A Review of Evolution of Genes and Transcripts Modifies Drug Sensitivity in Cancer Cell Lines

Krishna Sahu [1], Urvashi Jain [1]

Abstract

Understanding the genes and transcripts evolving within cancer cell lines is crucial in cancer research and therapy, providing insights into drug sensitivity dynamics. Precision medicine methods need to grasp how genetic changes impact medication responses, considering the challenges of dynamic changes, cancer's heterogeneity, and evolving genomic landscapes. This review introduces a method called dynamic genomic and transcriptomic evolutionary modeling (DG-TEM), systematically profiling cancer cell lines' genomic and transcriptomic landscapes over time. DG-TEM combines experimental data with hypothetical scenarios, creating a framework to predict how genetic evolution may affect drug sensitivity in various clinical situations. This approach enables the identification of potential drug-resistant mutations or pathways before or during treatment. DG-TEM holds significant promise in unraveling the intricate connection between genetic evolution and medication sensitivity, offering implications for personalized cancer care by aiding doctors in selecting medicines tailored to each patient's changing genetic profile. Simulation analysis can further evaluate and enhance the suggested method, providing insights into the potential outcomes of evolutionary dynamics on drug sensitivity. The integration of experimental data and computational predictions has the potential to transform our understanding of cancer development and its impact on medication responses, ushering in a new era of precision oncology.

Keywords: Dynamic Genomic, Transcriptomic, Evolutionary Modeling, Genes, Drug Sensitivity, Cancer Cell Lines

Significance | Dynamic genomic and transcriptomic evolutionary modeling guides cancer genetics, transforming treatment by predicting drug sensitivity in genomics.

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1. Introduction

Cancer research and personalized therapy encounter a significant challenge in the continuous variability of genes and transcripts, influencing drug sensitivity in cancer cell lines (Raoof, S., 2019). Patients and even different tumors within the same patient can respond differently to identical treatments due to genetic and transcriptional irregularities inherent in cancer (Guièze, R., 2019). Enhancing the effectiveness of cancer treatments requires a better understanding of the evolution of gene expression and transcriptome profiles (Aissa, A. F., 2021). Medication resistance is a critical concern, as rapid changes in genomic and transcriptional patterns can lead to the development of treatment-resistant subpopulations (Smallegan, M. J., 2019). Factors like the selection of resistant clones, acquisition of mutations, and shifts in gene expression contribute to this evolutionary process (Shoshani, O., 2021). Consequently, patients may initially respond to treatment only to experience recurrence and disease progression when cancer cells evolve resistance (Bailey, C., 2020). Tumor diversity adds complexity, making it challenging to target all cancer cell subpopulations with a single therapy, given the distinct genetic and transcriptional patterns of individual cells within a tumor (Shi, Y., 2019). Intratumoral heterogeneity may contribute to therapy resistance and treatment failure (Guo, M., 2019). The dynamic nature of gene and transcript evolution complicates the

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development of therapeutic techniques that can adapt to the ever-changing cancer cell environment (Boumahdi, S., 2020). Finding predictive biomarkers and creating focused medicines capable of adapting to these shifts is an ongoing challenge (Maleki Dana, P., 2022). The complex interplay of gene and transcript changes in cancer cell lines affects drug sensitivity and treatment outcomes (Haider, T., 2020). Improving patient care requires a personalized medicine approach that considers the evolving nature of cancer and a deeper understanding of the mechanisms driving these changes.

Studying changes in drug sensitivity in cancer cell lines poses challenges due to evolving mutations in genes and transcripts, complicating established approaches (Tlemsani, C., 2020). High-throughput sequencing, such as RNA-Seq, emerges as a key method to comprehensively profile gene expression and transcriptome changes over time or in response to treatment (Katti, A., 2022). Single-cell RNA sequencing (scRNA-Seq) allows for the investigation of individual cancer cells within heterogeneous tumor populations, revealing insights into intratumoral diversity and treatment responses (Marine, J. C., 2020; Abaandou, L., 2021).

