Austra & Lian Journal of Basic Sciences

australiansciencejournals.com/aljbs

E-ISSN: 2643-251X

VOL 05 ISSUE 05 2024

The Role of Biochemistry in Cancer Research and Therapy

Dr. Laura M. Chen

Department of Molecular Medicine, Harvard Medical School, Boston, USA

Email: *laura.chen@hms.harvard.edu*

Abstract: *Biochemistry plays a pivotal role in unraveling the molecular mechanisms of cancer, enabling early diagnosis, accurate prognosis, and the development of targeted therapies. From understanding oncogene expression and tumor metabolism to designing enzyme-inhibitor-based drugs, biochemical approaches provide deep insights into cancer pathophysiology. This article reviews recent advances in cancer biochemistry and their translation into therapeutic strategies. Furthermore, we examine the role of biomarkers, cell signaling cascades, and drug resistance mechanisms to demonstrate the utility of biochemistry in modern oncology.*

Keywords: *cancer metabolism, molecular biomarkers, signaling pathways, targeted therapy, drug resistance*

INTRODUCTION:

Cancer remains one of the leading causes of mortality worldwide, with millions of new cases diagnosed each year. The complexity of cancer lies in its molecular diversity and ability to adapt to therapeutic interventions. Biochemistry offers essential tools and perspectives to decipher this complexity at the molecular and cellular levels. Through the study of biomolecules and their interactions, biochemistry provides a framework to understand tumorigenesis, cell proliferation, apoptosis evasion, metastasis, and therapeutic resistance. Advances in biochemical methods have revolutionized cancer diagnostics and therapies, leading to precision medicine and improved patient outcomes.

1. Biochemical Basis of Tumorigenesis:

The biochemical foundation of cancer is rooted in the disruption of normal cellular homeostasis through genetic and epigenetic changes. **Proto-oncogenes** are genes that, under normal conditions, regulate cell growth and differentiation. When these genes undergo mutations, chromosomal translocations, or amplification, they become **oncogenes**—potent drivers of tumorigenesis. For instance, the **RAS gene**, when mutated, produces a constitutively active RAS protein that continuously sends growth-promoting signals via the MAPK and PI3K/AKT pathways, even in the absence of external stimuli. Similarly, **HER2** amplification leads to aggressive breast cancer subtypes by enhancing mitogenic signaling.

Tumor suppressor genes, on the other hand, function as cellular "brakes," regulating the cell cycle, DNA repair, and apoptosis. The **TP53 gene**, often called the "guardian of the genome," encodes the p53 protein, which halts the cell cycle in response to DNA damage and induces apoptosis if the damage is irreparable. Loss-of-function mutations in **TP53** occur in over 50% of human cancers, eliminating a crucial checkpoint that prevents malignant transformation. **BRCA1** and **BRCA2**, essential for homologous recombination repair of DNA double-strand breaks, when mutated, increase the risk of breast and ovarian cancers due to the accumulation of unrepaired genetic damage.

In addition to these genetic mutations, **epigenetic modifications** play a pivotal biochemical role in cancer development. Epigenetic regulation involves changes that affect gene expression without altering the DNA sequence. **DNA methylation**, particularly at **CpG islands** in promoter regions, can silence critical tumor suppressor genes. For example, **CDKN2A**, which encodes the p16 protein, is frequently hypermethylated in various carcinomas, leading to unregulated cyclin D/CDK4 activity and progression through the G1 phase of the cell cycle. **Histone modifications**, such as acetylation by histone acetyltransferases (HATs) or deacetylation by histone deacetylases (HDACs), further control chromatin accessibility. Hypoacetylation of histones often correlates with gene repression and is associated with aggressive tumor phenotypes.

The biochemical landscape of tumor cells is also marked by a **loss of cell cycle control**. Cyclins and cyclin-dependent kinases (CDKs) orchestrate the orderly progression of the cell cycle. In cancer, overexpression of cyclins (e.g., cyclin D1) or mutation of CDKs leads to unchecked cell cycle progression. Furthermore, the degradation of CDK inhibitors such as **p21** and **p27**, often mediated by proteasomal pathways, further enhances this dysregulation.

