When the Krebs Cycle Breaks: Dynamical Modeling of Cancer Metabolism

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Abstract

Cancer is increasingly recognized as a disease of systems-level dysfunction, where metabolic rewiring plays a central role in sustaining tumor growth and survival. Among these metabolic changes, alterations in the Krebs cycle are particularly notable, as mutations and dysregulation of enzymes such as isocitrate dehydrogenase (IDH), succinate dehydrogenase (SDH), and fumarate hydratase (FH) lead to the accumulation of oncometabolites and disruption of redox homeostasis. Such metabolic perturbations connect directly to the hallmarks of cancer, including sustained proliferative signaling, resistance to cell death, and adaptation to a hostile microenvironment. We employ a mathematical modeling framework based on the Brusselator system of nonlinear oscillators to capture the dynamics of the Krebs cycle under both normal and dysregulated conditions. The canonical Brusselator demonstrates stable oscillations between metabolites, serving as an abstraction of healthy metabolic cycling. We then extend the model to incorporate cytosolic calcium, redox balance, mitochondrial potential, and insulin resistance—factors known to interact with and destabilize mitochondrial metabolism in cancer. Simulations reveal that these extensions lead to dampened oscillations, frequency slowing, and coupled abnormalities across regulatory variables, reflecting a loss of metabolic flexibility consistent with tumorigenesis. By linking Krebs cycle dysfunction to emergent hallmarks of cancer, our approach provides a conceptual bridge between biochemical observations and systems-level insights. This work underscores the utility of nonlinear dynamical models for understanding the complexity of cancer metabolism and suggests new directions for identifying metabolic vulnerabilities that may be exploited therapeutically.

Introduction

Cancer remains as one of the leading causes of death worldwide, as well a global burden. In 2022, there were an estimated 20 million new cancer cases and 9.7 million deaths worldwide [1]. Around 1 out of every 5 people develop cancer in their life, and about 1 in 9 men and 1 in 12 women die from this disease. In 2024, around 2,001,140 new cancer cases and 611,720 cancer deaths were projected to occur in the United States [10, 9].The economic burden of cancer shares the same staggering stats: between 2020 and 2050, the world will spend approximately $25 trillion in international dollars on cancer. That will be around 0.55% of the global GDP. Cancer doesn't just stop at being a disease, it's an economic crisis causing millions to suffer around the globe. This data emphasizes the urgent need to understand cancer better as a whole to ensure that in the future we can see better treatment and better access to fighting cancer. Douglas Hanahan and Robert A. Weinberg have proposed nine hallmarks of cancer over the span of 22 years (2000-2022)[4, 3, 2]. Global recognition of these concepts, as well as their applicability to science will allow for further advancement in the treatment of cancer, as these nine hallmarks form the framework for the diverse function of cancer.

The first hallmark proposed is sustained proliferative signaling, also otherwise known as uncontrolled cell division, which allows malignant cells to undergo uncontrolled cell growth and division

