

Understanding the Warburg Effect Yields New Insights into the Metabolic Control of Cancer

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Abstract: Human cells may use either aerobic or anaerobic cellular respiration processes to produce energy, depending on cellular conditions. When there is enough oxygen, cells respire aerobically, but in case of oxygen deficiency, anaerobic cellular respiration is used, which leads to lactic acidosis and an increased risk of cancer according to Warburg's hypothesis.

This paper reviews key aspects related to the historical evolutionary origins of metabolic pathways in cancer cells and compares similarities between cancer cells and ancient unicellular organisms to address the origins of metabolic change in cancer cells and provide new insights into the metabolic control of cancer.

Understanding the main causes of cancer and the biological origin of their behavioral abnormalities is essential for the metabolic control of cancer. Environmental stressors to cells may include lack of essential nutrients, poor oxygenation, excess acids, viruses, infections, and exposure to chemicals, toxins, and radiation. These cellular stressors can cause normal cells to mutate and become cancerous in an attempt to survive in the harsh conditions.

According to the research findings, creating appropriate conditions at the cellular level in terms of pH, sufficient oxygenation and the availability of good sugars, essential vitamins, minerals, enzymes and coenzymes through a healthy diet can lead to a metabolic switch in cancer cells that controls mutations, which can help prevent and control cancer.

Keywords: Cancer, cancer origin, cancer resistance, Warburg effect, metabolic pathways, cell stressors, cancer diet.

INTRODUCTION

Life on our planet appeared about four billion years ago following several million years of geological and chemical evolution. During that time, a single ancestral molecule eventually created a single-celled organism, which all the living organisms on Earth today descend from that intelligent single cell, as a common ancestor of all known forms of modern life. The early-time living systems were intelligent and had an ability for self-replication and adaptive biological evolution to keep their stored genetic information develop further over generations [1,2].

The first single cells on Earth were formed in small rock-pools of water, in a Darwin's hypothetical "warm little ponds", where reactants and organic matter were available for chemical reactions needed for life, in wet soils rich in sulfur compounds such as hydrogen sulfide (in an environment like a smelly wet mud) [2,3]. During the ancient time, concentration of atmospheric oxygen was very low and life evolved anaerobically, where in lack of oxygen as an oxidant, sulfur oxidation was the key metabolic process in the early single cell systems, using H₂S as a source of energy [4,5].

The energy production from anaerobic processes had poor efficiency, as well as required high amounts of energy sources to be available [6], hence, with the limitations, the ancient living organisms evolved very slowly [5]. Ancient life was also exposed to higher levels of damaging radiation because there were higher levels of exposure to cosmic rays and ultraviolet rays in the absence of the protective ozone layer at that time [7,8]. But with passage of time, living conditions on earth were improved, as ozone layer was gradually formed, capable of protecting life from harmful wavelengths of ultraviolet radiation. Also, a part of radioactive elements on surface of earth was gradually decayed and overall exposure of the living cells to natural radioactivity slowly decreased [7,9].

Another key change in evolution history of life on earth was significant increase of atmospheric oxygen from around 600 million years ago. The increased level of oxygen was toxic for the ancient cells and the systems living anaerobically, and much of anaerobic life were wiped out, creating a great extinction event. This brought an end to use of H₂S as a common energy source, and most H₂S-dependent living organisms died [4]. During the period, only those cells, according to Darwinian Natural Selection, which could adapt to the conditions and gain resistance, as well as pass on their survival keys to next generations, could

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manage to survive [10,11]. The new intelligent cells eventually found a way to utilize the rich potential of oxygen in respiration, and soon, oxygen became essential for metabolic activities in oxygenated environments [11]. Oxygen acted as an ideal terminal electron acceptor to generate energy after nutrient breakdown, and life as an aerobic activity evolved faster and more effectively [1,2,11].

