Global Conference on Multidisciplinary Research and Innovation
Hosted Online from Berlin, Germany
Date: 2nd June, 2026
Website: https://econferencia.com

METABOLIC REPROGRAMMING AS A KEY MECHANISM OF ONCOGENESIS: FROM THE CLASSICAL THEORY OF SOMATIC MUTATIONS TO AN INTEGRATED MODEL OF CANCER

Amangeldieva Zhazira Nurlanovna
2nd-year student, Faculty of Pediatrics, EMU University Scientific

Bakhtiyar Utmisovich Pirnazarov,
Supervisor, Senior Lecturer, PhD,
Department of Chemical Sciences, EMU University
bakhtiyarpirnazar@gmail.com

Abstract

Cancer has traditionally been viewed as a genetic disease caused by the sequential accumulation of mutations in oncogenes and tumor suppressor genes. However, the literature increasingly shows a significant paradigm shift: oncogenesis is now understood as a complex, multilevel process in which metabolic and epigenetic disturbances may play a role that is at least as important as, and potentially more primary than, genetic alterations. This article provides a comprehensive analysis of modern views on the biochemical mechanisms of carcinogenesis. It examines the limitations of the classical mutation theory, discusses metabolic reprogramming in detail, including the Warburg effect and its modern interpretation, and considers the roles of reactive oxygen species, oncometabolites, environmental factors such as heavy metals, and the clinical prospects of targeted therapy. Special attention is given to the critical relationship among the genome, epigenome, and metabolome, the disruption of which underlies malignant transformation.

Global Conference on Multidisciplinary Research and Innovation
Hosted Online from Berlin, Germany
Date: 2nd June, 2026
Website: https://econferencia.com

Introduction

Despite decades of intensive research, cancer remains one of the leading causes of death worldwide. The somatic mutation theory has long been the dominant framework, according to which the accumulation of mutations in key genes regulating cell proliferation is the primary cause of carcinogenesis. This theory successfully explains many hereditary forms of cancer and is supported by the presence of characteristic mutations in tumor cells. However, it faces serious difficulties in explaining why normal tissues containing numerous mutations often do not become malignant, and how environmental factors that are not direct mutagens can induce cancer. Based on key publications from recent years, this review summarizes current evidence that integrates genetic, metabolic, and epigenetic aspects into a single, more complex model of oncogenesis.

Classical Paradigm: Oncogenes and Tumor Suppressors

To understand oncogenesis, it is necessary to distinguish between the two major classes of genes involved in this process. Proto-oncogenes encode proteins that stimulate cell division, differentiation, and survival. These include growth factors, their receptors such as EGFR, intracellular signaling proteins such as Ras and Src, and transcription factors such as Myc. Activating mutations, gene amplifications, or chromosomal translocations can convert proto-oncogenes into oncogenes, resulting in constitutive activation of proliferative pathways independent of external signals.

In contrast, tumor suppressor genes such as TP53, RB1, PTEN, and APC function as the “brakes” of the cell cycle by initiating DNA repair, cell-cycle arrest, or apoptosis in response to damage. According to Knudson’s two-hit hypothesis, both alleles must be inactivated for these genes to lose function. In the mutation-centric view of cancer, oncogenesis is driven by the gradual accumulation of key mutations

that provide selective advantage, while neutral mutations are considered biologically insignificant.

Challenges to the Somatic Mutation Theory

However, carcinogenesis cannot be explained solely by genetic abnormalities. Several studies have raised important objections to the idea that mutations alone are sufficient.

First, studies of normal tissues have shown that extensive genetic alterations, including mutations in canonical driver genes such as NOTCH1 and TP53, are widespread in phenotypically normal tissues such as eyelid skin and the esophagus, yet they rarely lead to tumor formation. This suggests that the presence of a mutation is necessary but not sufficient for malignant transformation.

Second, tumors have been identified that lack known key mutations. For example, in one study of brain ependymoma subtypes, a group displayed malignant behavior driven exclusively by aberrant epigenetic modifications in the complete absence of somatic mutations in genes that regulate tumor growth. In another subtype, neither mutations nor epigenetic abnormalities were detected, indicating the existence of yet unknown mechanisms that challenge the dogma of mutations as the sole primary cause of cancer.