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by evading the normal regulatory functions that control cell division. This occurs when proto-oncogenes, normal genes coding for proteins involved in stimulating cell proliferation, mutate or become overly expressed transforming into oncogenes. These oncogenes are continuously sending growth signals, even in the absence of regulatory cues, becoming permanently active. Mutations in proto-oncogenes result in oncogenes such as RAS, MYC, EGFR, and HER2–providing constant growth signals. Targeted therapies, inhibitors of specific molecular components, have been found to target this hallmark. One therapy is the EGFR inhibitor, which blocks ligands from binding to the receptor, blocking the pathway from the cell surface (the beginning) which inhibits the downstream signaling cascade pathways. In order to block the mutations occurring in downstream effectors (such as RAF), RAS/RAF/MEK inhibitors are used to block these molecules so that cells are now no longer able to receive or act on signals that stimulate cell proliferation. The next hallmark proposed was cancer's ability to evade growth suppressors. The suppressor mechanisms are regulated by tumor suppressor genes such as RB and TP53. These genes evaluate cells as they pass by cell cycle checkpoints, evaluating whether they can process through the cell cycle or have to undergo apoptosis due to factors such as DNA damage. Mutations in these genes lead to a loss of function in these critical checkpoints, allowing for uncontrolled cell proliferation. Additionally, the TGF-β pathway, normally a powerful inhibitor of cell growth, can become mutated in complex cancers turning it into a tumor-promoter gene. SMAD proteins take a major role in the TGF-β pathway, further inhibiting cell growth and promoting apoptosis. However, when these SMAD proteins become mutated, they can allow cells to evade the TGF-β pathway, evading growth inhibition. This hallmark can also be treated with targeted therapies such as CDK inhibitors. Cyclin-dependent kinases and cyclins form a compound which promotes progression through the cell cycle. In cancer, CDKs become overactive due to mutations, allowing for continuous cell proliferation. CDK inhibitors block CDK's halting the progression of the cell from the G1 to the S phase of the cell cycle, slowing tumor growth and regaining control of cell proliferation. The third hallmark proposed is the ability of cancer to evade cell death, or apoptosis. Cancer cells often evade apoptosis due to a mutation in TP53, which suppresses apoptosis and ends up upregulating anti-apoptotic proteins. When TP53 is mutated, we see BAX, a pro-apoptotic protein, being inhibited, while BCL-2, an anti-apoptotic protein becomes overexpressed–allowing cells to evade programmed cell death. Proapoptotic BH3 mimetics and chemotherapy are used to induce apoptosis in cancer cells. BH3 mimetics are targeted drugs acting as pro-apoptotic BH3, which bind to proteins such as BCL-2, and release proteins such as BAX, triggering mitochondrial-mediated cell death. Chemotherapy specifically targets cells that undergo rapid proliferation, inducing stress/DNA damage which activate apoptotic pathways.

The next hallmark proposed is the enabling of replicative immortality in cancer cells. Cancer cells are able to upregulate telomerase, elongating the telomeres, the protective caps at the end of chromosomes that shorten as cells divide. When the telomeres become too short, cells enter senescence (an irreversible non proliferative state) and crisis (widespread cell death). Through the elongation of telomeres, cells can evade senescence and crisis, allowing for limitless replicative potential. TERT promoter mutations are found in cancers which increase the expression of TERT (a subunit of telomerase), allowing for unlimited cell division and tumor growth. Additionally, ALT (alternative lengthening of telomeres) acts independently of telomerase, also elongating telomeres in cancerous cells. Both TERT and ALT are able to allow cancer cells to achieve replicative immortality. Therapies such as telomerase inhibitors are able to fight against this by blocking the activity of TERT, allowing cells to undergo senescence or apoptosis.

Angiogenesis is the formation of new blood vessels, being a fundamental hallmark that enables tumors to grow and metastasize within tissues. During tumor development, angiogenesis is a critical point where the balance of pro-angiogenic (blood vessel-promoting) factors switches to overpowering anti-angiogenic (blood vessel-inhibiting) factors. This allows a small dormant tumor to activate new blood vessel formation and grow into a large, metastatic mass. The hypoxia-inducible factor (HIF-1α) plays a central role in this shift. Under low oxygen, HIF-1α is stabilized and upregulates vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and angiopoietins, all of which stimulate endothelial cell proliferation and vessel sprouting. VEGF targeted therapy depends on the tumor type, stage, and treatment history, as it increases vascular