In the new form of life, the aerobic processes that used oxygen as an oxidant for converting nutrients to energy, were significantly more efficient in providing cellular energy [1,2,11,12]. Enzymes were also utilized for catalyzing chemical reactions within the cell, which greatly speeded up the biochemical reactions and allowed some larger and more complex living systems to be evolved with influence on their own development [12-14]. During this evolution phase, the cells were first surrounded by their membranes and then membranous cells evolved to have sensors and other components, forming different types of cells with different capabilities [12].

The single-celled, bacteria-like organisms on the ancient Earth were independent and self-contained, cared only about themselves, and looked for nutrients to survive under the tough living conditions. But in the next evolution phase, to continue more effectively, the cells used a cooperative approach and became more dependent on other cells, ultimately producing a multicellular organism consisting of different cells with specialized roles [13]. The cells worked together to interact with the environment, take up nutrients and water, get rid of wastes, and produce sufficient cellular energy (ATP) to survive [12,14]. Furthermore, the key information on survival mechanisms in the cells were passed from one generation of cells to the next, and ultimately, from parent organisms to their offspring, giving rise to plants, animals, and later, modern humans [12-14].

As all the living cells in modern world have their roots in anaerobic life on ancient Earth when the atmosphere was extremely oxygen deficient, the modern cells are still able to utilize anaerobic pathways where required. Hence, even the modern cells in the current complex multi-cellular systems that respire aerobically, can still switch metabolism from aerobic to anaerobic or vice versa, depending on their environmental conditions [1,2,14].

The modern cells in normal conditions obey the co-operative rules, do not move around the body, intelligently control their development and stop growing

when they encounter other cells to respect their territory, and fairly divide the nutrients to ensure that different organs are maintained [15,16]. But under stressful conditions, such as cell exposure to toxins and injuries, the cells may mutate in response to environmental stressors, become cancerous, and return to the behavior of their single celled ancestors (an evolutionary throwback) to survive better by the metabolic switch to anaerobic cellular respiration [15]. An exemplary case for this metabolic switch, is in human cancer cells, which utilize anaerobic cellular respiration in case of experiencing oxygen deficiencies or exposure to environmental stressors [17].

The cells that have mutated and altered their metabolism to increase resistance to cellular damage, may not be problematic under normal circumstances, and even the immune system helps these mutated cells to survive and grow, protecting them instead of attacking [16]. However, in a chronically deficient intracellular environment, particularly in hypoxic regions of the body, the mutated cells struggling to survive may act selfishly, take over the body's resources for their own survival, grow out of control, disrupt multicellular co-operation, hide from the immune system, and eventually invade other tissues in a process known as metastasis [15].

The mystery of aerobic and anaerobic cellular respiration processes in normal cells and cancer cells was first unlocked by Dr. Otto Heinrich Warburg (1883–1970), a German scientist and Nobel Prize winner, following his comprehensive research studies on the subject [17]. Warburg realized that cancer cells utilize anaerobic respiration and fermentation processes to produce their required energy in absence of oxygen, known as the Warburg effect [18]. According to the Warburg findings, cancer cells are commonly developed in poorly-oxygenated (hypoxic) regions of the body, consume greater amounts of glucose and other nutrients, and form significant amounts of lactic acid and additional acidic/toxic wastes as byproducts, which acidifies the cellular environment and further increases the risk of development of cancer tumors [17-19].

METABOLIC SWITCH IN CANCER CELLS

In human body, the cells normally respire aerobically and consume glucose as their preferred source of energy, producing water and carbon dioxide as byproducts of the cellular respiration. But in case of insufficient oxygen supply, the cells produce energy via anaerobic cellular respiration processes that produce

lactic acid as the main byproduct. Depending on the conditions at cellular level, aerobic and anaerobic metabolism always occur, although not in the same cell simultaneously [14,18,19].