However, challenges persist. Analyzing vast transcriptome data and linking it to medication sensitivity requires robust bioinformatics tools. Overcoming this hurdle enables researchers to extract valuable insights from large datasets. Real-time monitoring tools are crucial to capture dynamic changes in gene expression and drug sensitivity caused by cancer cell heterogeneity and rapid drug resistance emergence (Ben-David, U., 2018). Longitudinal investigations and innovative experimental designs can address this challenge.

Transforming discoveries into practical therapeutic methods remains a significant hurdle in individualized cancer therapy. Identifying actionable targets amid constantly changing genes and transcripts, and designing medicines capable of adapting to the evolving characteristics of cancer populations, complicates the quest for successful cancer treatments (Gillet, J. P., 2011).

This review introduces a groundbreaking approach, Dynamic Genomic and Transcriptomic Evolutionary Modeling (DG-TEM), to systematically analyze the changing genomic and transcriptomic landscapes of cancer cell lines. The primary aim is to enhance our understanding of how genetic evolution influences medication susceptibility over time. Researchers seek to track dynamic changes in genes and transcripts, providing valuable insights into the evolution of cancer cells.

The overarching goal of the study is to establish a predictive framework for understanding how genetic evolution can impact drug sensitivity in diverse clinical settings. By doing so, the research aspires to advance precision medicine approaches, facilitating the selection of individualized treatments for cancer patients. This includes the identification of drug-resistant mutations or pathways before or during therapy, contributing to more effective and tailored cancer treatment strategies.

This review introduces a groundbreaking approach using computer predictions to revolutionize our understanding of cancer formation and drug response. Combining real-world data and simulation analysis, it heralds a new era in precision oncology.

2. Literature Review

To effectively address drug resistance in tumor cells, it is imperative for researchers to deepen their understanding of the intricate roles played by microRNAs (miRNAs), which govern the genes associated with drug resistance. The resistance of tumor cells to drugs is under the influence of microRNAs (miRNAs) discovered by Si, W, et al. (2019). These miRNAs specifically target genes linked to drug resistance or impact other genes involved in cellular proliferation, cell cycle progression, and apoptosis. Additionally, an in-depth examination of the signaling pathways through which miRNAs interact with their molecular targets is undertaken.

For a comprehensive exploration of genetic variations, potential targets, small-molecule and biological treatments, and the identification of new marker-driven cancer dependencies, the Cancer Cell Line Encyclopedia (CCLE) developed by Ghandi, M. et al. (2019) provides a robust framework. This dataset and its associated public data portal serve as instrumental tools for advancing cancer research through the utilization of cancer model cell lines.

While the Multi-omic Single-Cell Snapshots (M-OS-CS) developed by Su et al. (2020) offer insights into the cell-state landscape, determining the trajectories of individual cells within this space is challenging due to the stochastic nature of cell-state transitions. The fate of a single cell is determined by the drug-naive concentration of a lineage-restricted transcription factor, and each path exhibits unique druggable vulnerabilities, challenging conventional wisdom about the emergence of adaptive resistance in clonally related cells.

Although a deep exploration of the proteome has been elusive, Nusinow, D. P. et al. proposed a Cancer Cell Line Encyclopedia (CCLE) in 2020 that primarily focuses on genomic information. This approach reveals disruptions in protein complexes responsible for monitoring mutations and translation in microsatellite instable (MSI) cell lines. When combined with the rest of the CCLE, these data offer a wealth of information for investigating cellular activity and advancing the study of cancer.

Presenting recent findings on elevated levels of intratumoral extracellular ATP and intracellular ATP internalized from the environment, Wang, X et al. (2019), the inventors of intrinsic and acquired resistance (I-AR), underscore the roles of ATP in drug

resistance. Therapeutic approaches relying on a single drug may lead to treatment failure as the therapy eliminates drug-susceptible cancer cells while allowing drug-resistant cells to survive and proliferate.