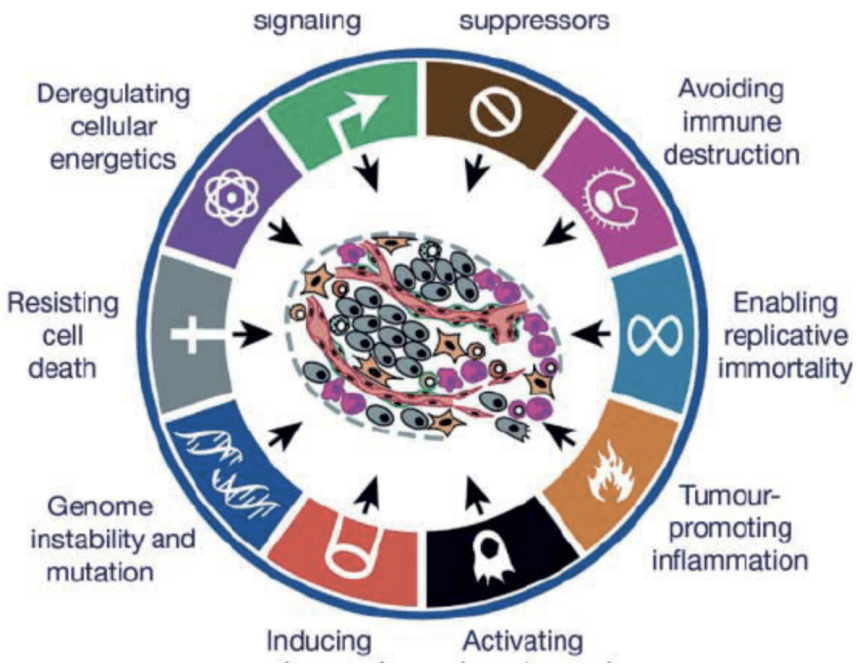

Figure 1: The hallmarks of cancer proposed by Hanahan and Weinberg (2000–2022). These hallmarks provide a unifying framework for understanding the diverse biological processes that enable tumor initiation, growth, and progression.

permeability. The monoclonal anti-VEGF antibody bevacizumab was the first therapeutic agent inhibiting tumoral angiogenesis, being approved for treating several cancers such as metastatic colorectal cancer, glioblastoma, breast cancer, and lung cancer. However, the use of this antibody has often been limited due to immune response and toxicity. Because tumors often become resistant to anti-angiogenic treatments, researchers have explored alternative mechanisms that allow cancer cells to enter the blood supply, including vessel co-option and greater invasiveness under hypoxic conditions. Blocking the VEGF signaling pathway has been the main target in the development of anti-angiogenetic drugs. With high VEGF levels, there are lower survival rates with more cancerous diseases; thus, their levels were often used to predict the metastatic potential and an independent risk factor that must be evaluated when determining new drugs.

Metastasis is the key process responsible for the spread of cancer cells from a primary tumor to distant organs. Being multi-step, it starts from local invasion, intravasion into blood vessels, circulation through cells, extravasation into new surrounding organ tissue, and finally into colonization to supply nutrients for the tumors and suppress the immune system. This staged progression begins with epithelial-to-mesenchymal transition (EMT), where cells lose epithelial characteristics such as E-cadherin (CDH1) and gain mesenchymal traits like vimentin (VIM), increasing motility and invasiveness. The transcription factors are Snail, Slug, Twist, and ZEB1/2, which suppress the expression of epithelial characteristics. Metastatic competence also depends on enzymes that support the extracellular matrix (ECM). Matrix metalloproteinases degrade the ECM by stopping the expression of CDH1, allowing cells to invade surrounding tissues. The reverse is the mesenchymal-to-epithelial transition (MET) to form epithelial tissue at specific sites during the development of the embryo– this process also gets hijacked by cancer cells metastasizing, staying epithelial. Immune cells known as macrophages essentially fight these tumor cells and supply them with enzymes to degrade the ECM so the cancer cells can be broken down. However, when affected directly by the tumor cells, the macrophages also supply growth factors to these cells, contributing to their invasion throughout all tissues and no longer degrading the ECM; this often

seems to be the end result of all colonizing cancerous tumors by the final stages.

