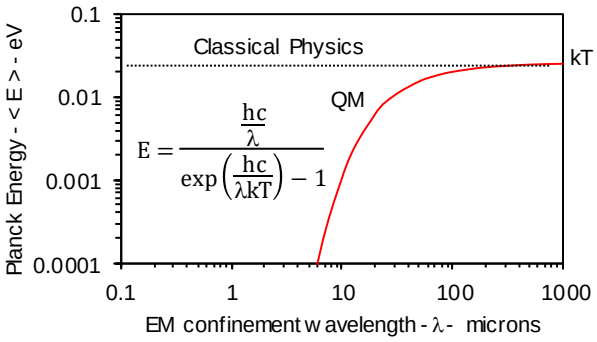

Fig. 4: Planck law of the Atom at 300 °K
In the inset, E is Planck energy, h Planck's constant, c light speed,
k Boltzmann's constant, T temperature, and λ the EM confinement wavelength

EM confinement occurs by the high surface-to-volume (S/V) ratio of nanostructures that requires the heat Q to almost totally be confined in the surface, the surface heat itself as EM energy providing the brief EM confinement necessary to create EM waves standing across the internal dimension d of the nanostructure. Specifically, heat or light having wavelength $\lambda >> d$, the light (yellow) immerses the NP and is absorbed in penetration depth δ over the full NP surface as shown in Figure 5.

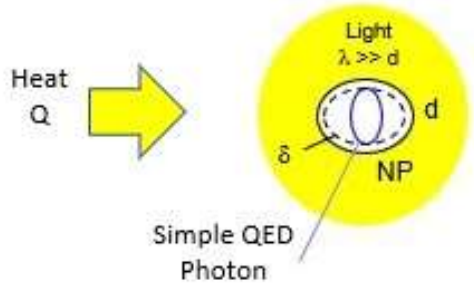

Figure 5. Heat Q absorbed in NP surface

Confinement of the light Q while creating the UVC standing wave requires EM confinement at least equal to the Planck energy E of the light. The pressure P acting on the surface is given for bulk modulus B and volume strain $\Delta V/V$ by, $P = B \cdot \Delta V/V = 6\delta B/d$. But $P = E / V = 6E/\pi d^3$ giving $\delta = Q/\pi B d^2$. For NPs, a typical absorption depth δ of a single UVC photon is $\delta \sim 0.2$ fm, a small but necessary depth necessary to confine the absorbed heat to the geometry of the standing wave.

Simple QED absorbs heat Q in the NP surface given by the penetration δ depth. Unable to conserve the surface heat by a change in temperature, conservation requires the creation of simple QED radiation, the time τ to create the standing wave, $\tau = 2d/(c/n)$. The Planck energy $E \sim h/\tau = hc/2nd$ depends on the refractive index n of the NP to correct for the velocity c of light within the NP. The simple QED Planck energy E is quantized by the dimension d of the NP that defines the half-wavelength $\lambda/2$ of the nanostructure. Fig. 6 illustrates the standing EM radiation in a spherical NP of diameter d, but NP atoms still follow their quantized electron energy levels.

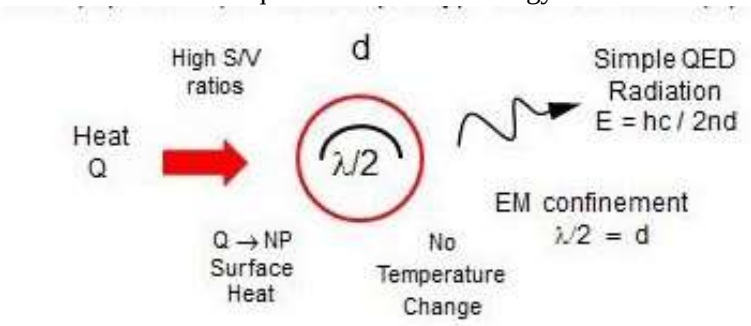

Fig. 6: Planck Energy of EM Radiation

In a rectangular NP with different dimensions of width, thickness, and length there are 3 simple QED quantum states corresponding to the different dimensions of the NP. However, only the minimum dimension is important as by Fermat's principle, the absorbed heat is dissipated in minimum time. Continuous variation in internal nanostructure dimensions produces a broadband spectrum of simple QED dissipated in continuous QED quantum states. Historically, the notion of size dependent quantum states is not found in the literature.

V. ANALYSIS

Similar to mitochondria, peroxisomes synthesize ATP by UV enhanced dehydration. The peroxisomes [9] differ from spaced cristae in that are spherical < 1 μm membrane enclosed organelle containing catalase including a randomly disposed irregular < 100 nm crystalized electron-dense urate oxidase core as shown in Figure 7.

