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Review Article

Cancer as a Systems Biochemical Disease: Multi-Omics Integration of Metabolomics, Proteomics, and Epigenomics

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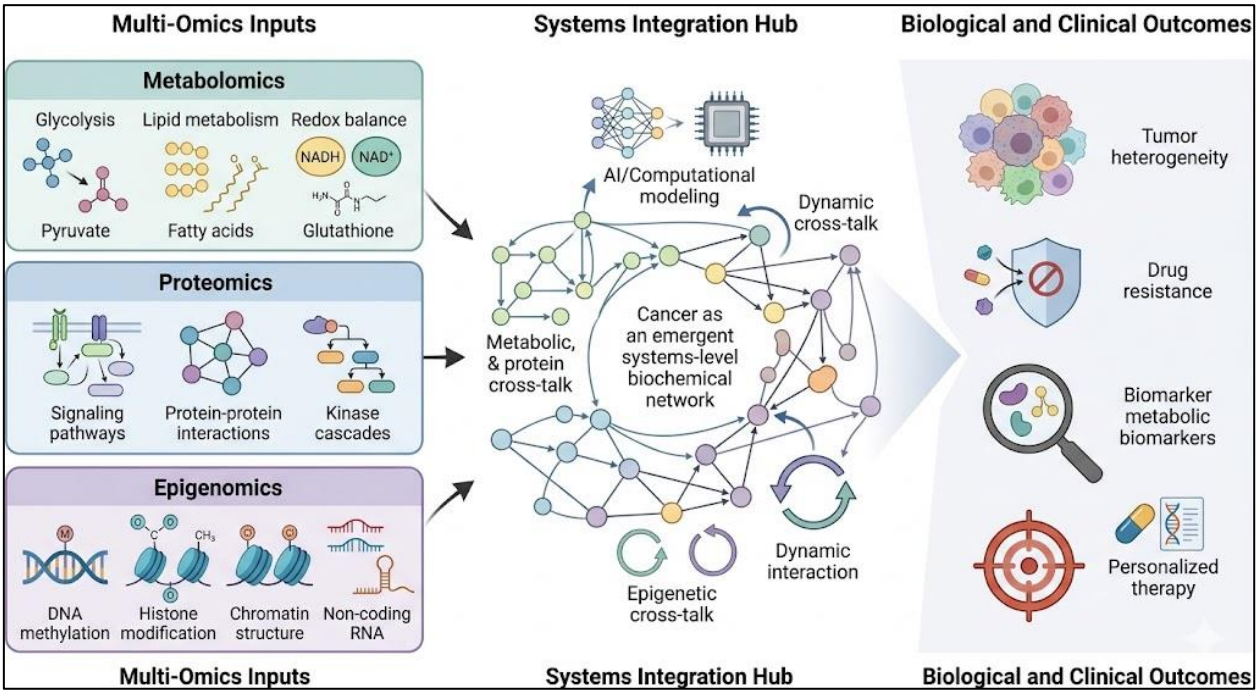
Abstract



Graphical Abstract

Cancer is now being viewed not as a single genetic disease but as a multi-layered, multi-level disease that exists on a systems level and is a biochemical process that is powered by dynamic, multi-layered interactions with molecules. This review will take the systems biology approach by combining metabolomics, proteomics, and epigenomics to explain the biochemical heterogeneity and adaptive plasticity of cancer. The bioenergetic requirements of growing tumor cells are manifested through metabolomic reprogramming which is the altered glycolysis, lipid metabolism, and redox balance. Simultaneously, proteomic changes remodel signaling pathways, which mediate cell survival, immune resistance, and treatment resistance. Additional epigenomic changes such as DNA methylation, changes in histone positioning and regulation of non-coding RNAs also coordinate the pattern of gene expression without changing the sequence of the DNA itself. The intersection of these layers of omics points to cancer as an outcome of interdependent biochemical processes, and not single events at the molecular level. Recent developments in the field of multi-omics integration, which has been

made possible by the high-throughput and computational modeling technologies, have allowed the discovery of new biomarkers and therapeutic targets with greater specificity and predictive capability. Notably, this integrative model changes the existing paradigm of reductionist approaches to the holistic tumor biology concept. This review identifies the opportunity of systems-level knowledge in informing precision oncology by mapping cross-talk between metabolic pathways, protein networks, and epigenetic landscapes. Finally, the combination of multi-omics information offers a strong foundation to unlock the complexity of tumors, enhance the early diagnosis of cancer, and inform the design of tailored therapeutic approaches during cancer treatment.

Keywords: Tumor heterogeneity, Systems biology, Precision oncology, Molecular networks, Biomarker discovery, Therapeutic resistance.

1. INTRODUCTION

Cancer is one of the major causes of death in the global population and is highly complex and heterogeneous in terms of biology of the tissues, people, and the progression of the disease (Pina-Sanchez *et al.,* 2021). Conventionally, cancer has been cognized under a gene-based paradigm with oncogenes and tumor suppressor genes taking center stage. Although this view has greatly enhanced our knowledge of tumorigenesis, it does not fully explain the dynamic and interdependent nature of biochemical processes that regulate cancer development and progression (Hanahan *et al.,* 2022). There is growing evidence that cancer needs to be viewed as a systems-level biochemical disease, in which multiple layers of interaction between molecules can result in emergent pathological phenotypes. The main concept of this systems view is the combination of multi-omics technologies, especially metabolomics, proteomics, and epigenomics. All these domains offer a unique but complementary perspective on cellular functioning. Metabolomics is a downstream biochemical reflection of cells and provides real-time data of metabolic fluxes and pathway changes (Patti *et al.,* 2012). Cancer cells undergo significant metabolic reorganization with increased glycolysis, mitochondrial dysfunction, and lipid and amino acid catabolic derangements. These metabolic changes are not just a result of genetic mutations but rather an active process that drives tumor growth, survival, and adaptation to the microenvironmental stress. Proteomics, conversely, enlist the functional agents of cellular processes. Proteins mediate signaling pathways, enzymes reactions and cell structure, and thus are at the forefront of cancer biology (Hanahan *et al.,* 2011). Post-translational alterations, aberrant protein expression, and protein-protein interactions all play a role in oncogenic signaling cascades and mechanisms of resistance. Proteomic changes, in contrast to genomic alterations, are extremely dynamic and context-specific and indicate intrinsic cellular conditions and extrinsic environmental effects. This renders proteomics especially useful in the identification of actionable therapeutic targets and interpretation of variability in drug response (Prasad *et al.,* 2017).