This hallmark of cancer focuses on when cancer cells essentially alter their metabolism process to fuel rapid growth and proliferation for their colonization. During cellular respiration, the cell utilizes more glucose even in the presence of oxygen; though the glycolysis stage yields less ATP per molecule of glucose than oxidative phosphorylation, it still provides enough fuel for pathways needed for proliferation. This process is also known as the Warburg effect, which uses aerobic glycolysis and lactic acid fermentation for cells' energy production. Most of the mutations that trigger these pathways lie in the mitochondrial enzymes of the Krebs cycle– damaged mitochondria are able to accumulate more metabolites that activate oncogenic cascades promoting cell proliferation. The mutations in the metabolic genes include the Fumarate hydratase (FH), Succinate dehydrogenase (SDH), and isocitrate dehydrogenase (IDH), becoming oncometabolites. In addition, hypoxia can amplify this oncometabolic cascade. Therapeutic strategies for this process target these metabolic pathways, known as metabolic oncology. The most current successful approach has been attacking IDH inhibitors that starve tumor cells of its necessary substrates to be activated. In addition to this therapeutic approach, there has been some research of combining metabolic inhibitors with immunotherapy to overcome metabolic resistance that cancer cells possess.

Avoiding immune destruction is where tumor cells employ various strategies to hide from or suppress the immune system. Typically, the immune system constantly surveys tissues for abnormal cells, but cancer cells evade their detection by downregulating the antigen production of major histocompatibility complex (MHC) class I. They manipulate immune checkpoint pathways to deactivate immune cells, creating an immunosuppressive tumor environment. The tumor cells also downregulate the expression of chemokines that normally activate immune response pathways. Cancer-associated fibroblasts (CAFs) also prevent immune cells like T-cells from infiltrating the tumour environment. The therapeutic response to this cancer immunotherapy employs immune checkpoint inhibitors to reactivate the immune system for advanced recognition. According to recent clinical trials, Ipilimumab, Nivolumab, and Pembrolizumab were some of the checkpoint inhibitors that have demonstrated durable responses in melanoma, lung, and renal cancer; however, there is still much more to explore regarding CAR-T cell therapy and immunotherapy.

The final hallmark of cancer is genomic instability and mutation – an increased tendency for mutations and other genetic changes to occur and persist while mutations cause alterations in DNA sequence and number of chromosomes. This promotes diversity amongst the tumors and resilience against tumor treatments. Amongst solid malignancies, microsatellites, nucleotide repeats, has been commonly detected. The tumor supressor p53 has mutated in over 50% of human cancers as it allows damaged cells to escape apoptosis. During signal transduction,the p53 pathway is responsible for recognizing diverse forms of oncogentics and directs them to appropriate cellular response of apoptosis. However, cancer cells posses proto-onco genes with mutations such as MDM2 that act as p53 supressors, binding and neutralizing the signaling pathway. This inhibits its transcriptional activity of identifying oncogenes and allows infected cells to avoid apoptosis and replicate uncontrollably – passing the cell checkpoints incorrectly. Therapeutically, tumors with a height mutational impact respond to immunotherapy since these mutations release antigens that can be recognized by T cells. Currently, targeting the replication stress and exploiting DNA damage response pathways in the cell cycle have been the most prominent and recurring areas of research regarding this issue.

Methods

Cancer cells exhibit profound alterations in metabolism to support both ATP synthesis and the biosynthesis of macromolecules, including fatty acids, amino acids, nucleotides, and proteins. These processes demand a steady supply of reducing equivalents (NADH, NADPH) and high levels of ATP. Unlike differentiated cells that rely primarily on oxidative phosphorylation, many cancer cells resemble stem cells in that they preferentially utilize aerobic glycolysis (the Warburg effect) [11], while maintaining a flexible relationship with mitochondrial respiration.

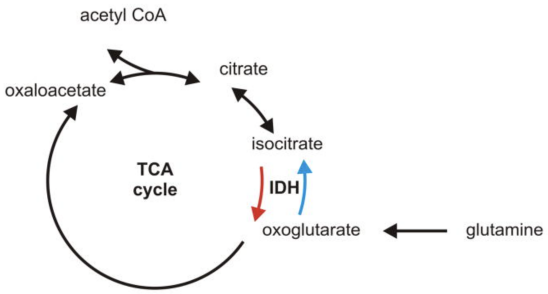

Figure 2: Mutant IDH reverses the normal step between isocitrate and oxoglutarate, causing buildup of harmful metabolites and making cancer cells rely more on glutamine.

