Texila International Journal of Public Health
Special Issue 2-2025
DOI: 10.21522/TIJPH.2013.SE.25.02.Art005

Perineural Invasion is a Poor Prognostic Factor for Sinonasal Squamous Cell Carcinoma

Neha Brahma[1], Prabakaran B [2], Akshaya Viswanathan[2], Debalina Sen[1], Vimal S.[1*]
[1]Department of Biochemistry, Saveetha Medical College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India
[2]Department of Pathology, Saveetha Medical College, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India

Abstract

Cancer, a multifaceted disease, arises from a complex interplay of genetic mutations, epigenetic modifications, and proteomic alterations that drive tumor progression and therapeutic resistance. Traditional genomic approaches have identified key oncogenes and tumor suppressors; however, the functional consequences of these alterations at the protein level often remain elusive. Proteogenomics, an integrative approach combining next-generation sequencing and mass spectrometry-based proteomics, bridges this gap by linking genomic aberrations to proteomic changes, enabling a deeper understanding of cancer biology. This review highlights the pivotal role of proteogenomics in unraveling cancer mechanisms, focusing on its contribution to understanding signaling pathways, post-translational modifications (PTMs), and tumor heterogeneity. Proteogenomic studies have elucidated key oncogenic pathways, such as PI3K/AKT/mTOR and MAPK, revealing how dysregulated proteins and PTMs drive tumor growth and therapeutic resistance. The approach has also identified novel biomarkers and molecular subtypes across cancers, facilitating precision medicine. Furthermore, proteogenomics has been instrumental in addressing therapeutic resistance by uncovering compensatory mechanisms, clonal evolution, and proteomic adaptations in resistant tumor cells. Breast cancer and melanoma case studies illustrate its potential in developing combination therapies to counter resistance. With clinical applications advancing, proteogenomics holds promise for transforming cancer treatment through personalized medicine, patient stratification, and biomarker-driven therapies. Integrating multi-omic data provides a dynamic and comprehensive view of tumor biology, paving the way for innovative strategies to improve patient outcomes and combat therapeutic resistance. This review underscores proteogenomics as a cornerstone in the evolving landscape of oncology research.

Keywords: *Proteogenomics, Precision Medicine, Post-Translational Modifications (PTMs), Therapeutic Resistance.*

Introduction

Cancer, a multifaceted and heterogeneous disease, arises from a complex interplay of genetic mutations, epigenetic modifications, and proteomic alterations that collectively drive tumor initiation, progression, and therapeutic resistance. Traditional genomic approaches have played a pivotal role in identifying key cancer drivers, including oncogenes and tumor suppressors [5]. However, the functional consequences of these genetic alterations, particularly in terms of protein expression, signaling pathways, and post-translational modifications (PTMs), remain inadequately understood. This gap limits our ability to fully elucidate the molecular underpinnings of

Received: 26.01.2025 ***Accepted: 16.02.2025*** ***Published on: 27.06.2025***
****Corresponding Author: vimals.smc@saveetha.com***

cancer biology and develop effective therapeutic strategies [1, 19].

Proteogenomics, an integrative approach combining next-generation sequencing (NGS) and mass spectrometry-based proteomics, bridges this gap by linking genomic aberrations to proteomic changes. By correlating genomic data from DNA and RNA sequencing with proteomic insights into protein expression, PTMs, and protein-protein interactions, proteogenomics provides a dynamic and comprehensive view of the tumor's molecular landscape. This approach has enabled researchers to uncover intricate proteogenomic networks, revealing how dysregulated proteins and PTMs contribute to cancer progression, signaling dysregulation, and therapeutic resistance [9, 12, 18].

Proteogenomic studies have shed light on critical oncogenic pathways, such as PI3K/AKT/mTOR and MAPK, elucidating how these pathways are altered through mutations, PTMs, and protein expression changes [11, 22]. Dysregulated signaling within these pathways often promotes tumor growth, survival, and therapeutic resistance. Furthermore, proteogenomics has been instrumental in identifying novel cancer biomarkers and defining molecular subtypes across different tumor types. These discoveries have significant implications for precision medicine, enabling patient stratification, biomarker-driven therapies, and the development of targeted treatments tailored to the molecular characteristics of individual tumors [6].

Another critical contribution of proteogenomics lies in addressing therapeutic resistance, a major challenge in cancer treatment. By uncovering compensatory mechanisms, clonal evolution, and proteomic adaptations in resistant tumor cells, proteogenomics has provided new avenues to counter resistance. Case studies in breast cancer and melanoma exemplify the potential of this approach in guiding combination therapies to overcome resistance mechanisms. For instance, proteogenomic analyses have identified phosphorylation events and proteomic alterations in resistant tumors, highlighting potential therapeutic targets and strategies to inhibit therapeutic pathways [4, 16].