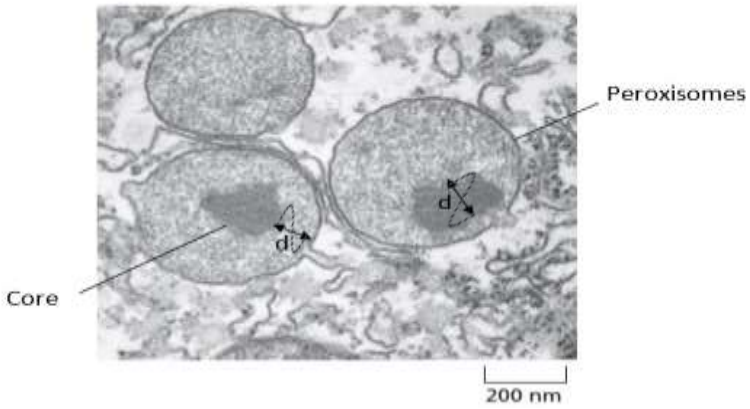

Figure 7. Peroxisomes containing crystalized cores

Not all peroxisomes contain cores. Figure 7 shows 3 peroxisomes, 2 of which contain cores and the other absent core. Unlike mitochondria with spaces between cristae, peroxisomes induce UV radiation characterized by the dimensions d representing the wavelength $\lambda = 2nd$ between irregular surfaces in the core, and between surfaces of the core and the membrane.

In applying simple QED, the peroxisome core and glucose in the space between the core and membrane have dimensions d < 100 nm. The index of refraction for the core is taken as n ~ 1.5 similar [10] to the index of the HIV-1 virus particle and for the space n = 1.333 similar to water. For UVC (λ = 254 nm), the respective dimension d ~ 85 and 95 nm. The core UV emission is relatively constant, but the space changes with time giving broadband UV.

IV. DISCUSSION

Historical timeline

Warburg's theory of cancer [1] was published in 1956 before Mitchell's [2] discovery of chemiosmosis. In 1956, Warburg commented the chemical reactions where ATP is synthesized in respiration are still unknown, whereas the ATP fermentation reaction by which ADP is phosphorylated to ATP was discovered [11] in 1939. However, Warburg's ATP reaction based on an intermediate was questioned by Meyerhof' [12] who showed the intermediate was not necessary. Even so, the intermediate to ATP by fermentation could not be found, the consequence of which led to Mitchell's discovery of chemiosmosis in the 1960's.

In this historical timeline, endogenous UV activated ATP synthesis by dehydration [7] is proposed to supersede chemiosmosis in mitochondria.

ATP synthesis

Like mitochondria, peroxisomes are major sites of oxygen utilization. It is thought [9] mitochondria made peroxisomes obsolete because oxidation carried out in peroxisomes without producing ATP was replaced in mitochondria because ATP was produced by chemiosmosis. Today, mitochondrial oxidation is thought to produce ATP, but oxidation alone in peroxisomes [13] does not synthesize ATP.

However, neither latter statements are valid as simple QED induces endogenous UV allowing ATP synthesis in mitochondria [7] to be extended to ATP synthesis in peroxisomes. In mitochondria, the UV is created in the spaces between cristae shown in Figure 2; whereas in peroxisomes, the UV is created in the core and the space between the core and membrane as shown in Figure 7. Both mitochondria and peroxisomes produce endogenous UV powered by metabolic heat.

Glucose in ATP synthesis

Meyerhof's laboratory [1] showed glycolysis in the cytosol caused the breakdown of carbohydrates to lactic acid and provided evidence that ATP synthesis was the byproduct of glucose. Biochemists today know both respiration and fermentation produce ATP, but peroxisomes lacking an oxidative electron transfer chain (ETC) are thought [14,15] to produce small amounts of ATP by fermentation. Indeed, oxidation in peroxisomes [14] does not make ATP, and instead releases heat energy.

In contrast, metabolic heat [7] produces endogenous UV in both mitochondria and peroxisomes, but the UV level and wavelengths differ because of organelle structure. Literature supporting UV enhancement of glycolysis is limited to the skin exposed to solar radiation, but suggests dendritic cells [16] irradiated with UVB (280 to 320 nm) produced more lactate, consumed more glucose, and had greater glycolytic flux.