Oxygen deficiency may occur for different reasons and in various situations. For instance, during intense exercise, muscle cells under a great pressure take oxygen at a higher rate to produce cellular energy faster via aerobic respiration processes, which depletes their environmental oxygen despite increased blood circulation around the cells during exercise, eventually leading to insufficient availability of oxygen for the cells. When this happens, in lack of oxygen availability, muscle cells utilize anaerobic respiration processes and lactic acid fermentation, leading to built-up of lactic acid that can make the muscles sore. The lactic acidosis caused by intense exercise is usually temporary in healthy people, and once the body slows down and oxygen becomes available again, the cells switch to aerobic metabolism, and the accumulated lactic acid is neutralized in normal conditions by the body survival mechanisms, normally within about an hour afterwards [19,20].

In hypoxic regions of the body where oxygenation is chronically poor, metabolic switch to anaerobic respiration is more likely to occur. In this case, according to the Warburg effect, the chronic oxygen deficiency may transform normal cells into cancerous cells, eventually forming cancerous tumors. But reversing the metabolic pathways by providing an oxygenated nutrient-rich environment with optimum alkalinity at the cellular level, may retain healthy cells and inhibit cancer cells growth [18,19].

According to the Warburg Hypothesis, a fundamental cause of cancer is damage of cellular respiration caused by the cell stressors, such oxygen deficiency, acidic cellular environment, and exposure to environmental carcinogens including chemicals, toxins and radiation [18]. If cellular respiration is impaired, cells may respond in a variety of ways, including activating survival pathways to inducing programmed cell death, while attempting to maintain a balance between cell survival and cell death. The cells that die due to the damage, may not be a major problem, if not too many of them die, because they can be replaced with new cells. But some damaged cells can manage to resist cell death and survive by repairing themselves following some targeted cell mutations that build-up in the cells [16,21]. These cell mutations are not necessarily caused by a defect, but as result of

activation of survival mechanisms that help cells evolve towards gaining more resistance under difficult living situations [22].

For the cells that are exposed to a damage, chances of gaining resistance and surviving are significantly increased if there are favorable conditions at the cellular level, in terms of pH level, sufficient absorption of oxygen, and availability of good sugars, essential vitamins, minerals, enzymes, and co-enzymes, which play key roles in regulation of cellular metabolism, differentiation, and maturation [14,18]. But, unfavorable cellular conditions such as pH imbalances, deficiency in key nutrients, and poor oxygenation may cause excessive mutations during cellular adaptation to stressful conditions, resulting in abnormal cell functioning [14,18,23,24]. In this case, the mutated cells ignore signals that normally command cells to stop dividing or to die (a process known as programmed cell death, or apoptosis) and grow out of control [16,21]. As a result, a benign tumor may be formed that does not spread to other parts of the body and remains unproblematic, or, depending on the cellular conditions and accumulation rate of DNA mutations over time, it may form aggressive cancerous malignant tumors that can be life threatening [16,25].

In general, the cancer-causing environmental stressors may be associated with unhealthy dietary habits such as a high intake of animal proteins and a low intake of vegetables and fruits, consumption of alcohol and addictive drugs, smoking, sleep disorders and chronic insomnia, use of chemical cosmetics, high intake of artificial supplements, viruses, infections, stress, physical inactivity, and exposure to toxins and radiation [18,26,27]. The cell stressors can change a normal cell struggling to survive, to a cancer cell that returns to the behavior of their single-celled ancestors by acting inconsiderately to take over our body's resources for their own survival, leading to uncontrollable cell growth [14,18].

In case of appropriate conditions as the cell level concerning optimal alkalinity and oxygenation, as well as sufficient availability of key essential nutrients from healthy plant-based foods, the tension and stresses at the cells may be reduced, leading to control of cancer cells [14,18]. Studies have shown that traditional diets rich in plant-based foods can reduce the risk of cancer [28,29]. But, there are higher risk of developing these cancers in people who live a typical western-world's lifestyle and frequently consume unhealthy fast foods and sugary beverages, as well as have high intakes of

animal proteins, but low intake of plant-based foods [18]. In a study on the effect of dietary habits on African-Americans, those who followed fatty meat-heavy diets (a typical Western diet) had a significantly higher risk of colorectal cancer than those consuming rural African foods rich in beans and vegetables [30].