Another important dimension that is critical is epigenomics, which controls the expression of genes without causing changes in the DNA sequence (Chatterjee *et al.,* 2015). DNA methylation, histone modifications and chromatin remodelling are epigenetic processes that have a key role in controlling cellular identity and plasticity. They are often dysregulated in cancer, causing silencing of tumor suppressor genes and activation of oncogenic pathways. In addition, the epigenetic changes can be reversed, and this feature makes them be of interest to therapeutic interventions. The interrelationship between epigenetic regulation and metabolic processes further reflects the interconnected nature of cancer biology with metabolites frequently acting as cofactors of epigenetic enzymes (Wang *et al.,* 2021). Combining metabolomics, proteomics and epigenomics is a paradigm shift in cancer studies. Multi-omics integration does not analyze the layers separately, but instead allows cross-talks between molecular networks to be identified, and thus how perturbations in one area spread throughout the system to affect the overall cellular behavior. The recent developments in the field of high-throughput sequencing, mass spectrometry, and computational modeling have enabled the creation and analysis of mass-scale multi-omics data. Such technologies enable the researcher to create a complete molecular portrait of the tumor, revealing new biomarkers and therapeutic weaknesses (Jiang *et al.,* 2025).

Notably, this knowledge at the systems level has important implications for precision oncology. Multi-omics can help treat patients more effectively and stratify them more accurately by capturing the complexity of tumor biology (Raufaste-Cazavieille *et al.,* 2022). As an example, metabolic signatures can be combined with proteomic and epigenetic data to enhance the prediction of drug response and establish drug resistance mechanisms. Moreover, the capability of tracking dynamic alterations among various omics strata can give insights into tumor development and the adaptation of treatment over time. Despite these developments, there are still a few challenges. Integration, standardization, and interpretation of data are complex computational processes that need interdisciplinary knowledge (Abdelaziz *et al.,* 2024). Moreover, to translate the multi-omics results into clinical practice, there is a need to have strong validation and cost-effective implementation measures. However, the further evolution of integrative models is very promising in redefining cancer as a systems-biochemical disease. In that regard, this review will synthesize the existing knowledge on the integration of metabolomics, proteomics, and epigenomics in cancer studies. By emphasizing the interrelationship of these molecular layers, it offers a broad view of tumor biology

and emphasizes the possible power of multi-omics methodologies to propel radiological, prognostic, and treatment innovation.

2. Reframing Cancer as a Systems Biochemical Disease

2.1 Limitations of Reductionist and Gene-Centric Models

The established paradigm of gene-centric research has held preeminence in cancer research since the discovery of oncogenes and tumor suppressor genes and has focused on these events as the major cause of tumorigenesis (Huang *et al.,* 2025). Although this model has given important insights on how cancer starts and progresses, it is overly simplistic in the understanding of tumor biology. Cancer is not the sum of the independent genetic changes but is, in fact, the result of dynamic, context-specific interactions on a number of molecular layers. The reductionist methods do not tend to explain the phenotypic diversity observed between tumors of similar mutational background, pointing to the lack of connection between genotype and cellular phenotype. Furthermore, these models do not explain well the adaptive responses to environmental stressors, metabolic rewiring, and the development of therapeutic resistant situations. There is growing evidence that the same genetic mutations may have divergent effects based on cellular context, epigenetics and metabolic conditions (Chen *et al.,* 2022). This weakness highlights the fact that it is necessary to shift away beyond linear causality and to integrative models that reflect the multidimensionality of cancer biology.

2.2 Emergence of Systems Biology in Cancer Research

Systems biology has become a paradigm shift approach that aims to understand how biological systems are interconnected and interacting networks, rather than focusing on individual components (Wang, Maron *et al.,* 2015). When applied in the context of cancer, the method allows the study of the whole set of molecular interactions at the genomic, transcriptomic, proteomic, and metabolomic levels. Systems biology can be used by exploiting the high-throughput technology and computational modeling to construct network-based models of the dynamic behaviour of tumor cells. Such a change enables one to determine important nodes, feedback, and regulatory circuits controlling cancer development. Particularly, systems-level studies have shown that tumor phenotypes are the result of a collective action of the interrelated pathways and not individual molecular events. This is similar to the conception of cancer as a biochemical system whereby perturbation moves through networks to affect cellular behavior (Kuenzi and Ideker 2020). Subsequently, systems biology is not only more useful in improving mechanistic knowledge but also in finding multi-target therapeutic solutions and predictive biomarkers.

2.3 Biochemical Network Theory and Disease Emergence

Biochemical network theory offers an underlying theory of the development of complex diseases such as cancer by the failure of molecular systems that are tightly regulated as shown in Figure 1 (Ryall and Tan 2015). Cellular functions are regulated by complex systems of metabolic routes, protein-protein interactions and regulation systems that ensure homeostasis in physiological settings. These networks in cancer get out of control resulting to nonlinear and emergent behaviour which cannot be predicted by individual analysis. Robustness, redundancy and adaptability are common features of network perturbations, which allow tumor cells to continue growing in the presence of genetic instability and external stress. The emergence concept is especially important, since it is the way global phenotypic properties are formed, including uncontrolled proliferation, immune evasion and metastasis, through local interactions of molecules (Haynes, Chadwick *et al.,* 2024). Moreover, network theory draws attention to the existence of hub molecules and critical transition points, the dysregulation of which can have a disproportional effect on the behavior of the system. Knowledge of these network dynamics is fundamental to the detection of vulnerability that can be used in the therapeutic intervention.

2.4 Interconnected Molecular Layers Driving Tumor Complexity

The complexity of tumors is basically the interaction between several layers of molecules such as metabolism, protein activities, and the regulation of epigenetics (Catalano, D'Angelo *et al.,* 2025). These layers are not independent; rather, they are closely related with each other in terms of bidirectional feedback processes. An example is that the metabolic intermediate may act as a cofactor to an epigenetic enzyme and thus, affect the chromatin structure and the expression of genes. Similarly, proteomic changes coordinate enzymatic functions and signal transduction which, respectively, rearrange metabolism and epigenetic conditions. Such cross-talk results in a very adaptive and heterogeneous tumor environment, which allows cancer cells to adapt very quickly to therapeutic forces, as well as changes in microenvironment. Particularly, the combination of these molecular dimensions shows that tumor behavior cannot be determined by only one dominant pathway but is a result of the synchronized actions of complex biochemical networks (Yang, Yu *et al.,* 2023). It is important to note that this interrelatedness is the key to the redefinition of cancer as a systems biochemical disease and that it forms the fundamental basis to develop integrative and precision-based treatments.