Two mitochondrial enzymes play pivotal roles in linking Krebs cycle dysfunction to oncogenesis: succinate dehydrogenase (SDH) and fumarase (FH). Mutations or loss of function in these enzymes lead to the accumulation of succinate and fumarate, which act as oncometabolites. Both intermediates inhibit prolyl hydroxylases (PHDs), stabilizing hypoxia-inducible factor 1α (HIF1α) even under normoxia [5]. Stabilized HIF1α activates transcriptional programs that promote aerobic glycolysis, cell survival, and resistance to cell death. This provides cancer cells with a growth advantage under metabolic stress.

The Krebs cycle itself can proceed along two complementary pathways. In the *canonical oxidative branch*, reducing equivalents are generated as NADH via sequential transfer of electrons through complexes I–IV of the respiratory chain. In contrast, the *non-canonical reductive branch* allows cells to use fumarate as an electron acceptor, an adaptation reminiscent of ancient anaerobic metabolism. This pathway consumes NADH, permitting continued ATP synthesis when oxygen is scarce, and is frequently co-opted by cancer cells.

Another key metabolic node is isocitrate dehydrogenase (IDH), which exists in both NAD^+-dependent (IDH1/2) and $NADP^+$-dependent (IDH3) isoforms. Wild-type IDH catalyzes the oxidative decarboxylation of isocitrate to α-ketoglutarate, producing NADH or NADPH depending on the isoform. Importantly, under conditions of NADPH abundance or mitochondrial redox imbalance, IDH can operate in reverse, converting α-ketoglutarate back to isocitrate, thereby fueling reductive carboxylation. This reversal is strongly driven by high glutamine uptake, a hallmark of proliferating tumor cells [7, 6].

Mitochondrial potential further regulates the balance between NADH and NADPH. When ATP demand is low, ATP synthase activity slows, leading to hyperpolarization of the inner mitochondrial membrane and increased electron leakage, which promotes reactive oxygen species (ROS) formation. To counteract oxidative stress, mitochondria employ nicotinamide nucleotide transhydrogenase (NNT) to convert NADH into NADPH, thereby lowering membrane potential and supplying reducing power for antioxidant defense. Conversely, during periods of high ATP demand, ATP synthase accelerates proton flux, mitochondrial potential decreases, and NADH oxidation predominates, sustaining Krebs cycle turnover [8].

The dysregulation of succinate/fumarate metabolism, IDH-mediated redox cycling, and mitochondrial potential dynamics constitute interdependent mechanisms through which cancer cells reprogram energy metabolism. These processes form the biological foundation for our mathematical modeling approach, wherein we use nonlinear oscillator systems to capture the stability and breakdown of Krebs cycle dynamics.

Results

To capture the dynamic behavior of the Krebs cycle under both healthy and perturbed conditions, we modeled the system using canonical and extended Brusselator frameworks.