With advancements in multi-omic platforms and clinical applications, proteogenomics holds promise for transforming cancer research and treatment. By integrating genomic and proteomic data, this approach not only enhances our understanding of cancer biology but also paves the way for innovative strategies to improve patient outcomes. From personalized medicine and biomarker-driven therapies to identifying novel drug targets, proteogenomics is poised to become a cornerstone in the evolving landscape of oncology research [11].

Proteogenomics: An Integrative Approach

Proteogenomics represents the intersection of genomics and proteomics, leveraging next-generation sequencing (NGS) technologies for genomic data and mass spectrometry (MS) for proteomic analysis. This approach provides a more comprehensive view of cancer biology by correlating genomic mutations with protein expression, PTMs, and protein-protein interactions (PPIs) [18] (Fig 1).

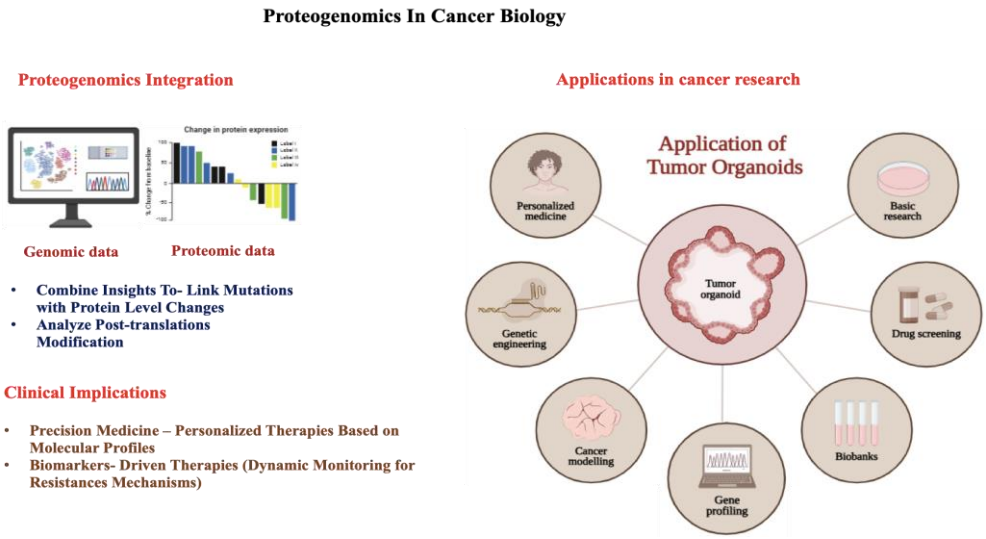

Figure 1. This diagram illustrates proteogenomics integration, combining genomic and proteomic data to link mutations with protein-level changes. Applications in cancer research include personalized medicine, tumor organoid-based research, genetic engineering, drug screening, biobanks, gene profiling, and cancer modeling for precision therapies.

Technological Advancements

The evolution of multi-omic platforms has accelerated proteogenomic research, allowing for the integration of transcriptomics, exome sequencing, and MS-based proteomics. These platforms provide high-throughput, high-resolution data, enabling the identification of specific molecular alterations and their functional consequences at the protein level. The Clinical Proteomic Tumor Analysis Consortium (CPTAC) is a notable example of how proteogenomic datasets have contributed to cancer research, generating extensive multi-omic data across various tumor types [10, 12, 20].

Proteogenomic research also emphasizes the analysis of modifications occurring after protein translation. PTMs, such as phosphorylation, ubiquitination, and glycosylation, which regulate protein function and stability. Mapping these modifications helps to elucidate how cancer cells manipulate signaling pathways to sustain malignancy [17].

Proteogenomic Networks in Cancer Biology

The dynamic interplay between proteomics and genomics creates intricate networks that regulate tumor behavior. Genomic mutations lead to alterations in protein expression and function, driving the dysregulation of signaling pathways and cellular processes [17, 21].

Signaling Pathways and Tumor Behavior

Proteogenomic analysis has been critical in understanding cancer-associated signaling pathways, such as the PI3K/AKT/mTOR (Fig 2), MAPK (Fig 3), and Wnt pathways. Mutations in key genes within these pathways lead to aberrant activation or inhibition of downstream signaling molecules, often resulting in unchecked cellular proliferation, survival, and metastasis [8, 14].