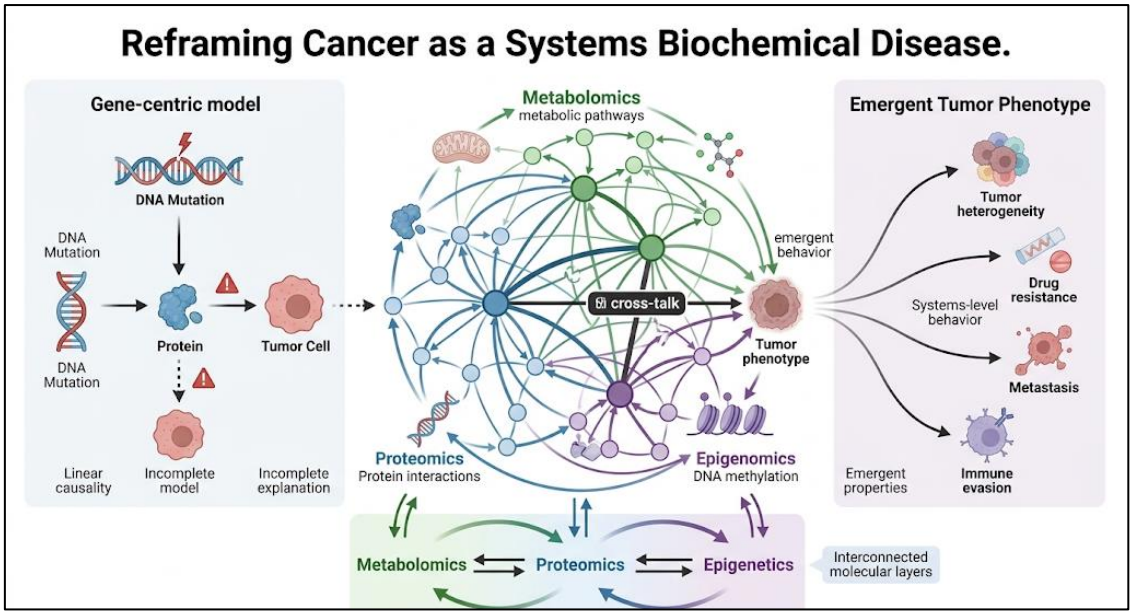


Figure 1: Cancer reframed as a systems-level biochemical disease, where interconnected metabolic, proteomic, and epigenetic networks drive complex tumor behaviors beyond simple gene mutations.

3. Metabolomic Reprogramming as the Biochemical Core of Cancer

Metabolomic reprogramming is one of the most characteristic elements of cancer and metabolism is not only a secondary effect of oncogenic remodelling, but it is also a primary cause of tumor initiation, development, and plasticity. Metabolic changes in a systems biology context are closely connected to proteomic signal networks and epigenetic regulation, which collectively determine tumor behavior in the context of dynamic constraints of the microenvironment. There is a constant reorganization of the metabolic circuitry of cancer cells to maintain high proliferation, avoid immune surveillance and survive nutrient starvation and hypoxia (Zhang, Li *et al.,* 2024). This metabolic plasticity is a very well-coordinated biochemical adaptation, in which flux via glycolytic, lipid and amino acid pathways is regulated to address bioenergetic and biosynthetic needs. Also, there is growing evidence that metabolites themselves are regulatory molecules, which mediate signaling cascades and epigenomic conditions, which further support cancer as a systems-level biochemical illness.

3.1 Aerobic Glycolysis and Energy Redistribution (Warburg Effect Revisited)

The classical theory of aerobic glycolysis, known as the Warburg effect has been transformed into a complex theory of resource allocation in metabolism (DeBerardinis and Chandel 2020). The conversion of glucose to lactate is not only preferred by cancer cells over glucose breakdown in the mitochondria despite the presence of oxygen, but it is also a calculated move on the part of the cancer cell to assist in anabolic growth. The diversion of the glycolytic intermediates into the biosynthetic pathways (nucleotide, amino acid, and lipid) is made possible by this shift and is needed to support the rapid cell division. Recent studies indicate that this metabolic phenotype is dynamically controlled by oncogenic signaling pathways and tumor microenvironmental signals. Metabolic flux is connected to proteomic alterations, with key enzymes of glycolysis being regulated by post-translational modification. Moreover, lactate, which was previously regarded as a waste product of metabolism, has been identified as a signaling molecule, which regulates the activity of immune cells, stimulates angiogenesis, and causes tumor invasion (Wu, Zhang *et al.,* 2026). Therefore, aerobic glycolysis is not only an energy-producing pathway but also a metabolic signaling and intercellular communication node in the tumor ecosystem.

3.2 Lipid and Amino Acid Metabolic Plasticity

In addition to glucose metabolism, cancer cells have high levels of flexibility in the use of lipids and amino acids, which allow them to respond to changes in nutrient supply. Lipid metabolism is commonly increased to aid in the membrane biosynthesis, storage of energy and the generation of signaling molecules (Cheng, Geng *et al.,* 2018). The increased de novo lipogenesis with the augmented fatty acid oxidation enables the tumor cells to keep the energy homeostasis and remain resistant to metabolic stress. The lipid derived molecules are also involved in signaling pathways in which they control inflammation, cell survival, and metastasis. Metabolism of amino acids especially glutamine, serine and branched-chain amino acids are essential in supporting the growth of tumor. Glutamine is an important anaplerotic precursor, which restores tricarboxylic acid (TCA) cycle intermediates and promotes the production of nucleotides as summarized in Table 1 (Jin, Byun *et al.,* 2023). Moreover, the metabolism of amino acids also promotes the redox and epigenetic regulation by producing

metabolites like α-ketoglutarate. The capacity to alternate among various nutrient resources is evidence of the metabolic strength of cancer cells and the interrelationship of metabolic networks in tumor biology.

3.3 Redox Balance and Oxidative Stress Adaptation

The cancer cells are exposed to increased oxidative stress because of the increased rate of metabolism and dysfunction of the mitochondria. In response to this, they regulate redox homeostasis by forming advanced antioxidant systems to retain signaling functions of reactive oxygen species (ROS) (Halliwell 2024). Instead of getting rid of ROS completely, tumor cells have a highly regulated response in which moderate levels of ROS ensure proliferation, survival signaling, and genetic variability. The pentose phosphate pathway and glutathione metabolism are among the important metabolic pathways, which are stimulated to produce reducing equivalents, including NADPH. These mechanisms cushion cancer cells against oxidative stress and help to develop resistance to chemotherapy and radiotherapy which are frequently based on ROS-mediated cytotoxicity. Notably, redox regulation is tightly connected with the alterations of proteomics and epigenomics since oxidative stress may affect the functionality of proteins and the activity of epigenetic enzymes, also incorporating metabolic adjustment into the bigger systems network in cancer (Ma, Fan *et al.,* 2025).