A defining biochemical hallmark of cancer is **apoptosis evasion**—the ability of tumor cells to resist programmed cell death. This resistance is mediated through upregulation of **anti-apoptotic proteins** like **Bcl-2, Bcl-xL**, and **IAPs** (inhibitor of apoptosis proteins), and downregulation or mutation of **pro-apoptotic proteins** such as **Bax**, **Bak**, and **caspase-3**. The mitochondrial (intrinsic) apoptosis pathway is particularly affected, where disruption of mitochondrial membrane potential and cytochrome c release is prevented, leading to survival of genetically abnormal cells.

These biochemical abnormalities work in concert to promote **genomic instability**, a key enabler of cancer evolution. Genomic instability allows for the accumulation of additional mutations that confer resistance to therapy, metastatic potential, and immune evasion. Thus, understanding the biochemical basis of tumorigenesis provides a critical platform for developing molecular diagnostics, prognostic markers, and targeted therapeutic interventions.

2. Cancer Metabolism and the Warburg Effect:

Cancer cells exhibit a profound shift in energy metabolism, a phenomenon famously described as the **Warburg effect**, wherein they preferentially utilize **aerobic glycolysis** over mitochondrial oxidative phosphorylation, even in oxygen-rich environments. This metabolic reprogramming is not a consequence of damaged mitochondria—as once assumed—but rather a strategic adaptation to support rapid growth, survival in hypoxic conditions, and immune evasion. By channeling glucose through glycolysis, cancer cells produce ATP at a faster rate and accumulate biosynthetic precursors (e.g., ribose-5-phosphate, acetyl-CoA) essential for nucleic acid, lipid, and protein synthesis—crucial for tumor proliferation. The overexpression of **glucose transporters (GLUT1, GLUT3)** facilitates enhanced glucose uptake, while key glycolytic enzymes such as **hexokinase 2 (HK2)** and **pyruvate kinase M2 (PKM2)** are upregulated to sustain flux through the glycolytic pathway.

A significant biochemical consequence of aerobic glycolysis is the **elevated production of lactate**, catalyzed by **lactate dehydrogenase A (LDH-A)**, which converts pyruvate into lactate. The excessive

lactate is expelled into the extracellular space via **monocarboxylate transporters (MCT1/4)**, resulting in acidification of the tumor microenvironment. This acidic environment plays a critical role in promoting angiogenesis, enhancing matrix degradation, and facilitating cancer cell invasion and metastasis. Furthermore, it impairs immune surveillance by inhibiting cytotoxic T-cell function and promoting regulatory T-cell activity. Such biochemical changes make the tumor more aggressive and resistant to immune-mediated clearance.

Moreover, while mitochondria in cancer cells are not universally defective, many exhibit **mitochondrial dysfunction** or downregulate oxidative phosphorylation to evade apoptosis. **Mutations in TCA cycle enzymes** such as **isocitrate dehydrogenase (IDH1/2)**, **succinate dehydrogenase (SDH)**, and **fumarate hydratase (FH)** contribute to the accumulation of oncometabolites (e.g., 2-hydroxyglutarate, succinate, fumarate) that inhibit DNA and histone demethylases, leading to widespread epigenetic alterations and tumorigenesis. Transcription factors like **hypoxia-inducible factor-1α (HIF-1α)** further exacerbate this metabolic shift by activating genes encoding glycolytic enzymes and angiogenic factors under hypoxic conditions—common within solid tumors.

Given these distinct metabolic features, cancer metabolism is an attractive therapeutic target. Inhibitors like **FX11 (LDH-A inhibitor)**, **3-bromopyruvate (HK2 inhibitor)**, and **2-deoxy-D-glucose (2-DG)** interfere with glycolysis and have shown promise in preclinical studies. **Metformin** and **phenformin**, known mitochondrial complex I inhibitors, reduce ATP production and increase AMP/ATP ratio, activating **AMP-activated protein kinase (AMPK)** and inhibiting **mTOR**, thereby impeding tumor growth. **Glutaminase inhibitors** target the glutamine addiction of many tumors, especially those with MYC overexpression. These approaches, particularly when combined with immunotherapy or chemotherapy, may enhance treatment efficacy and reduce relapse.

In conclusion, the Warburg effect illustrates how cancer cells rewire their biochemical processes to create a survival advantage. This metabolic plasticity not only fuels tumor growth but also orchestrates immune evasion and therapy resistance. Understanding and therapeutically targeting these cancer-specific metabolic pathways offers a promising route to disrupt tumor progression and improve patient outcomes in modern oncology.