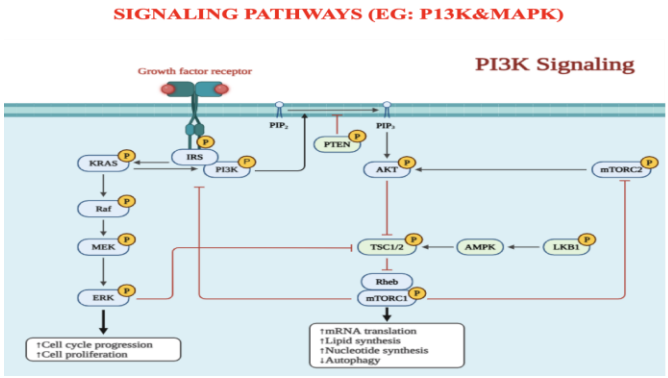

Figure 2. PI3K and MAPK signaling pathways depict cellular processes initiated by growth factor receptors. Key molecules include KRAS, AKT, and mTOR, regulating cell cycle progression, proliferation, mRNA translation, lipid synthesis, nucleotide synthesis, and autophagy.

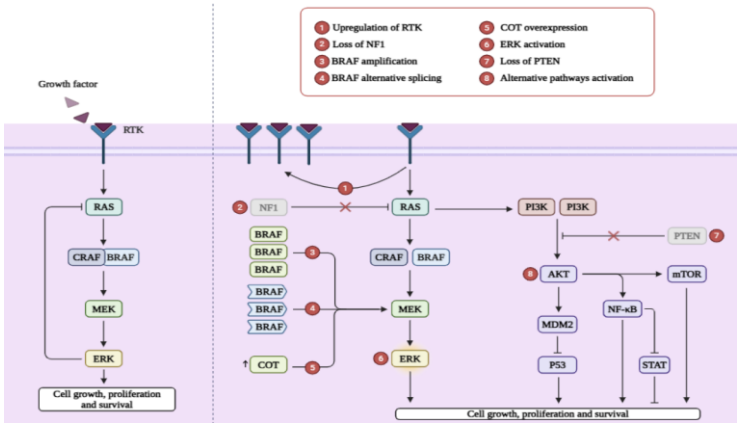

Figure 3. The diagram depicts the MAPK signaling pathway, outlining the molecular mechanisms involved in cell growth, proliferation, and survival. It highlights disruptions such as upregulation of receptor tyrosine kinases (RTK), loss of NF1, BRAF amplification, and alternative splicing of BRAF. Additionally, COT overexpression, ERK activation, loss of PTEN, and activation of alternative pathways are shown as contributing factors to dysregulated signaling. These alterations can lead to enhanced cell survival and proliferation, emphasizing their roles in pathological conditions.

For instance, mutations in the PI3K/AKT/mTOR pathway are commonly found in breast cancer and are associated with therapeutic resistance. Proteogenomic studies have identified phosphorylation events within this pathway that correlate with disease progression, highlighting potential therapeutic targets [23].

Post-translational Modifications (PTMs) in Cancer

PTMs are crucial in regulating protein activity, localization, and interactions, and their dysregulation is a hallmark of cancer. Proteogenomic approaches have revealed how PTMs contribute to the activation of oncogenic pathways. For example, hyperphosphorylation of kinases such as ERK and AKT is frequently observed in cancers, leading to persistent signaling that promotes tumor growth. Proteogenomics enables the mapping of these PTMs and their regulatory networks, providing new opportunities for targeted therapy [14, 15].

Unraveling Disease Mechanisms Through Proteogenomics

While genomic studies can identify mutations and structural variations, they do not always predict functional outcomes. Proteogenomics fills this gap by linking genetic alterations to protein level changes, enabling the identification of molecular drivers of cancer

that may not be evident from genomic data alone.

Oncogenic Drivers and Tumor Suppressors

Proteogenomics has proven invaluable in distinguishing between passenger mutations and true oncogenic drivers. For example, proteogenomic studies have identified key alterations in tumor suppressors like TP53 and oncogenes like KRAS, clarifying their impact on protein function. These studies also reveal how mutations influence PTMs and PPIs, which can significantly affect tumor progression.

Discovery of Novel Biomarkers

Proteogenomics has facilitated the identification of novel cancer biomarkers that are critical for diagnosis, prognosis, and therapeutic targeting. Researchers have identified biomarkers that better reflect tumor biology and therapeutic response by correlating genomic mutations with specific proteomic signatures. For instance, proteogenomic profiling of colorectal cancer has revealed distinct molecular subtypes, each associated with different treatment outcomes.