3.4 Metabolites as Signaling and Epigenetic Modulators

One of the conceptual changes in the field of cancer biology is the identification of metabolites as functional modulators of cellular signal and gene expression. The epigenetic enzymes also directly connect cellular metabolism and chromatin dynamics as well as transcriptional control through metabolite intermediates including acetyl-CoA, S-adenosylmethionine (SAM), and α-ketoglutarate (Li, Egervari *et al.,* 2018). Such processes allow epigenetic landscapes to be determined by metabolic states, which in turn determine cell fate choices and tumor development. Along with epigenetic control, the metabolites are signaling molecules that regulate important proliferation, apoptosis and immune evasion pathways. As an example, oncometabolites like 2-hydroxyglutarate have the potential to perturb regular cell differentiation pathways, and lactate has the potential to disrupt immune cell polarization in the tumor microenvironment. The combination of these two functions of metabolites as biochemical substrates and regulatory signals supports the notion that cancer is an emergent characteristic of interlocking networks of molecules. Altogether, metabolomic reprogramming is not an autonomous event but rather a core integrative pathway linking metabolic flux, protein activity, and epigenetic control (Sun, Zhang *et al.,* 2022). The knowledge of these multidimensional interactions is necessary to determine new therapeutic targets and enhance precision oncology interventions.

Table 1: Metabolic Reprogramming Pathways in Cancer

Pathway	Key Metabolites	Enzymes/Regulators	Functional Role	Clinical Relevance
Glycolysis	Glucose	HK2	Energy	Target
Lactate production	Lactate	LDHA	Immune evasion	Biomarker
TCA cycle	Citrate	IDH	Energy	Oncometabolite
Glutaminolysis	Glutamine	GLS	Growth	Drug target
Lipogenesis	Fatty acids	FASN	Membrane	Tumor growth
FA oxidation	Acetyl-CoA	CPT1	Energy	Survival
PPP	NADPH	G6PD	Redox	Resistance
ROS detox	ROS	SOD	Survival	Therapy
Methionine cycle	SAM	MAT	Methylation	Epigenetics
Serine pathway	Serine	PHGDH	Growth	Target
Cholesterol	Cholesterol	HMGCR	Stability	Therapy
Arginine metabolism	Arginine	ARG1	Immune evasion	Target
Proline metabolism	Proline	PYCR	Redox	Growth
NAD metabolism	NAD+	NAMPT	Energy	Drug target
Acetate metabolism	Acetate	ACSS2	Lipid synthesis	Tumor survival
Hypoxia metabolism	HIF-1α	HIF	Adaptation	Therapy
Ketone metabolism	Ketones	BDH1	Energy	Adaptation
Pyruvate metabolism	Pyruvate	PDH	Energy	Growth
Aspartate synthesis	Aspartate	GOT	DNA synthesis	Target
Nucleotide synthesis	Purines	DHFR	Growth	Chemotherapy
Sphingolipids	Ceramide	SMase	Apoptosis	Therapy
Glycosylation	Glycans	OGT	Signaling	Biomarker
Redox signaling	ROS	NRF2	Survival	Resistance
Mitochondrial metabolism	ATP	ETC	Energy	Therapy
Ferroptosis	Iron	GPX4	Cell death	Target

Pathway	Key Metabolites	Enzymes/Regulators	Functional Role	Clinical Relevance
Autophagy metabolism	LC3	ATG	Survival	Drug target
Lactate shuttle	Lactate	MCT	Transport	Microenvironment
Immune metabolism	Cytokines	mTOR	Immune evasion	Therapy
Alanine metabolism	Alanine	ALT	Growth	Target
Glycine metabolism	Glycine	SHMT	DNA synthesis	Therapy
Urea cycle	Urea	CPS1	Detox	Cancer survival
Polyamine synthesis	Spermidine	ODC	Growth	Target
Tryptophan metabolism	Kynurenine	IDO	Immune evasion	Immunotherapy
Citrate export	Citrate	ACLY	Lipid synthesis	Drug target
Glucose uptake	Glucose	GLUT1	Growth	Biomarker

4. Proteomic Network Dynamics and Functional Execution

Proteomics represents the functional backbone of cellular systems, translating genomic information and metabolic states into dynamic biological actions. In cancer, proteomic landscapes are extensively remodeled, enabling tumor cells to rapidly adapt to fluctuating microenvironmental conditions and therapeutic pressures. Unlike static genomic alterations, proteomic changes are highly context-dependent and temporally regulated, reflecting the real-time functional state of the tumor. From a systems biology perspective, proteins do not operate in isolation but form intricate, interconnected networks that govern signal transduction, metabolic coordination, and cellular decision-making (Wright, Colton *et al.,* 2024). The integration of proteomic data with metabolomic and epigenomic layers further reveals how signaling pathways are modulated by metabolic intermediates and epigenetic cues, reinforcing the concept of cancer as an emergent property of multi-layered biochemical interactions. Understanding proteomic network dynamics is therefore essential for deciphering tumor behavior, identifying actionable vulnerabilities, and advancing precision oncology.

4.1 Oncogenic Signaling Pathways and Network Rewiring

Cancer progression is driven by the extensive rewiring of oncogenic signaling networks that regulate proliferation, survival, and cellular plasticity. PI3K/AKT/mTOR, MAPK/ERK, and JAK/STAT are frequently dysregulated, not only through genetic mutations but also via proteomic alterations that reshape pathway architecture and signaling intensity (Li, Li *et al.,* 2022). This network rewiring enables tumor cells to bypass regulatory checkpoints, sustain growth signals, and evade apoptosis. Importantly, signaling pathways in cancer exhibit a high degree of redundancy and cross-talk, allowing compensation when one pathway is inhibited. Such adaptability is further influenced by metabolic reprogramming, where metabolites act as signaling modulators, and by epigenetic states that alter the expression of key signaling proteins. Consequently, oncogenic signaling should be viewed as a flexible and adaptive network rather than a linear cascade, highlighting the importance of systems-level proteomic analyses in identifying critical nodes and vulnerabilities within these pathways (Kabella, Bayer *et al.,* 2025).

4.2 Post-Translational Modifications and Protein Function Diversity

Post-translational modifications (PTMs) are central to expanding the functional diversity of the proteome without requiring changes at the genetic level. In cancer, PTMs such as phosphorylation, acetylation, ubiquitination, glycosylation, and methylation dynamically regulate protein activity, stability, localization, and interaction potential (Liang, Yao *et al.,* 2025). These modifications act as molecular switches that fine-tune signaling pathways and cellular responses to environmental cues. Aberrant PTM patterns are a hallmark of tumor cells, often resulting in constitutive activation of oncogenic proteins or inactivation of tumor suppressors. Furthermore, PTMs serve as critical points of integration between metabolic and epigenetic processes. For instance, the availability of metabolic cofactors can directly influence acetylation and methylation events, while epigenetic enzymes themselves are regulated through PTMs. This bidirectional interplay underscores the complexity of proteomic regulation in cancer and emphasizes the need to study PTMs within a multi-omics framework to fully understand their contribution to tumor progression and therapeutic response (Wang, Wang *et al.,* 2025).