3. Biochemical Signaling Pathways in Cancer Progression:

The uncontrolled progression of cancer is not merely the result of genetic mutations alone but is critically sustained by the **dysregulation of intricate biochemical signaling pathways** that mediate essential cellular functions such as proliferation, differentiation, apoptosis, angiogenesis, and immune evasion. Three of the most widely implicated and biochemically complex pathways in cancer are the **PI3K/AKT/mTOR**, **MAPK/ERK**, and **JAK/STAT** cascades, each functioning as central conduits of external and internal cues that guide cellular fate.

The **PI3K/AKT/mTOR pathway** is frequently activated in a broad spectrum of malignancies. When growth factors bind to **receptor tyrosine kinases (RTKs)**—such as EGFR or HER2—it triggers phosphorylation cascades that recruit and activate **phosphoinositide 3-kinase (PI3K)**. PI3K converts PIP2 to PIP3, which in turn recruits **AKT** to the plasma membrane where it becomes phosphorylated and fully activated. Activated AKT orchestrates a wide array of downstream responses: it inhibits pro-apoptotic proteins (e.g., Bad, Bax), promotes glucose uptake via GLUT1 translocation, and activates **mTOR**, a master regulator of protein synthesis, autophagy, and cell cycle progression. Mutations in **PIK3CA**, the gene encoding the catalytic subunit of PI3K, or loss of the tumor suppressor **PTEN** (a phosphatase that degrades PIP3) result in constitutive AKT signaling, fostering a microenvironment that supports uncontrolled proliferation and survival.

The **MAPK (Mitogen-Activated Protein Kinase) pathway**, often triggered in parallel, is initiated by binding of ligands to RTKs followed by activation of **RAS**, a small GTPase. RAS activates **RAF** kinases, which phosphorylate **MEK1/2**, which in turn activate **ERK1/2**. These ERK kinases translocate into the nucleus to regulate transcription factors like ELK1, MYC, and FOS, thereby promoting expression of genes responsible for cell cycle progression (e.g., cyclin D), migration, and angiogenesis. Oncogenic mutations in **RAS (e.g., KRAS)** or **BRAF (especially BRAF V600E)** result in persistent downstream signaling independent of external growth signals, contributing to the hallmark cancer trait of self-sufficiency in growth signals.

The **JAK/STAT pathway**, although originally recognized for its role in immune regulation and hematopoiesis, is now acknowledged as a major contributor to solid tumor biology. Upon cytokine or growth factor binding (e.g., IL-6, IFN-γ), **Janus kinases (JAKs)** phosphorylate specific tyrosine residues on the receptor, creating docking sites for **Signal Transducers and Activators of Transcription (STATs)**. Phosphorylated STATs dimerize and translocate to the nucleus, where they upregulate genes involved in anti-apoptosis (e.g., Bcl-xL), angiogenesis (e.g., VEGF), and immune suppression (e.g., PD-L1). Hyperactivation of **STAT3**, often due to aberrant upstream cytokine signaling or constitutively active JAKs (as seen in JAK2 V617F mutation in myeloproliferative disorders), has been linked to tumor proliferation, inflammation-driven cancers, and resistance to chemotherapy.

Importantly, these signaling pathways exhibit **extensive crosstalk** and **redundancy**, which not only enhances cellular plasticity but also complicates therapeutic targeting. For example, inhibition of the MAPK pathway with MEK inhibitors often leads to compensatory activation of the PI3K/AKT axis, thereby sustaining cell survival. Additionally, STAT3 can be activated downstream of both RTKs and non-receptor tyrosine kinases (like Src), integrating signals from multiple sources to maintain malignancy. This crosstalk is particularly relevant in **epithelial-to-mesenchymal transition (EMT)**, where signals from TGF-β, MAPK, and STAT3 converge to induce transcriptional repressors (e.g., Snail, Twist) that diminish E-cadherin and promote metastatic potential.

Recognizing these pathways' centrality to tumor biology has catalyzed the development of **pathway-specific inhibitors**, especially **tyrosine kinase inhibitors (TKIs)** that block upstream RTKs or downstream effectors. Examples include **erlotinib** and **gefitinib** (targeting EGFR in lung cancer), **trastuzumab** (targeting HER2 in breast cancer), **vemurafenib** (targeting BRAF V600E in melanoma), and **ruxolitinib** (JAK1/2 inhibitor in myelofibrosis). However, the development of **resistance**—via secondary mutations, bypass signaling, or feedback reactivation—necessitates the use of **combination therapies** and **adaptive treatment regimens**. Current research emphasizes integrating **genomic profiling** with targeted therapy selection, enabling personalized strategies that overcome compensatory signaling and prolong treatment efficacy.