Finally, the mutator phenotype has been discussed, namely the hypothesis that an early mutation in DNA repair genes causes hypermutability and accelerates tumor evolution. Although this is observed in hereditary nonpolyposis colorectal cancer (Lynch syndrome), mathematical models indicate that the accumulation of thousands of mutations typical of many solid tumors does not necessarily require an increased basal mutation rate. Prolonged clonal expansion from normal stem cells may be sufficient, particularly in rapidly renewing tissues such as the colon.

Metabolic Reprogramming and the Warburg Effect

A central concept in alternative models of carcinogenesis is metabolic reprogramming. In the 1920s, Otto Warburg observed a paradoxical phenomenon: even in the presence of adequate oxygen, cancer cells preferentially use aerobic glycolysis rather than oxidative phosphorylation. This phenomenon, known as the Warburg effect, involves increased glucose uptake and conversion of glucose to lactate. Although this pathway is energetically inefficient, yielding only 2 ATP per glucose molecule rather than the approximately 36 ATP generated by oxidative phosphorylation, it provides several key advantages to cancer cells.

First, glycolytic intermediates are diverted into the pentose phosphate pathway and other biosynthetic routes, supporting the production of nucleotides, amino acids, and lipids needed for rapid cell proliferation. Second, glycolytic metabolism allows cells to survive and proliferate under hypoxic conditions, whereas cells dependent on mitochondrial respiration are more vulnerable to death. Third, lactate secretion acidifies the extracellular environment, promoting degradation of the extracellular matrix and facilitating invasion and metastasis.

Activation of oncogenes such as MYC, KRAS, and PIK3CA, as well as inactivation of tumor suppressors such as TP53, directly reprogram cellular metabolism by increasing the expression of glucose transporters such as GLUT1 and key glycolytic enzymes including hexokinase 2 and pyruvate kinase M2.

Epigenetics and Metabolism

One of the most significant recent advances has been a deeper understanding of how metabolic changes influence the epigenome. Epigenetic modifications, including DNA methylation and histone acetylation and methylation, critically depend on the availability of metabolic substrates.

A classic example is one-carbon metabolism, which includes serine, glycine, and folate metabolism. These pathways generate S-adenosylmethionine (SAM), the universal methyl donor for DNA and histone methylation. Activation of MYC increases the expression of enzymes in this pathway, which supports proliferation but can also induce hypermethylation of tumor suppressor genes and thereby inactivate them.

The reverse relationship also exists: epigenetic enzymes regulate the expression of metabolic genes. In addition, so-called oncometabolites — metabolites that accumulate in tumor cells as a result of metabolic mutations — can directly inhibit epigenetic enzymes. Classical examples include succinate and fumarate in mutations of succinate dehydrogenase (SDH) and fumarate hydratase (FH), as well as 2-hydroxyglutarate (2-HG) in mutations of isocitrate dehydrogenase (IDH1/2). These metabolites competitively inhibit 2-oxoglutarate-dependent dioxygenases, including TET proteins involved in DNA demethylation and JmjC-domain-containing histone demethylases, thereby producing a global hypermethylation phenotype.

Reactive Oxygen Species and Toxic Metabolites

Paradoxically, tumor cells often display high levels of reactive oxygen species (ROS) despite strengthened antioxidant defenses, because of their hyperactive metabolism. Moderate ROS levels act as signaling molecules that promote proliferation, while excessive ROS cause oxidative damage to DNA, proteins, and lipids, contributing to genomic instability, another major driver of oncogenesis.

Researchers are also increasingly considering the accumulation of endogenous toxic metabolites as a therapeutic target. Recent studies have proposed exploiting metabolic vulnerabilities: if a pathway producing a toxic intermediate such as methylglyoxal or deoxyuridine triphosphate is hyperactive in a tumor cell,

inhibition of the next enzyme in that pathway may selectively poison and kill the cancer cell. This strategy differs from classical chemotherapy, which primarily targets DNA replication.

Environmental Triggers and Carcinogenesis

The mechanisms described above do not operate in isolation. They are activated by external factors. In addition to classical mutagens such as ultraviolet and ionizing radiation, non-mutagenic carcinogens also play an important role.