Therapeutic Resistance in Cancer

One of the most significant challenges in cancer treatment is the development of therapeutic resistance, where tumors adapt to evade targeted therapies. Proteogenomics provides a comprehensive understanding of the molecular changes that underlie resistance mechanisms, revealing new strategies for overcoming this hurdle.

Mechanisms of Therapeutic Resistance

Cancer cells develop resistance through various mechanisms, including secondary mutations, activation of compensatory pathways, and alterations in protein signaling. For example, resistance to EGFR inhibitors in non-small cell lung cancer (NSCLC) is often driven by secondary mutations in EGFR or activation of bypass pathways such as MET amplification. Proteogenomic studies have elucidated how these resistance mechanisms manifest at both the genomic and proteomic levels.

Tumor Heterogeneity and Clonal Evolution

Intra-tumor heterogeneity, both at the genetic and proteomic levels, plays a crucial role in therapeutic resistance. Subpopulations of cancer cells within a tumor may exhibit distinct proteomic profiles, allowing them to survive therapy and drive recurrence. Proteogenomic studies have highlighted how clonal evolution the process by which certain clones gain a survival advantage leads to the emergence of resistant cell populations. By identifying these subclones, proteogenomics can help develop strategies to target resistant cells more effectively.

Overcoming Therapeutic Resistance: Proteogenomic Approaches

Proteogenomics offers novel insights into overcoming therapeutic resistance by identifying compensatory pathways and potential drug targets. Through the integration of proteomic and genomic data, researchers can better understand the molecular adaptations that cancer cells undergo in response to therapy.

Case Study: Breast Cancer Resistance

In breast cancer, resistance to HER2-targeted therapies has been linked to upregulation of the PI3K/AKT pathway. Proteogenomic analyses have shown that phosphorylation of downstream effectors mediates this resistance, suggesting that combining HER2 inhibitors with PI3K/AKT pathway inhibitors could improve therapeutic efficacy [3, 13].

Case Study: Melanoma Resistance

In melanoma, resistance to BRAF inhibitors is often driven by reactivation of the MAPK pathway through alternative mechanisms, such as NRAS mutations or receptor tyrosine kinase activation. Proteogenomic profiling has

revealed the proteomic changes associated with these resistance mechanisms, highlighting the potential for combination therapies that target multiple signaling pathways [2].

Clinical Implications of Proteogenomics

Proteogenomics is poised to transform clinical oncology by facilitating personalized cancer treatment and improving patient outcomes. The integration of genomic and proteomic data allows for more accurate patient stratification and identification of therapeutic targets [15].

Precision Medicine and Proteogenomics

Proteogenomic profiling enables clinicians to tailor therapies based on the specific molecular characteristics of a patient's tumor. For instance, patients with breast cancer who exhibit distinct proteomic signatures have been shown to respond differently to targeted therapies. By identifying these signatures, proteogenomics can help guide treatment decisions and improve patient outcomes.

Biomarker-Driven Therapies

Proteogenomic studies have identified numerous biomarkers that can be used to predict therapeutic response. For example, proteomic signatures of phosphorylation in key signaling pathways have been associated with resistance to certain therapies, allowing clinicians to adjust treatment strategies accordingly. These biomarkers provide a more dynamic view of tumor biology compared to traditional genomic markers, enhancing the precision of cancer therapies [3, 7].

Conclusion

Proteogenomics has revolutionized the study of cancer biology by linking genomic mutations to proteomic changes, offering new insights into tumor heterogeneity, disease progression, and therapeutic resistance. The integration of proteomic data with genomic information provides a more comprehensive understanding of cancer, paving the way for novel therapeutic targets and personalized treatment strategies. As proteogenomic technologies continue to advance, the field holds immense potential for improving cancer outcomes and overcoming therapeutic resistance.

Future research in proteogenomics will likely focus on developing new methods to integrate multi-omic data, further elucidating the mechanisms behind resistance, and identifying biomarkers for precision medicine. By continuing to explore the proteogenomic landscape of cancer, researchers can unlock new opportunities for targeted therapies and improved patient care.

Conflict of Interest Statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

The authors are grateful to Saveetha Medical College and Hospital, SIMATS for providing a forum to share our knowledge.

References

[1]. Balasooriya, E. R., et al., 2024, Integrating clinical cancer and PTM proteomics data identifies a mechanism of ACK1 kinase activation. *Molecular cancer research: MCR*. 22, 2, 137–151.