Peroxisomes function

It generally thought [17] that without peroxisomes there could be no way for cells to produce peroxides necessary for metabolism, but peroxides are also toxic and there could not be any way to rid peroxides from the body. However, simple QED refutes this argument as hydrogen peroxide may be produced and detoxified by endogenous UV. Indeed, simple QED creates endogenous UV in peroxisomes and reacts with water to create hydroxyl radicals and hydrogen ions.

$$H_2O + UV \rightarrow OH^- + H^+$$

Upon UV reacting with oxygen, the superoxide anion is formed and combining with hydroxyl radicals form hydrogen peroxide.

$$O_2 + UV \rightarrow O_2^- \rightarrow \quad O_2^- + 2OH^- \rightarrow H_2O_2$$

The anti-oxidant catalase in peroxisomes is thought [15] to convert hydrogen peroxide to water. But catalase is not required as UV can directly split hydrogen peroxide into hydroxyl radicals.

$$H_2O_2 + \text{Catalase} \rightarrow H_2O \rightarrow H_2O_2 + UV \rightarrow 2OH^-$$

Endogenous UV in peroxisomes is sufficient to both produce and detoxify hydrogen peroxide without conveniently available catalase and other enzymes.

Fatty acid β oxidation

Mitochondria and peroxisomes both play major roles in cell metabolism, especially in fatty acid metabolism, ROS production and scavenging, and now are considered to metabolically [18] interact with each other.

Peroxisomes are involved in the β oxidation of long chain fatty acids to acetyl CoA, a process that is not possible in mitochondria. The breaking of single and double carbon bonds along the fatty acid backbone require UV energies of 3.6 and 6.3 eV, but UVC energy of 4.88 eV is not sufficient to break carbon double bonds. UV at 200 nm is required that is obtained by simple QED in peroxisome core and space at d ~ 67 and 75 nm, respectively.

Unlike mitochondrial oxidation which produces ATP, oxidation in peroxisomes is claimed [19] to not make ATP and only release heat energy. However, this claim is incorrect as simple QED induces ATP synthesis by UV enhanced dehydration in peroxisomes.

Cancer - Genetics vs. Energy

In the early 20th century, Sutton and Boveri [20] are credited with linking Mendel's production of gametes in peas with the behavior of chromosomes at meiosis. Boveri proposed the genetic origin of cancer based on the observation that fertilized sea-urchin eggs with two sperm instead of one having the wrong number of chromosomes later developed deformations. In the 1920's, Warburg proposed the cancer metabolism theory [1] that cells fueled by the energy of rapid growth developed deformities. Warburg's theory was independent of chromosomes describing cancer in terms of rapid metabolic growth utilizing fermentation of glucose initiate by a loss of oxygen in the cell, a theory that prevailed over genetic theory over several decades.

In 1953, Watson and Crick's structure of the DNA became the hallmark of molecular biology's gene-centered approach to cancer as a disease governed by mutated genes driving cells into a state of rapid division and proliferation. Since then, Warburg's cancer metabolism theory based on genetic mutations as the consequence of rapid cell growth was rejected with the opposite of rapid cell growth as the consequence of genetic change.

Recently, there has been a revival [21] in Warburg's theory on cancer metabolism because for over 70 years genetic research to stop cancer growth has been generally not successful. Today, the causal link between genetics as the cause of cancer metabolism appears unlikely. In 2016, an older Watson who with Crick initiated DNA structure as the control of living organisms is reportedly [21] stated that locating the genes that cause cancer is a cruel illusion. In so doing, Watson himself suggested a revival in Warburg's cancer metabolism, but still unanswered is the question of what causes the cell to activate the Warburg effect leading and cancer.

Warburg thought that rapid cancer growth was caused by defects in normal cells that reduced the available oxygen for oxidative metabolism in respiration necessary for ATP production, the lack of oxygen requiring the cell to use fermentation of glucose to maintain ATP levels, but a genetic basis was never invoked. In fact, Warburg [1] believed the origin of cancer can only be explained by physics and chemistry, and therefore mutation and carcinogenic agents are empty words, unless having a metabolic base.

Warburg's statement [1] that no physical or chemical agent can instantly initiate fermentation requires clarification. UVC and even UVB induce DNA mutations by promptly kill the cell, but lower UVA energy cannot. By simple QED, UVA energy accumulates until UVB levels in the electronic state are reached over time, a process not possible classically as UVA energy is dissipated by increasing temperature. Hence, UVA requires a delay of mutations in nanoscale regions of peroxisomes. Indeed, mutations in Chinese hamster fibroblasts [22] may be delayed many cell generations after UVA.

As though heeding Warburg, a few genetic scientists [21] have recently questioned whether cancer genes in DNA are in fact the source of rapid growth of cancer, and following Warburg's cancer metabolism suggested instead that metabolic genes in DNA were the origin of rapid consumption of nutrients and cancer growth. Without conceding to Warburg's defect of lack of oxygen initiating growth as the basis for cancer, the genetic scientists simply argued that instead of cancer genes, rapid cancer growth was caused by a DNA mutation of metabolic genes controlling consumption of nutrients.