In summary, the biochemical signaling pathways PI3K/AKT, MAPK, and JAK/STAT are master regulators of cancer cell behavior. Their dysregulation not only drives uncontrolled proliferation and survival but also promotes invasion, metastasis, immune escape, and resistance. A deep biochemical understanding of these pathways is essential for the rational design of targeted therapies and the ongoing evolution of precision oncology.

4. Molecular Biomarkers and Diagnostic Applications:

The advancement of cancer diagnostics and treatment has been profoundly influenced by the discovery and clinical application of **molecular biomarkers**, which serve as biochemical fingerprints of tumor presence, behavior, and response to therapy. These biomarkers, which may include **proteins, nucleic acids, metabolites, or cellular receptors**, provide a window into the molecular makeup of cancer cells and enable

a more **individualized approach** to diagnosis and treatment planning. A quintessential example is **HER2 (Human Epidermal Growth Factor Receptor 2)**, a transmembrane receptor tyrosine kinase that is amplified or overexpressed in a subset of breast and gastric cancers. HER2 status is now routinely tested in patients with these cancers, as HER2-positive tumors respond favorably to targeted monoclonal antibody therapies like **trastuzumab** and **lapatinib**, which have significantly improved survival rates. Another notable biomarker, **prostate-specific antigen (PSA)**, is a serine protease produced by prostatic epithelial cells; its elevation in serum serves as a cornerstone in prostate cancer screening, prognosis, and post-treatment surveillance. Similarly, **CA-125**, a high-molecular-weight glycoprotein, is extensively used for monitoring therapy and recurrence in ovarian cancer.

These **biochemical markers serve multiple roles** in oncology. They enable **early detection**, often before clinical symptoms emerge, which is crucial for improving long-term survival. They aid in **stratifying patients** by molecular subtype, thereby guiding therapeutic decisions, and help in assessing **treatment efficacy** and disease recurrence through serial monitoring. Biomarkers also assist in **risk assessment**, as seen with germline mutations in **BRCA1/2**, which predict susceptibility to breast and ovarian cancers and influence preventive strategies. Furthermore, the advent of **liquid biopsy**, involving the detection of circulating tumor DNA (ctDNA), RNA, or exosomes in blood, allows for non-invasive and dynamic monitoring of tumor evolution and minimal residual disease—particularly useful in metastatic settings or when tissue biopsy is not feasible.

The detection and quantification of biomarkers rely heavily on **biochemical assays** and molecular techniques. **ELISA (enzyme-linked immunosorbent assay)** remains a mainstay for quantifying circulating protein biomarkers like CEA and AFP in clinical laboratories due to its simplicity and sensitivity. **Western blotting** and **mass spectrometry** offer higher resolution and specificity, especially for novel biomarker discovery in research settings. **Immunohistochemistry (IHC)** and **fluorescence in situ hybridization (FISH)** are tissue-based methods employed to assess protein expression and gene amplification respectively, particularly for HER2, ALK, or PD-L1 testing. These methods not only confirm histopathologic diagnoses but also determine patient eligibility for targeted immunotherapies. Moreover, **real-time PCR**, **digital droplet PCR**, and **next-generation sequencing (NGS)** have become essential in the detection of single nucleotide mutations, insertions/deletions, gene fusions, and copy number variations, such as **EGFR mutations in lung cancer**, or **BRAF mutations in melanoma**.

In parallel, **molecular imaging techniques** are playing an increasingly significant role in visualizing biomarkers in vivo. **PET (positron emission tomography)** scanning with radiolabeled tracers like **18F-FDG** enables visualization of tumor metabolic activity. Advanced radiotracers that specifically target PSMA, HER2, or somatostatin receptors have been developed to enhance diagnostic specificity and enable **theranostics**—the combination of diagnostics and therapeutics—such as using **radioligand therapy** in metastatic prostate cancer. Fluorescent and bioluminescent probes are also being explored for **intraoperative imaging**, allowing surgeons to better identify tumor margins during resection.