[2]. Eroglu, Z., and Ribas, A., 2016. Combination therapy with BRAF and MEK inhibitors for melanoma: latest evidence and place in therapy. *Therapeutic advances in medical oncology*. 8, 1, 48–56.

[3]. Fujimoto, Y., et al., 2020, Combination treatment with a PI3K/Akt/mTOR pathway inhibitor overcomes resistance to anti-HER2 therapy in PIK3CA-mutant HER2-positive breast cancer cells. *Scientific reports*. 10, 1, 21762.

[4]. Gerlinger, M., et al., 2012, Intratumor

heterogeneity and branched evolution revealed by multiregion sequencing. *The New England journal of medicine*. 366, 10, 883–892.

[5]. Kannan, B., Pandi, C., Pandi, A., Jayaseelan, V. P., & Arumugam, P. 2024, Triggering receptor expressed in myeloid cells 1 (TREM1) as a potential prognostic biomarker and association with immune infiltration in oral squamous cell carcinoma. *Archives of oral biology*, *161*, 105926.

[6]. Hanahan, D., and Weinberg, R. A., 2011, Hallmarks of cancer: the next generation. *Cell*. 144, 5, 646–674.

[7]. Lei, J. T., and Zhang, B., 2021, Proteogenomics drives therapeutic hypothesis generation for precision oncology. *British journal of cancer*. 125, 1, 1–3.

[8]. Li, Q., et al., 2022, Targeting the PI3K/AKT/mTOR and RAF/MEK/ERK pathways for cancer therapy. *Molecular biomedicine*. 3, 1, 47.

[9]. Li, Y., et al., 2023, Proteogenomic data and resources for pan-cancer analysis. *Cancer cell*. 41, 8, 1397–1406.

[10]. Ramarajyam, G., Murugan, R., and Rajendiran, S. 2024, Network pharmacology and bioinformatics illuminates punicalagin's pharmacological mechanisms countering drug resistance in hepatocellular carcinoma. *Human Gene*, *42*, 201328.

[11]. Mertins, P., et al., 2016, Proteogenomics connects somatic mutations to signalling in breast cancer. *Nature*. 534, 7605, 55–62.

[12]. Nesvizhskii, A. I., 2014, Proteogenomics: concepts, applications and computational strategies. *Nature methods*. 11, 1, 1114–1125.

[13]. Pan, L., et al., 2024, HER2/PI3K/AKT pathway in HER2-positive breast cancer: A review. *Medicine*. 103, 24, e38508.

[14]. Rascio, F., et al., 2021, The pathogenic role of PI3K/AKT pathway in cancer onset and drug resistance: An updated review. *Cancers*. 13, 16, 3949.

[15]. Rodriguez, H., et al., 2021, The next horizon in precision oncology: Proteogenomics to inform cancer diagnosis and treatment. *Cell*. 184, 7, 1661–1670.

[16]. Sekaran, S., and Ganapathy, D., 2024, Tumor-grafted chorioallantoic membrane model: A versatile approach to study head and neck squamous cell carcinoma physiopathology and therapeutics testing. *Oral Oncology Reports*. 10, 100360, 100360.

[17]. Sever, R., and Brugge, J. S., 2015, Signal transduction in cancer. *Cold Spring Harbor perspectives in medicine*. 5, 4, a006098–a006098.

[18]. Tariq, M. U., et al., 2021, Methods for proteogenomics data analysis, challenges, and scalability bottlenecks: A survey. *IEEE access: practical innovations, open solutions*. 9, (2021), 5497–5516.

[19]. Terekhanova, N. V., et al., 2023, Epigenetic regulation during cancer transitions across 11 tumour types. *Nature*. 623, 7986, 432–441.

[20]. Yadalam, P. K., and Ardila, C. M., 2024, Artificial intelligence-driven multiomics network analysis reveals resistance mechanisms in oral cancer. *International dental journal*. 74, 5, 1180–1181.

[21]. Yip, H. Y. K., and Papa, A., 2021, Signaling pathways in cancer: Therapeutic targets, combinatorial treatments, and new developments. *Cells (Basel, Switzerland)*. 10, 3, 659.

[22]. Zhang, B., et al., 2014, Proteogenomic characterization of human colon and rectal cancer. *Nature*. 513, 7518, 382–387.

[23]. Zhang, Y., et al., 2017, A pan-cancer proteogenomic atlas of PI3K/AKT/mTOR pathway alterations. *Cancer cell*. 31, 6, 820–832.e3.