Heavy metals such as arsenic, cadmium, chromium, and nickel are classified as Group 1 carcinogens. However, their primary mechanism of action is often not direct DNA damage. Instead, they induce chronic oxidative stress, deplete intracellular antioxidant reserves such as glutathione, and, most importantly, cause profound epigenetic alterations. These include global or local changes in DNA methylation, histone modifications, and dysregulation of microRNAs, leading to aberrant gene expression without changes in nucleotide sequence.

Inflammation is another critical factor linking metabolism and oncogenesis. Chronic inflammation creates a microenvironment characterized by high levels of ROS and reactive nitrogen species, low pH, and hypoxia, all of which directly promote metabolic reprogramming and the selection of clones carrying mutations that help cells adapt to these stressful conditions.

Electron Acceptor Hypothesis

A novel and intriguing hypothesis suggests that carcinogens may act as artificial electron acceptors in glycolysis. According to this idea, a carcinogen binds to NADH and oxidizes it back to NAD+ in the cytosol. This replenishment of the NAD+ pool occurs without the involvement of mitochondria or the malate-aspartate shuttle, creating a “short-circuited” glycolytic pathway that is

energetically favorable for anaerobic survival and transformation. In this way, chronic exposure to such compounds may induce metabolic stress that precedes and contributes to genetic alterations.

Therapeutic Perspectives

Modern models of oncogenesis present genetic, epigenetic, and metabolic abnormalities as inseparably linked components of a complex system that generates a self-reinforcing cycle driving tumor progression. Metabolic reprogramming is no longer viewed as a passive consequence of mutations, but as an active driver of disease that itself contributes to genomic instability and epigenetic deregulation.

This understanding opens several therapeutic opportunities:

1. Inhibitors of metabolic enzymes, including molecules that block key enzymes of aerobic glycolysis such as pyruvate kinase M2 or enzymes involved in serine/glycine metabolism.
2. Dietary interventions, including calorie restriction and intermittent fasting, which are being studied as methods to reduce glucose and amino acid availability for tumor cells.
3. Targeted therapy against oncometabolites, with the successful use of mutant IDH inhibitors such as ivosidenib and enasidenib in gliomas and acute myeloid leukemia providing strong support for this approach.
4. Exploitation of metabolic plasticity by targeting compensatory pathways activated when the primary metabolic route is blocked, thereby helping overcome drug resistance.

Conclusion

The future of oncology requires a holistic systems-level approach that integrates genomics, metabolomics, and epigenomics. Only by understanding how metabolism, genetics, and the environment interact in the complex process of carcinogenesis can more effective and less toxic strategies for cancer prevention and treatment be developed.

References

1. Ibrahim, S. I., & Muhammad, F. Y. (2020). Cancer Aetiology and Progression: The Crucial Link between Genome, Epigenome and Metabolome. "Nigerian Journal of Basic and Clinical Sciences", 17(2), 77–83.
2. Zhu, Y., & Costa, M. (2020). Metals and molecular carcinogenesis. "Carcinogenesis", 41(9), 1161–1172.
3. Lee, N., Kim, D., & Kim, J. (2020). Endogenous toxic metabolites and implications in cancer therapy. "Oncogene", 39(35), 5709–5720.
4. Pan, S., Fan, M., Liu, Z., Li, X., & Wang, H. (2020). Serine, glycine and one-carbon metabolism in cancer (Review). "International Journal of Oncology", 58(2), 158–170.
5. Rao, U. S., et al. (2020). Are carcinogens electron acceptors? A novel hypothesis. "Medical Hypotheses", 144, 110235.
6. Park, J. H., Pyun, W. Y., & Park, H. W. (2020). Cancer Metabolism: Phenotype, Signaling and Therapeutic Targets. "Cells", 9(10), 2308.
7. Lemaire, J., et al. (2020). Fundamental aspects of oncogenesis. "Bulletin du Cancer", 107(11), 1148–1160.
8. Kontomanolis, E. N., et al. (2020). Role of Oncogenes and Tumor-suppressor Genes in Carcinogenesis: A Review. "Anticancer Research", 40(11), 6009–6015.