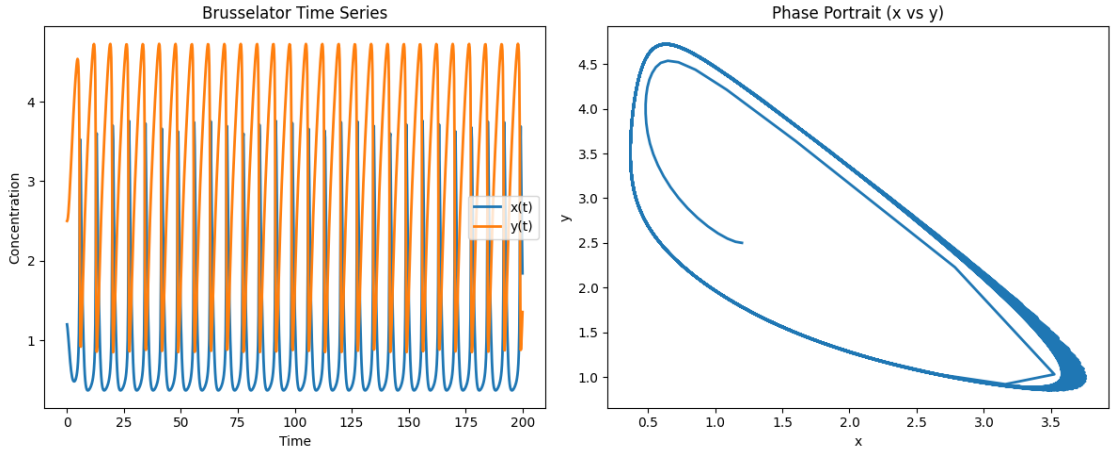

Figure 3: Normal Brusselator dynamics representing a healthy Krebs cycle. Time series (left) and phase portrait (right) of the canonical Brusselator model, illustrating stable oscillations between metabolites $x(t)$ and $y(t)$. These oscillations serve as an abstract representation of rhythmic metabolic activity in the Krebs cycle under physiological conditions.

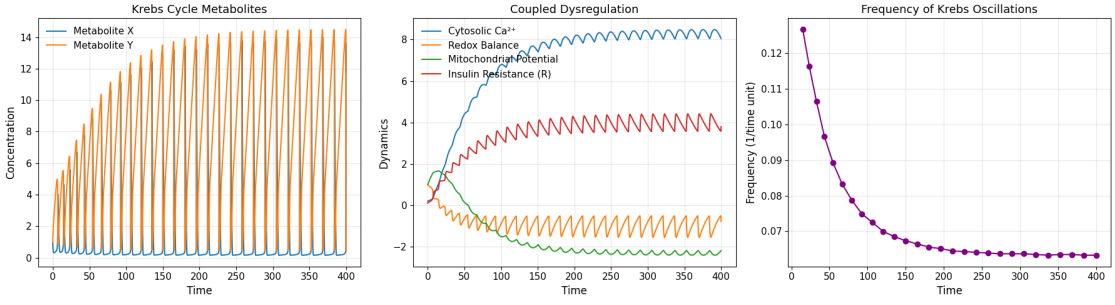

Figure 4: Extended Brusselator dynamics capturing metabolic dysregulation. Left: Oscillations of Krebs cycle metabolites (x, y) under perturbed conditions. Middle: Coupled dynamics of cytosolic calcium, redox balance, mitochondrial potential, and insulin resistance, showing progressive dysregulation. Right: Decline in the frequency of Krebs cycle oscillations, indicating slowed metabolic cycling associated with higher cancer risk.

Normal Krebs Cycle Dynamics

The canonical Brusselator reproduced robust oscillations between two representative metabolites (x, y), which we interpret as a simplified abstraction of normal tricarboxylic acid (TCA) cycle activity. As shown in Figure 3, the time series of $x(t)$ and $y(t)$ (left) exhibited sustained periodic oscillations, while the corresponding phase portrait (right) revealed a stable limit cycle. These results demonstrate how the healthy Krebs cycle maintains rhythmic metabolic fluxes essential for cellular homeostasis.

Metabolic Dysregulation in the Extended Model

When additional physiological factors such as cytosolic calcium, redox balance, mitochondrial potential, and insulin resistance were incorporated into the extended Brusselator model, the oscillatory behavior of the system changed markedly. As shown in Figure 4, the left panel illustrates how metabolite oscillations (x, y) became progressively dampened, indicating reduced metabolic robustness. The middle panel highlights coupled dysregulation, where abnormal calcium handling, impaired redox balance, declining mitochondrial potential, and insulin resistance interacted nonlinearly. Finally, the right panel quantifies this disruption, revealing a progressive decline in the frequency of Krebs cycle oscillations. This slowing of metabolic cycles is consistent with experimental observations of metabolic inflexibility and energetic stress in cancer cells.

These results demonstrate that while the canonical model captures stable rhythmic behavior of the Krebs cycle, the extended system recapitulates critical aspects of metabolic dysfunction associated with tumorigenesis.