CONCLUSIONS

Understanding the origin of cancer and metabolic pathways in cancer cells bring new insights to treating cancer as a metabolic disease, as well as developing some complementary or alternative solutions accordingly.

Deficiencies in oxygen and key nutrients may be a primary root cause that changes a normal cell struggling to survive, to a cancer cell that returns to the behavior of their single-celled ancestors by a metabolic switch to take over our body's resources for their own survival, leading to uncontrollable cell growth. In contrast, providing a cellular condition rich in oxygen with sufficient availability of essential nutrients from natural healthy foods, may reduce the tension, leading to control of cancer cells and domination of normal cells.

To change the metabolic pathway and resolve cancer, providing an oxygen-rich cellular environment with optimal alkalinity may be effective, by maintaining conditions that lead to a sustained aerobic cellular respiration that naturally improves body resistance to developing cancers.

In general, a nutrient-rich plant-based healthy diet rich in natural fruits, fresh vegetables, legumes and alkalizing nuts, as well as following a healthy life style that avoids smoking, drinking alcoholic beverages, and a high intake of animal proteins and processed foods, as well as reducing exposure to the environmental carcinogens, may be effective in providing appropriate condition at the cellular level, helping with controlling cell mutations and preventing cancers.

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REFERENCES

- [1] Jheeta S. The Landscape of the Emergence of Life. *Life (Basel)* 2017; 7(2): 27. <https://doi.org/10.3390/life7020027>
- [2] Kunnev D. Origin of Life: The Point of No Return. *Life* 2020; 10(11): 269. <https://doi.org/10.3390/life10110269>
- [3] Kump L. The rise of atmospheric oxygen. *Nature* 2008; 451: 277-278. <https://doi.org/10.1038/nature06587>
- [4] Olson KR, Straub KD. The Role of Hydrogen Sulfide in Evolution and the Evolution of Hydrogen Sulfide in Metabolism and Signaling. *Journal of Physiology* 2015; 31(1): 2-72. <https://doi.org/10.1152/physiol.00024.2015>
- [5] West JB. The strange history of atmospheric oxygen. *Physiol Rep* 2022; 10(6): e15214. <https://doi.org/10.14814/phy2.15214>
- [6] Zhang XJ. *Comprehensive Water Quality and Purification* 2014; 3: 108-122. Elsevier Inc. ISBN 978-0-12-382183-6. <https://doi.org/10.1016/B978-0-12-382182-9.00046-3>
- [7] Plant JA, Saunders AD. *Radiation Protection Dosimetry* 1996; 68(1-2): 25-36. <https://doi.org/10.1093/oxfordjournals.rpd.a031847>
- [8] Cockell CS, Raven JA. Ozone and life on the Archaean Earth. *Philos Trans A Math Phys Eng Sci* 2007; 365(1856): 1889-901. <https://doi.org/10.1098/rsta.2007.2049>
- [9] Ershov B. Natural Radioactivity and Chemical Evolution on the Early Earth: Prebiotic Chemistry and Oxygenation. *Molecules* 2022; 27(23): 8584. <https://doi.org/10.3390/molecules27238584>
- [10] Gregory TR. Understanding Natural Selection: Essential Concepts and Common Misconceptions. *Evo Edu Outreach* 2009; 2: 156-175. <https://doi.org/10.1007/s12052-009-0128-1>
- [11] Schirmer BE, Gugger M, Donoghue PC. Cyanobacteria and the Great Oxidation Event: evidence from genes and fossils. *Palaeontology* 2015; 58(5): 769-785. <https://doi.org/10.1111/pala.12178>
- [12] Ma'ayan A. Complex systems biology. *J R Soc Interface* 2017; 142017039120170391. <https://doi.org/10.1098/rsif.2017.0391>
- [13] Bich L, Pradeu T, Moreau JF. Understanding Multicellularity: The Functional Organization of the Intercellular Space. *Front Physiol* 2019; 10: 1170. <https://doi.org/10.3389/fphys.2019.01170>
- [14] Cooper MG, Housman RE. *The Cell: A Molecular Approach Fifth Edition*, Publisher: Sinauer Associates, Inc. 2009; (ISBN-13: 978-0878933006).
- [15] Rasnitsyn A. Cancer: A Throwback to Ancient Cells? 2019. <https://torontoriot.com/2019/11/26/cancer-a-throwback-to-ancient-cells/>
- [16] National Cancer Institute. What Is Cancer? 2021. <https://www.cancer.gov/about-cancer/understanding/what-is-cancer>
- [17] Warburg O. On the Origin of Cancer Cells. *Science* 1956; 123(3191): 309-314. <https://doi.org/10.1126/science.123.3191.309>
- [18] Bahrami H, Tafrihi M, Mohamadzadeh S. Reversing the Warburg effect to control cancer: A review of diet-based solutions. *Journal of Current Oncology and Medical Sciences* 2022; 2(3). <https://submission.journalofcoms.com/index.php/JCOMS/article/view/54>
- [19] Bahrami H, Greiner T. The alkaline diet and the Warburg effect. *World Nutrition* 2021; 12(1): 20-39. <https://doi.org/10.26596/wn.202112120-39>
- [20] Theofilidis G, Bogdanis GC, Koutedakis Y, Karatzaferi C. Monitoring Exercise-Induced Muscle Fatigue and Adaptations: Making Sense of Popular or Emerging Indices and Biomarkers. *Sports (Basel)* 2018; 6(4): 153. <https://doi.org/10.3390/sports6040153>