4.3 Protein–Protein Interaction Networks and Signal Integration

Protein–protein interaction (PPI) networks form the structural and functional basis of intracellular communication, enabling the integration of multiple signaling inputs into coordinated cellular responses (Rahmani, Castaño *et al.,* 2025). In cancer, these networks are extensively reconfigured, leading to the formation of aberrant signaling hubs and altered network topology. Hub proteins, which interact with multiple partners, often serve as critical regulators of cellular behavior and are frequently co-opted by tumor cells to amplify oncogenic signals. The dynamic nature of PPIs allows cancer cells to rapidly reorganize their signaling networks in response to stress, nutrient availability, or therapeutic intervention. Moreover, PPI networks act as convergence points where metabolic signals and epigenetic modifications are integrated, further

reinforcing the interconnected nature of tumor biology. Advanced proteomic technologies, such as affinity purification mass spectrometry and proximity labeling, have enabled the high-resolution mapping of these interaction networks, providing valuable insights into system-wide regulatory mechanisms and identifying novel targets for therapeutic intervention (Jablonska 2024).

4.4 Proteomic Drivers of Drug Resistance and Tumor Survival

Therapeutic resistance remains a major challenge in cancer treatment, and proteomic adaptations play a pivotal role in enabling tumor survival under drug-induced stress (Wang, Wang *et al.,* 2025). Cancer cells often reprogram their proteomic networks to activate alternative signaling pathways, enhance DNA repair mechanisms, and modulate apoptotic thresholds. For example, the upregulation of survival pathways and anti-apoptotic proteins can counteract the effects of targeted therapies, while changes in protein expression and PTMs can alter drug targets, reducing treatment efficacy. Additionally, proteomic plasticity allows tumor cells to enter transient adaptive states, such as drug-tolerant persister phenotypes, which contribute to relapse and disease progression. These resistance mechanisms are frequently driven by cross-talk with metabolic and epigenetic processes, where metabolic shifts support survival under stress and epigenetic reprogramming stabilizes resistant phenotypes. A systems-level understanding of these proteomic adaptations is essential for identifying predictive biomarkers of resistance and for designing combination therapies that target multiple nodes within the network, thereby improving therapeutic outcomes (Tan, Gao *et al.,* 2024).

5. Epigenomic Plasticity and Regulatory Control Systems

Epigenomic regulation represents a central axis of cancer as a systems-level biochemical disease, governing how genetic information is dynamically interpreted without altering the underlying DNA sequence as summarized in Table 2. Unlike static genomic mutations, epigenetic mechanisms are inherently plastic, enabling tumor cells to rapidly adapt to environmental stressors, metabolic fluctuations, and therapeutic pressures. This plasticity underpins phenotypic heterogeneity, cellular reprogramming, and lineage flexibility key hallmarks of cancer progression. Within a multi-omics framework, epigenomic alterations do not operate in isolation but are tightly interconnected with metabolic states and proteomic signaling networks. Metabolites such as S-adenosylmethionine (SAM), acetyl-CoA, and α-ketoglutarate act as essential cofactors for epigenetic enzymes, thereby linking cellular metabolism to chromatin dynamics (Verma and Lindroth 2025). Consequently, epigenomic plasticity emerges as both a driver and a responder within the broader biochemical network, orchestrating transcriptional programs that define tumor identity and adaptability.

5.1 DNA Methylation and Transcriptional Silencing

DNA methylation is one of the most extensively studied epigenetic modifications in cancer, typically involving the addition of a methyl group to cytosine residues within CpG dinucleotides (Lavoro, Ricci *et al.,* 2025). Aberrant methylation patterns are a defining feature of tumor cells, characterized by global hypomethylation alongside localized hypermethylation at promoter regions of tumor suppressor genes. This duality contributes to genomic instability while simultaneously enforcing transcriptional silencing of critical regulatory pathways. From a systems perspective, DNA methylation acts as a molecular switch that integrates environmental cues and intracellular signaling to modulate gene expression landscapes. Importantly, methylation patterns are influenced by metabolic fluxes, particularly through the availability of methyl donors such as SAM, highlighting a direct interface between metabolomics and epigenomics. Furthermore, proteomic regulators, including DNA methyltransferases (DNMTs), are subject to post-translational modifications that fine-tune their activity, reinforcing the interconnected nature of regulatory control systems in cancer (Hegde and Joshi 2021).

5.2 Histone Modifications and Chromatin Accessibility

Histone proteins play a crucial role in organizing DNA into chromatin, and their post-translational modifications such as acetylation, methylation, phosphorylation, and ubiquitination serve as key determinants of chromatin structure and gene accessibility (Millán-Zambrano, Burton *et al.,* 2022). In cancer, dysregulated histone modification patterns lead to profound alterations in chromatin architecture, shifting the balance between transcriptionally active (euchromatin) and repressive (heterochromatin) states. Histone acetylation, for instance, is generally associated with open chromatin and active transcription, whereas deacetylation promotes chromatin compaction and gene silencing. These modifications are mediated by enzyme systems such as histone acetyltransferases (HATs) and histone deacetylases (HDACs), whose activity is closely linked to intracellular metabolite availability, including acetyl-CoA and NAD^+ (Keating and El-Osta 2015). This metabolic dependency underscores how biochemical states directly influence epigenetic landscapes. Moreover, chromatin remodeling complexes and histone-modifying enzymes interact extensively with signaling proteins, positioning histone dynamics as a convergence point for proteomic and epigenomic regulation. Such coordinated control enables cancer cells to rapidly reprogram transcriptional outputs in response to external and internal stimuli.

5.3 non-coding RNAs in Gene Regulatory Networks

Non-coding RNAs (ncRNAs), including microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), have emerged as critical regulators of gene expression within epigenomic networks (Nemeth, Bayraktar *et al.,* 2024). These molecules do not encode proteins but exert regulatory functions by modulating mRNA stability, translation, and chromatin organization. In cancer, ncRNAs contribute to the fine-tuning of oncogenic and tumor-suppressive pathways, often acting as network hubs that integrate signals across multiple molecular layers. For example, miRNAs can simultaneously regulate dozens of target genes, thereby reshaping entire signaling cascades, while lncRNAs can recruit chromatin-modifying complexes to specific genomic loci, influencing histone marks and DNA methylation patterns. Importantly, the expression of ncRNAs is itself regulated by epigenetic modifications, creating feedback loops that amplify or suppress specific cellular programs. These multilayered interactions highlight the role of ncRNAs as key mediators of systems-level regulation, bridging epigenomic, transcriptomic, and proteomic domains. Their dysregulation is strongly associated with tumor progression, metastasis, and therapeutic resistance, making them attractive candidates for biomarker development (Xu, Yu *et al.,* 2021).