Despite their immense promise, molecular biomarkers come with challenges. Tumor **heterogeneity** can result in variable biomarker expression across different regions or metastatic sites, affecting diagnostic accuracy. Some biomarkers lack **specificity** and may be elevated in benign conditions (e.g., PSA in prostatitis), leading to false positives. Moreover, **resistance mutations** may alter biomarker profiles over time, necessitating continuous monitoring and adaptive therapeutic strategies.

In conclusion, molecular biomarkers are indispensable tools in the modern cancer care continuum—from **early detection and diagnosis** to **therapeutic targeting and monitoring**. As biochemical technologies

continue to evolve, the discovery of novel biomarkers and the refinement of detection platforms will pave the way for more **personalized, accurate, and effective** cancer management strategies.

5. Biochemical Approaches in Drug Discovery and Resistance:

The integration of biochemistry into cancer drug discovery has ushered in a new era of **precision oncology**, where therapeutic agents are no longer discovered by chance but are **intelligently designed** based on the detailed molecular architecture of their targets. This approach, known as **structure-based drug design (SBDD)**, uses high-resolution structural data of biomolecules—such as enzymes, receptors, or mutated proteins—obtained through techniques like **X-ray crystallography**, **nuclear magnetic resonance (NMR)**, and **cryo-electron microscopy (cryo-EM)**. These tools allow researchers to visualize **binding pockets, allosteric sites, and conformational dynamics** of target proteins, enabling the design of small molecules or biologics that interact with exceptional specificity and affinity. For instance, the development of **kinase inhibitors** was significantly enhanced by understanding the active site conformations of enzymes such as **ABL**, **BRAF**, or **EGFR**. The **EGFR T790M mutation**, which causes resistance to first-generation inhibitors, was counteracted by designing third-generation molecules like **osimertinib** that bind irreversibly to the mutant receptor with improved selectivity and reduced toxicity. Such structure-guided innovation has led to the development of **hundreds of FDA-approved oncology drugs** in the past two decades.

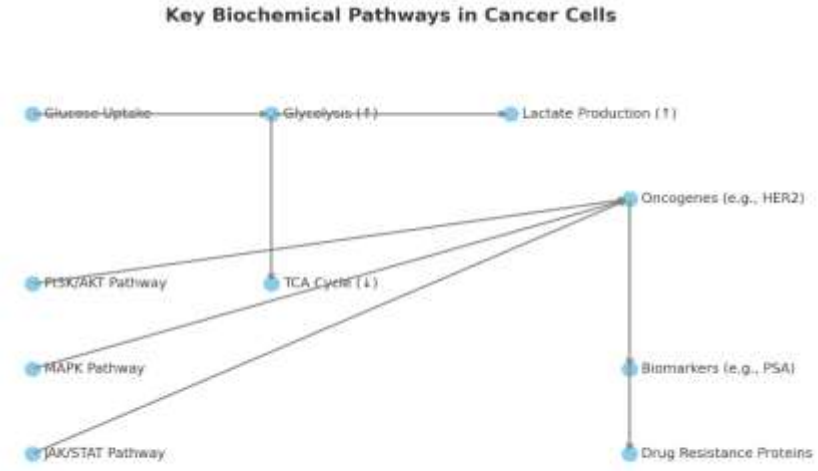
However, the dynamic nature of cancer biology often leads to **biochemical drug resistance**, a major hurdle in sustained therapeutic efficacy. This resistance is multifactorial and may arise through **pharmacokinetic**, **cellular**, or **molecular mechanisms**. One common biochemical route involves **overexpression of efflux transporters** such as **P-glycoprotein (P-gp)** and **MRP1 (multidrug resistance protein 1)**, which actively pump chemotherapeutic agents out of the cells using ATP hydrolysis, thus reducing drug accumulation to sub-lethal levels. These transporters are not only upregulated in response to drug exposure but can also be constitutively expressed in certain cancer subtypes. Another well-known mechanism is the **upregulation of detoxifying enzymes** like **glutathione S-transferases (GSTs)**, which conjugate toxic drugs to glutathione, making them more water-soluble and ready for excretion. This process reduces drug potency before it reaches its intended intracellular targets. Additionally, **mutations in drug targets**, such as in the **kinase domain of BCR-ABL (T315I)** or **EGFR**, result in decreased drug binding affinity. Cancer cells may also bypass the inhibited signaling node by **activating compensatory pathways** (e.g., PI3K/AKT or MET signaling), thereby maintaining downstream proliferation and survival signals despite the presence of a targeted inhibitor.