In this controversy, DNA metabolic genes in the AKT pathway [23] need to be activated to undertake a metabolic conversion from oxidative phosphorylation to anaerobic glycolysis, initiate rapid cancer growth when mitochondria are deprived of oxygen. But the direct UV activation [24] of the AKT pathway is excluded in favor of complex chemistry. By extending Warburg to include simple QED induced UV produced in peroxisomes, the AKT pathway is activated, but may not be necessary as ATP is also produced in peroxisomes.

Metabolic genes aside, simple QED induced UV from peroxisomes enhances glucose consumption. As described above, UV irradiated mice are known [16] to produce more lactate, consume more glucose, and had greater glycolytic flux. By Warburg, cancer may be stopped by removing the glucose necessary for fermentation, and in effect, drugs blocking peroxisome UV from glucose lower fermentation. In this regard, metformin [25] used by diabetics may be used to treat cancers by absorbing peroxisome UV. The UV absorption of metformin and sitagliptin (another diabetic drug) are shown in Figure 8.

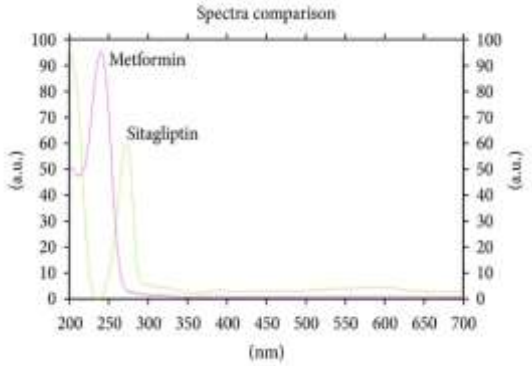

Figure 8. UV absorption of Metformin and Sitagliptin

The UV absorption peak for glucose [26] is 260-270 nm which is in the sharp decreasing region of metformin. But glucose metabolism from UV produced in peroxisomes is still blocked. Sitagliptin would appear optimum in blocking glucose metabolism. But cancer is likely to find a pathway other than glucose for peroxisomes to fuel cancer growth, e.g., glutamine and fatty acids.

V. CONCLUSIONS

Warburg's theory that cancer develops every time cells in respiration are deprived of oxygen for a sufficient period of time followed by fermentation by anaerobic glycolysis. In this paper, the Warburg theory is paraphrased:

> In a cell, cancer develops as runaway UV enhanced fermentation in peroxisomes cannot compensate for the loss of oxygen of respiration in mitochondria.

Warburg's theory modified to include endogenous UV in peroxisomes produced by the simple QED conversion of rapid metabolic heating explains the DNA mutations observed in cancer cells after rapid growth, a claim Warburg lacking a UV source could not make.

Warburg foretold the future of EM irradiation of tissue containing both normal and cancer cells. Normal cells survive PDT because of a higher residual respiration after irradiation concluding that radiation which kills cancer cells can also at the same time produce cancer - a lesson not yet learned by modern PDT research.

On the latency period to produce cancer, Warburg argued there is no physical or chemical agent by which the fermentation of cells can occur instantly, the latency period corresponding to the time at which fermentation increases after damaging. However, DNA mutagens from endogenous UVA produced in peroxisomes do delay fermentation.

Endogenous UV enhances glycolysis by increasing glucose consumption, lactate rate, and glycolytic flux. Conversely, diabetic drugs metformin and sitagliptin that block UV from glucose decrease fermentation and by Warburg reduce cancer growth.

DNA metabolic genes in the AKT pathway are activated by endogenous UV to make the metabolic conversion from oxidative phosphorylation to anaerobic glycolysis, but may not be necessary ATP is produced from dehydration synthesis.

The argument: "Without peroxisomes there could be no way for cells to produce peroxides necessary for metabolism, but peroxides are also toxic and there could not be any way to rid peroxides from the body" is false. Endogenous UV can both produce and rid peroxides.

Peroxisomes involved in the β oxidation of long chain fatty acids to acetyl CoA, a process that is not possible in mitochondria. The breaking of single and double carbon bonds along the fatty acid backbone require UV energies of 3.6 and 6.3 eV. UVC energy of 4.88 eV is not sufficient to break carbon double bonds, but simple QED can produce UV at 200 nm in peroxisomes.

Geneticists who agree with Warburg on the mechanism of metabolism cancer argue that metabolic gene mutations still explain cancer. But explanations of detailed mutation mechanisms are complex including the availability of convenient enzymes to complete chemical equations, i.e., empty words as mutations are far too complex.

Instead, any and all mutation mechanisms to explain cancer are proposed explained by Warburg's cancer theory extended to include endogenous UV.

The controversy between Warburg and geneticists on the origin of cancer is not resolved by endogenous UV. But endogenous UV raises Warburg's cancer metabolism to the level that the search for a metabolic gene initiating cancer may no longer be important.

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