5.4 Epigenetic Reversibility and Therapeutic Opportunities

A defining feature of epigenetic alterations is their reversibility, which distinguishes them from permanent genetic mutations and positions them as highly promising therapeutic targets. Epigenetic therapies aim to restore normal gene expression patterns by modulating the activity of enzymes involved in DNA methylation and histone modification. Agents such as DNMT inhibitors and HDAC inhibitors have demonstrated clinical efficacy in certain malignancies, underscoring the therapeutic potential of targeting epigenomic dysregulation (Suraweera, O'Byrne *et al.,* 2025). However, within a systems biology framework, the impact of epigenetic therapy extends beyond isolated pathways. Reversing epigenetic marks can rewire metabolic circuits, alter protein signaling networks, and enhance immune recognition of tumor cells. This highlights the importance of integrating epigenomic interventions with multi-omics strategies to achieve more durable and precise therapeutic outcomes. Additionally, the dynamic nature of epigenetic regulation enables real-time monitoring of treatment responses, offering opportunities for adaptive and personalized therapy. Despite these advances, challenges such as off-target effects, context-dependent responses, and resistance mechanisms remain significant. Future directions lie in the development of highly selective epigenetic modulators and the integration of epigenomic data with metabolomic and proteomic profiles to refine precision oncology approaches.

Title 2: Integrated Proteomic and Epigenomic Regulatory Mechanisms Driving Cancer Progression within a Systems Biology Framework

Mechanism	Molecules	Modification Type	Functional Impact	Therapeutic Potential
DNA methylation	DNMT1	Methylation	Gene silencing	DNMT inhibitors
DNA demethylation	TET enzymes	Hydroxymethylation	Gene activation	Epigenetic therapy
Histone acetylation	HATs	Acetylation	Chromatin opening	HAT modulators
Histone deacetylation	HDACs	Deacetylation	Gene repression	HDAC inhibitors
Histone methylation	EZH2	Methylation	Transcription repression	EZH2 inhibitors
Histone demethylation	KDMs	Demethylation	Gene activation	Targeted therapy
Chromatin remodeling	SWI/SNF	Structural	DNA accessibility	Synthetic lethality
Nucleosome positioning	Histones	Structural	Gene regulation	Epigenetic drugs
miRNA regulation	miR-21	ncRNA	Gene suppression	Biomarker
miRNA tumor suppressor	miR-34	ncRNA	Apoptosis induction	Therapeutic target
lncRNA scaffolding	HOTAIR	Epigenetic	Chromatin remodeling	Target
lncRNA regulation	MALAT1	Epigenetic	Metastasis	Biomarker
circRNA regulation	circRNAs	ncRNA	Gene modulation	Emerging therapy
Protein phosphorylation	AKT	PTM	Signal activation	Kinase inhibitors
Protein acetylation	p53	PTM	Stability regulation	Cancer therapy
Protein ubiquitination	MDM2	PTM	Protein degradation	Target
SUMOylation	SUMO proteins	PTM	Transcription control	Drug target
Glycosylation	OGT	PTM	Signal modulation	Biomarker
Proteasomal degradation	Proteasome	PTM	Protein turnover	Proteasome inhibitors
Chaperone regulation	HSP90	Folding	Protein stability	HSP90 inhibitors

Mechanism	Molecules	Modification Type	Functional Impact	Therapeutic Potential
Transcription factors	MYC	Regulatory	Cell proliferation	Target
Tumor suppressor silencing	p53	Epigenetic	Loss of function	Reactivation
Enhancer regulation	Super-enhancers	Epigenetic	Gene amplification	Target
DNA damage response	BRCA1	Repair	Genome stability	PARP inhibitors
Chromatin looping	CTCF	Structural	Gene regulation	Target
RNA methylation	m6A	Epitranscriptomic	RNA stability	Emerging therapy
Alternative splicing	Spliceosome	RNA processing	Protein diversity	Target
Metabolite-dependent acetylation	Acetyl-CoA	Epigenetic	Gene expression	Metabolic therapy
SAM-dependent methylation	SAM	Epigenetic	DNA methylation	Target
α-KG dependent demethylation	α-KG	Epigenetic	Histone regulation	Therapy
Oncometabolite regulation	2-HG	Epigenetic	Enzyme inhibition	Target
Immune checkpoint regulation	PD-L1	Proteomic	Immune evasion	Immunotherapy
Cytokine signaling	IL-6	Proteomic	Inflammation	Target
EMT regulation	Snail	Epigenetic	Metastasis	Therapy
Angiogenesis signaling	VEGF	Proteomic	Tumor growth	Anti-VEGF drugs
Hypoxia signaling	HIF-1α	Proteomic	Adaptation	Target
Feedback loops	NF-κB	Regulatory	Survival signaling	Inhibitors
Epigenetic memory	Chromatin marks	Epigenetic	Cell identity	Therapy
Drug resistance signaling	ABC transporters	Proteomic	Drug efflux	Target
Crosstalk regulation	Multi-omics nodes	Integrated	System adaptation	Combination therapy

6. Challenges and Current Limitations

Despite the transformative potential of multi-omics integration in redefining cancer as a systems-level biochemical disease, several critical challenges continue to hinder its full realization in both research and clinical settings. These limitations arise not only from technological and computational constraints but also from the inherent complexity of biological systems. Addressing these issues is essential to ensure that multi-omics approaches transition from exploratory frameworks to robust, clinically actionable tools.

6.1 Data Complexity and Standardization Issues

One of the foremost challenges in multi-omics research is the sheer complexity and heterogeneity of data generated across metabolomics, proteomics, and epigenomics platforms. Each omics layer produces high-dimensional datasets with distinct formats, scales, and dynamic ranges, making harmonization inherently difficult. Variability in sample preparation, instrumentation (e.g., mass spectrometry vs. sequencing platforms), and data acquisition protocols further exacerbates inconsistencies across studies. Moreover, the absence of universally accepted standards for data normalization, annotation, and reporting creates significant barriers to cross-study comparisons and meta-analyses. For instance, metabolomic datasets are highly sensitive to environmental and physiological fluctuations, while proteomic outputs are influenced by post-translational modifications and protein turnover rates. Epigenomic data, in turn, are context-dependent and vary across cell types and temporal states. Without standardized pipelines and reference frameworks, integrating these datasets risks introducing bias and reducing reproducibility (Kelly, Scherer *et al.,* 2024). Therefore, the development of unified data standards, robust quality control measures, and interoperable databases remains a critical priority for advancing systems-level cancer research.