In response to these biochemical adaptations, **omics technologies**—especially **proteomics** and **metabolomics**—have become indispensable in understanding resistance landscapes. **Proteomics**, using advanced mass spectrometry, enables researchers to examine the global protein expression profile of cancer cells before and after drug exposure. It reveals **phosphorylation events**, **protein–protein interaction networks**, and **feedback loops** that contribute to resistance. For example, resistance to PI3K inhibitors may be associated with reactivation of **MAPK signaling**, which can be detected through increased phosphorylation of ERK1/2 or MEK proteins. Meanwhile, **metabolomics** tracks the concentration of metabolites and flux through key pathways, such as **glycolysis, glutaminolysis, or lipid synthesis**. Resistant cancer cells often undergo metabolic rewiring to sustain ATP production and redox balance, which can be detected by elevated levels of **lactate, NADPH, or glutamate**. These insights are not only diagnostic but also **therapeutically actionable**, allowing for the development of **dual-targeting strategies**. The application of these biochemical findings has resulted in **rational drug combinations** aimed at **preempting or reversing resistance**. For instance, combining **MEK inhibitors** with **PI3K inhibitors** can block parallel survival pathways, while pairing **Bcl-2 inhibitors** with chemotherapy can restore apoptotic

sensitivity. Moreover, **co-administration of efflux pump inhibitors** or **glutathione synthesis inhibitors** with standard chemotherapy may improve drug retention and potency. **Artificial intelligence (AI)** and **systems biology** are also being employed to model resistance networks and simulate the effects of various drug combinations on signaling pathways and metabolic flux, accelerating the discovery of effective therapeutic regimens.

In essence, the modern paradigm of drug discovery in oncology is deeply rooted in **biochemical understanding**, and overcoming resistance requires **multi-dimensional strategies** grounded in molecular data. As biochemical profiling becomes more sophisticated, it will not only enable the creation of highly selective and potent drugs but also allow real-time monitoring of therapeutic responses and the early detection of resistance, paving the way for **adaptive and personalized cancer treatment frameworks**.

Key Biochemical Pathways in Cancer Cells



Summary:

Biochemistry has emerged as a cornerstone in cancer research, enabling the dissection of molecular abnormalities that drive tumor development and resistance. By focusing on altered biochemical pathways and identifying molecular targets, researchers have developed more effective diagnostic tools and therapeutic agents. As cancer treatment increasingly moves toward individualized approaches, the integration of biochemical techniques with genomic and proteomic data will be crucial. The continued evolution of biochemistry-based technologies promises earlier diagnoses, improved therapies, and a better understanding of cancer biology.

References:

- Hanahan, D., & Weinberg, R. A. (2011). Hallmarks of cancer: the next generation. Cell, 144(5), 646–674.
- Pavlova, N. N., & Thompson, C. B. (2016). The emerging hallmarks of cancer metabolism. Cell Metabolism, 23(1), 27–47.
- Vousden, K. H., & Lane, D. P. (2007). p53 in health and disease. Nature Reviews Molecular Cell Biology, 8(4), 275–283.
- Vander Heiden, M. G., et al. (2009). Understanding the Warburg effect: the metabolic requirements of cell proliferation. Science, 324(5930), 1029–1033.

- Sawyers, C. L. (2004). Targeted cancer therapy. Nature, 432(7015), 294–297.
- Hynes, N. E., & Lane, H. A. (2005). ERBB receptors and cancer: the complexity of targeted inhibitors. Nature Reviews Cancer, 5(5), 341–354.
- Jemal, A., et al. (2020). Global cancer statistics 2020. CA: A Cancer Journal for Clinicians, 70(1), 7–30.
- Sharma, S. V., et al. (2010). Drug resistance in cancer: mechanisms and models. Cell, 141(1), 69–80.
- Postovit, L. M., et al. (2007). Targeting the tumor microenvironment: a strategy to combat drug resistance. Current Drug Targets, 8(6), 688–695.
- Engelman, J. A. (2009). Targeting PI3K signalling in cancer: opportunities, challenges and limitations. Nature Reviews Cancer, 9(8), 550–562.
- Golub, T. R., et al. (1999). Molecular classification of cancer: class discovery and class prediction by gene expression monitoring. Science, 286(5439), 531–537.
- Wishart, D. S. (2016). Emerging applications of metabolomics in drug discovery and precision medicine. Nature Reviews Drug Discovery, 15(7), 473–484.