Conclusion

We developed mathematical models to explore how dysfunction in the Krebs cycle contributes to cancer-associated metabolic reprogramming. Using the canonical Brusselator, we showed that normal metabolic activity can be represented as stable oscillations, reflecting the rhythmic balance of energy production and metabolite turnover in healthy cells.

By extending the model to incorporate cytosolic calcium, redox balance, mitochondrial potential, and insulin resistance, we reproduced critical aspects of metabolic dysregulation observed in cancer. The extended Brusselator demonstrated dampened metabolite oscillations, coupled abnormalities across key regulatory pathways, and a decline in the frequency of Krebs cycle oscillations. Together, these features capture the loss of metabolic flexibility and energy homeostasis that underlies tumor growth and survival.

Importantly, these findings integrate with the broader framework of the hallmarks of cancer. Metabolic reprogramming, once considered a secondary effect, is now recognized as a core hallmark that supports sustained proliferation, resistance to cell death, and adaptation to the tumor microenvironment. Our modeling approach shows how disruptions in the Krebs cycle interact with other cellular processes—such as redox regulation and signaling pathways—to reinforce malignant phenotypes.

Overall, this work highlights the value of nonlinear dynamical models in bridging molecular observations with systems-level insights. By linking Krebs cycle dysfunction to hallmarks of cancer, our results underscore the centrality of metabolism in oncogenesis and suggest new avenues for identifying metabolic vulnerabilities that may be exploited therapeutically.

References

[1] J. Ferlay et al. “Global Cancer Statistics 2022: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries”. In: *CA: A Cancer Journal for Clinicians* 74.3 (2024), pp. 299–309. DOI: 10.3322/caac.21834.

[2] Douglas Hanahan. “Hallmarks of cancer: new dimensions”. In: *Cancer Discovery* 12.1 (2022), pp. 31–46. DOI: 10.1158/2159-8290.CD-21-1059.

[3] Douglas Hanahan and Robert A Weinberg. “Hallmarks of cancer: the next generation”. In: *Cell* 144.5 (2011), pp. 646–674. DOI: 10.1016/j.cell.2011.02.013.

[4] Douglas Hanahan and Robert A Weinberg. “The hallmarks of cancer”. In: *Cell* 100.1 (2000), pp. 57–70. DOI: 10.1016/S0092-8674(00)81683-9.

[5] Anthony King, Mary A. Selak, and Eyal Gottlieb. “Cancer metabolism: mitochondrial dysfunction in cancer cells due to mutations in SDH and FH”. In: *British Journal of Cancer* 95.3 (2006), pp. 273–277. DOI: 10.1038/sj.bjc.6602932.

[6] Chao Lu, Patrick S. Ward, Guneet S. Kapoor, et al. “IDH mutation impairs histone demethylation and results in a block to cell differentiation”. In: *Nature* 483.7390 (2012), pp. 474–478. DOI: 10.1038/nature10860.

[7] D. W. Parsons et al. “An integrated genomic analysis of human glioblastoma multiforme”. In: *Science* 321.5897 (2008), pp. 1807–1812. DOI: 10.1126/science.1164382.

[8] Julie A. Ronchi, Tereza R. Figueira, Fernanda G. Ravagnani, et al. “Nicotinamide nucleotide transhydrogenase and mitochondrial redox balance: from physiology to pathology”. In: *Antioxidants & Redox Signaling* 24.16 (2016), pp. 845–857. DOI: 10.1089/ars.2015.6492.

[9] Rebecca Siegel et al. “Cancer Statistics, 2025”. In: *CA: A Cancer Journal for Clinicians* 75.1 (2025), pp. 1–29. DOI: 10.3322/caac.21871.

[10] American Cancer Society. “Cancer Facts & Figures 2024”. In: *American Cancer Society Reports* (2024). Estimated 2,001,140 new cases and 611,720 deaths in the U.S. in 2024.

[11] Otto Warburg. “On the origin of cancer cells”. In: *Science* 123.3191 (1956), pp. 309–314. DOI: 10.1126/science.123.3191.309.