6.2 Integration and Interpretation Barriers

Beyond data generation, the integration of multi-omics datasets presents a profound analytical challenge. Combining metabolomic, proteomic, and epigenomic information requires sophisticated computational models capable of capturing nonlinear interactions and hierarchical dependencies across molecular layers. However, existing integration methods often rely on simplified assumptions that fail to fully represent the dynamic and context-specific nature of biological systems. The limitation lies in distinguishing causality from correlation. While integrated datasets can reveal associations between metabolic pathways, protein networks, and epigenetic modifications, identifying mechanistic drivers of tumor progression remains complex. Additionally, the lack of consensus on optimal integration strategies whether network-based, machine learning-driven, or pathway-centric, leads to variability

in outcomes and interpretability. Interpretation is further complicated by the presence of noise, missing data, and batch effects, which can obscure biologically meaningful signals (Morabito, De Simone *et al.,* 2025). As a result, translating integrated multi-omics outputs into coherent biological insights requires not only advanced computational tools but also domain expertise to contextualize findings within cancer biology. Bridging this gap between data integration and biological interpretation remains a major bottleneck in the field.

7. Future Directions and Emerging Frontiers

The rapid evolution of multi-omics technologies is redefining the conceptual and practical boundaries of cancer research, moving the field toward a predictive, dynamic, and systems-oriented paradigm. While current integrative approaches have substantially improved our understanding of tumor complexity, emerging innovations are poised to further resolve cancer at unprecedented spatial, temporal, and computational scales (Cilento, Sweeney *et al.,* 2024). These advancements are not only enhancing mechanistic insights into tumor biology but are also laying the foundation for next-generation precision oncology frameworks. By integrating high-resolution data acquisition with advanced computational modeling, future research is expected to transition from descriptive multi-omics profiling to actionable, real-time decision-making systems that can anticipate disease trajectories and therapeutic responses.

7.1 Single-Cell and Spatial Multi-Omics Integration

A critical limitation of conventional bulk omics approaches lies in their inability to capture intra-tumoral heterogeneity and microenvironmental context. Single-cell and spatial multi-omics technologies are addressing this gap by enabling the dissection of molecular profiles at cellular resolution while preserving spatial architecture. These approaches allow simultaneous interrogation of genomic, transcriptomic, proteomic, and epigenomic features within individual cells, thereby uncovering rare subpopulations, lineage hierarchies, and cell-state transitions that drive tumor progression and therapeutic resistance. Importantly, spatially resolved omics adds an additional layer of complexity by mapping molecular interactions within the tumor microenvironment (See, Barlow *et al.,* 2025). The spatial distribution of immune cells, stromal components, and malignant clones can now be analyzed in conjunction with their biochemical states, revealing localized signaling niches and metabolic gradients. This integrated perspective is particularly valuable for understanding immune evasion mechanisms and identifying spatially restricted therapeutic targets. As these technologies mature, their integration with systems biology frameworks will enable the construction of highly resolved tumor atlases, providing a blueprint for precision intervention at the cellular and microenvironmental levels.

7.2 Real-Time and Longitudinal Omics Monitoring

Cancer is inherently dynamic, characterized by continuous molecular evolution under both intrinsic and treatment-induced pressures. Static snapshots provided by traditional omics analyses fail to capture these temporal changes. Emerging real-time and longitudinal monitoring strategies, including liquid biopsy-based omics and minimally invasive sampling techniques, are transforming how tumor progression is studied and managed. By tracking circulating tumor DNA (ctDNA), extracellular vesicles, and metabolic signatures over time, researchers can monitor tumor evolution, clonal selection, and the emergence of resistance mechanisms with high temporal resolution (Casanova-Salas, Aguilar *et al.,* 2024). Integrating longitudinal metabolomic, proteomic, and epigenomic data enables the identification of early biochemical shifts that precede phenotypic changes, offering a window for timely therapeutic intervention. Furthermore, real-time data integration supports adaptive treatment strategies, where therapeutic regimens can be dynamically adjusted based on the evolving molecular profile of the tumor. This shift toward continuous monitoring represents a fundamental transition from reactive to proactive oncology.

CONCLUSION

Cancer is increasingly understood as an emergent property of interconnected biochemical networks rather than a disease driven by isolated genetic alterations. This review highlights how the integration of metabolomics, proteomics, and epigenomics provides a comprehensive framework for decoding tumor heterogeneity, adaptive plasticity, and therapeutic resistance. By elucidating the dynamic cross-talk between metabolic fluxes, protein signaling networks, and epigenetic regulation, a systems-level perspective offers deeper mechanistic insight into cancer progression. Importantly, this integrative paradigm enables the identification of multi-layered biomarkers and network-based therapeutic targets with improved specificity. Despite existing challenges in data integration, standardization, and clinical translation, emerging advances in single-cell technologies, longitudinal monitoring, and artificial intelligence are rapidly bridging these gaps. Collectively, multi-omics integration represents a transformative shift toward predictive and precision oncology, with the potential to redefine cancer diagnosis, prognosis, and treatment through a holistic, systems-driven approach.

REFERENCES

- Pina-Sanchez, P., Chavez-Gonzalez, A., Ruiz-Tachiquin, M., Vadillo, E., Monroy-Garcia, A., Montesinos, J. J., ... & Mayani, H. (2021). Cancer biology, epidemiology, and treatment in the 21st century: current status and future challenges from a biomedical perspective. *Cancer Control*, *28*, 10732748211038735.