- [21] Edwards G. Uranium: Known Facts and Hidden Dangers. The World Uranium Hearing conference, Salzburg 1992.
- [22] Isaacs T. What Causes Cancer and What Is it Really? 2016. [Online]. Available at: <https://thetruthaboutcancer.com/what-causes-cancer/>
- [23] Aranda-Anzaldo A, Dent MAR. Is cancer a disease set up by cellular stress responses? *Cell Stress Chaperones* 2021; 26(4): 597-609. <https://doi.org/10.1007/s12192-021-01214-4>
- [24] Drochioiu G. The influence of respiratory and pH imbalance in cancer development. *International Journal of Biochemistry Research and Review* 2014; 4(5): 386-409. <https://doi.org/10.9734/IJBCRR/2014/8617>
- [25] Laconi E, Marongiu F, DeGregori J. Cancer as a disease of old age: changing mutational and microenvironmental landscapes. *Br J Cancer* 2020; 122(7): 943-952. <https://doi.org/10.1038/s41416-019-0721-1>
- [26] International Agency for Research on Cancer. Cancer incidence rate data tables and maps for each country 2020. [Online]. Available at: <https://gco.iarc.fr/today/>
- [27] Bahrami H, Tafrihi M. Global Trends of Cancer: The Role of Diet, Life Style, and Environmental Factors. *Cancer Innovation* 2023. <https://doi.org/10.1002/cai2.76>
- [28] Schwingshackl L, Morze J, Hoffmann G. Mediterranean diet and health status: Active ingredients and pharmacological mechanisms. *Br J Pharmacol* 2020; 177(6): 1241-1257. <https://doi.org/10.1111/bph.14778>
- [29] Maruca A, Catalano R, Bagetta D, Mesiti F, Ambrosio FA, Romeo I, Moraca F, Rocca R, Ortuso F, Artese A, Costa G, Alcaro S, Lupia A. The Mediterranean Diet as source of bioactive compounds with multi-targeting anti-cancer profile. *European Journal of Medicinal Chemistry* 2019; 181: 111579. <https://doi.org/10.1016/j.ejmech.2019.111579>
- [30] O'Keefe SJ. Fat, fiber and cancer risk in African Americans and rural Africans. *Nature Communications* 2015. <https://doi.org/10.1038/ncomms7342>

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