- Hanahan, D. (2022). Hallmarks of cancer: new dimensions. *Cancer discovery*, *12*(1), 31-46.
- Patti, G. J., Yanes, O., & Siuzdak, G. (2012). Metabolomics: the apogee of the omics trilogy. *Nature reviews Molecular cell biology*, *13*(4), 263-269.
- Hanahan, D., & Weinberg, R. A. (2011). Hallmarks of cancer: the next generation. *cell*, *144*(5), 646-674.
- Prasad, B., Vrana, M., Mehrotra, A., Johnson, K., & Bhatt, D. K. (2017). The promises of quantitative proteomics in precision medicine. *Journal of Pharmaceutical Sciences*, *106*(3), 738-744.
- Chatterjee, A., & Eccles, M. R. (2015). DNA methylation and epigenomics: new technologies and emerging concepts. *Genome biology*, *16*(1), 103.
- Wang, G., & Han, J. J. (2021). Connections between metabolism and epigenetic modifications in cancer. *Medical Review*, *1*(2), 199-221.
- Jiang, Z., Zhang, H., Gao, Y., & Sun, Y. (2025). Multi-omics strategies for biomarker discovery and application in personalized oncology. *Molecular Biomedicine*, *6*(1), 115.
- Raufaste-Cazavieille, V., Santiago, R., & Droit, A. (2022). Multi-omics analysis: Paving the path toward achieving precision medicine in cancer treatment and immuno-oncology. *Frontiers in Molecular Biosciences*, *9*, 962743.
- Abdelaziz, E. H., Ismail, R., Mabrouk, M. S., & Amin, E. (2024). Multi-omics data integration and analysis pipeline for precision medicine: Systematic review. *Computational Biology and Chemistry*, *113*, 108254.
- Huang, S., Soto, A. M., & Sonnenschein, C. (2025). The end of the genetic paradigm of cancer. *PLoS biology*, *23*(3), e3003052.
- Chen, C., Wang, Z., & Qin, Y. (2022). Connections between metabolism and epigenetics: mechanisms and novel anti-cancer strategy. *Frontiers in pharmacology*, *13*, 935536.
- Casanova-Salas, I., *et al.,* (2024). "Circulating tumor extracellular vesicles to monitor metastatic prostate cancer genomics and transcriptomic evolution." Cancer cell 42(7): 1301–1312. e1307.
- Catalano, M., *et al.,* (2025). "Navigating cancer complexity: integrative multi-omics methodologies for clinical insights." Clinical Medicine Insights: Oncology 19: 11795549251384582.
- Cheng, C., *et al.,* (2018). "Lipid metabolism reprogramming and its potential targets in cancer." Cancer communications 38(1): 27.
- Cilento, M. A., *et al.,* (2024). "Spatial transcriptomics in cancer research and potential clinical impact: a narrative review." Journal of Cancer Research and Clinical Oncology 150(6): 296.
- DeBerardinis, R. J. and N. S. Chandel (2020). "We need to talk about the Warburg effect." Nature metabolism 2(2): 127–129.
- Halliwell, B. (2024). "Understanding mechanisms of antioxidant action in health and disease." Nature Reviews Molecular Cell Biology 25(1): 13–33.
- Haynes, N. M., *et al.,* (2024). "The complexity of immune evasion mechanisms throughout the metastatic cascade." Nature immunology 25(10): 1793–1808.
- Hegde, M. and M. B. Joshi (2021). "Comprehensive analysis of regulation of DNA methyltransferase isoforms in human breast tumors." Journal of Cancer Research and Clinical Oncology 147(4): 937–971.
- Jablonska, Z. (2024). "Proximity-based labelling for proteomic mapping." Nature Reviews Cardiology 21(8): 521–521.
- Jin, J., *et al.,* (2023). "Targeting glutamine metabolism as a therapeutic strategy for cancer." Experimental & molecular medicine 55(4): 706–715.
- Kabella, N., *et al.,* (2025). "Proteomic analyses identify targets, pathways, and cellular consequences of oncogenic KRAS signaling." Science Signaling 18(897): eadt6552.
- Keating, S. T. and A. El-Osta (2015). "Epigenetics and metabolism." Circulation research 116(4): 715–736.
- Kelly, K., *et al.,* (2024). "EpiCHAOS: a metric to quantify epigenomic heterogeneity in single-cell data." Genome biology 25(1): 305.
- Kuenzi, B. M. and T. Ideker (2020). "A census of pathway maps in cancer systems biology." Nature Reviews Cancer 20(4): 233–246.
- Lavoro, A., *et al.,* (2025). "Recent advances on gene-related DNA methylation in cancer diagnosis, prognosis, and treatment: a clinical perspective." Clinical epigenetics 17(1): 76.
- Li, Q., *et al.,* (2022). "Targeting the PI3K/AKT/mTOR and RAF/MEK/ERK pathways for cancer therapy." Molecular biomedicine 3(1): 47.
- Li, X., *et al.,* (2018). "Regulation of chromatin and gene expression by metabolic enzymes and metabolites." Nature Reviews Molecular Cell Biology 19(9): 563–578.
- Liang, X., *et al.,* (2025). "Immunoregulatory roles of post-translational modifications in colorectal cancer: mechanisms and therapeutic implications." Cellular and Molecular Life Sciences.
- Ma, X., *et al.,* (2025). "The interplay between oxidative stress and epigenetic reprogramming in cancer." International journal of cancer 157(10): 2004–2018.
- Millán-Zambrano, G., *et al.,* (2022). "Histone post-translational modifications—cause and consequence of genome function." Nature Reviews Genetics 23(9): 563–580.
- Morabito, A., *et al.,* (2025). "Algorithms and tools for data-driven omics integration to achieve multilayer biological insights: a narrative review." Journal of translational medicine 23(1): 425.

- Nemeth, K., *et al.,* (2024). "Non-coding RNAs in disease: from mechanisms to therapeutics." Nature Reviews Genetics 25(3): 211–232.
- Rahmani, N., *et al.,* (2025). "Cannabivarin and tetrahydrocannabivarin modulate nociception via vanilloid channels and cannabinoid-like receptors in Caenorhabditis elegans." Canadian Journal of Physiology and Pharmacology 104: 1–13.
- Ryall, K. A. and A. C. Tan (2015). "Systems biology approaches for advancing the discovery of effective drug combinations." Journal of cheminformatics 7(1): 7.
- See, J.-E., *et al.,* (2025). "Spatial omics: applications and utility in profiling the tumor microenvironment." Cancer and Metastasis Reviews 44(4): 87.
- Sun, L., *et al.,* (2022). "Metabolic reprogramming and epigenetic modifications on the path to cancer." Protein & cell 13(12): 877–919.
- Suraweera, A., *et al.,* (2025). "Epigenetic drugs in cancer therapy." Cancer and Metastasis Reviews 44(1): 37.
- Tan, Q., *et al.,* (2024). "Longitudinal plasma proteomic analysis identifies biomarkers and combinational targets for anti-PD1-resistant cancer patients." Cancer Immunology, Immunotherapy 73(3): 47.
- Verma, A. and A. M. Lindroth (2025). "The emerging intertwined activities of metabolism and epigenetics unveils culprits and prospects in cancer." Experimental & molecular medicine 57(9): 1928–1939.
- Wang, R. S., *et al.,* (2015). "Systems medicine: evolution of systems biology from bench to bedside." Wiley Interdisciplinary Reviews: Systems Biology and Medicine 7(4): 141–161.
- Wang, Y., *et al.,* (2025). "Integrating multi-omics proteomic approaches in deciphering the tumor microenvironment and therapeutic resistance mechanisms in prostate cancer." Biochimica et Biophysica Acta (BBA)-Reviews on Cancer: 189426.
- Wright, S. N., *et al.,* (2024). "State of the interactomes: an evaluation of molecular networks for generating biological insights." Molecular systems biology 21(1): 1.
- Wu, P., *et al.,* (2026). "Lactate-lactylation in tumor angiogenesis and progression: mechanisms, biomarker potential, and therapeutic implications." Biomarker research.
- Xu, T., *et al.,* (2021). "Dysregulated tumor-associated macrophages in carcinogenesis, progression and targeted therapy of gynecological and breast cancers." Journal of hematology & oncology 14(1): 181.
- Yang, G., *et al.,* (2023). "A multi-omics overview of colorectal cancer to address mechanisms of disease, metastasis, patient disparities and outcomes." Cancers 15(11): 2934.
- Zhang, H., *et al.,* (2024). "Metabolic reprogramming and immune evasion: the interplay in the tumor microenvironment." Biomarker research 12(1): 96.