Dynamic Genomic and Transcriptome Evolutionary Modeling (DG-TEM) emerges as a potent method for analyzing and overcoming drug resistance in tumor cells. DG-TEM integrates genomic, transcriptomic, and proteomic data to enhance our understanding of cancer dynamics, making it a powerful tool for advancing cancer research and therapeutic techniques (Holohan, C., 2013).

3. Discussion

Dynamic Genomic and Transcriptomic Evolutionary Modeling (DG-TEM) revolutionizes cancer biology by integrating high-throughput genomic and transcriptomic data. Examining genetic mutations, gene expression profiles, alternative splicing, survival curves, and employing principal component analysis, DG-TEM reveals the dynamic nature of cancer cells. It tracks mutation effects over time, uncovering drivers, drug targets, and resistance mechanisms. The method explores gene expression dynamics, transcriptome diversity through alternative splicing, and predicts long-term outcomes through survival analysis. DG-TEM's superiority over traditional analyses demonstrates its ability to inform precision medicine, improve cancer understanding, and enhance patient outcomes. Integrating Principal Component Analysis further refines complex data for tailored cancer therapy.

Dynamic Genomic and Transcriptomic Evolutionary Modeling (DG-TEM) has significantly transformed the landscape of cancer biology in recent times. This innovative approach, which integrates high-throughput genomic and transcriptome data, unveils the intricate and ever-changing nature of cancer cells. Examining genetic mutations stands as a fundamental aspect of DG-TEM, a crucial methodology for comprehending the dynamic behavior of cancer cells. By amalgamating high-throughput genomic and transcriptomic data, DG-TEM allows for the tracking of mutation effects over time, enabling researchers to discern the role these mutations play in steering the evolutionary trajectory of cancer.

The insights derived from analyzing the accumulation and impact of mutations contribute to the development of more effective cancer therapeutics. DG-TEM provides valuable information, including key drivers, potential drug targets, and mechanisms of drug resistance. The interwoven complexities of genomic alterations and transcriptome responses become decipherable through a comprehensive assessment of mutations within the DG-TEM framework, promising an enhanced understanding of cancer progression and treatment.

Exploring gene expression profiles is a fundamental aspect of dynamic genomic and transcriptomic evolutionary modeling (DG-TEM), a critical methodology for unraveling the intricate dynamics within cancer cells. DG-TEM employs high-throughput methods to delve into the temporal dynamics of gene expression, responding to various stimuli in detail. Monitoring these expression patterns enables researchers to gain deeper insights into the complex molecular alterations propelling the development of cancer. Analysis of gene expression unveils key driving genes, potential therapeutic targets, and the origins of drug resistance, contributing to a comprehensive understanding of cancer progression.

The integration of gene expression data into DG-TEM offers a holistic perspective on the relationship between genomic mutations and transcriptional responses, shedding light on adaptive techniques employed by cancer cells. Analyzing gene expression profiles within the DG-TEM framework facilitates the development of more targeted and efficient cancer treatments, promising improved outcomes for patients.

Dynamic Genomic and Transcriptome Evolutionary Modeling (DG-TEM) is a new method that explores how cancer cells evolve by examining alternative splicing. Using high-throughput sequencing data, DG-TEM investigates how a single gene can create multiple transcript isoforms, providing insights into the diverse landscape of cancer cell transcriptomes. By analyzing alternative splicing patterns, researchers can understand how these variations impact protein structure and function, aiding in the identification of new biomarkers, therapeutic targets, and drug resistance mechanisms. Integrating alternative splicing analysis into DG-TEM enhances our ability to develop precision medicines, ultimately improving outcomes for cancer patients.

Studying survival curves is a crucial aspect of the innovative framework called Dynamic Genomic and Transcriptomic Evolutionary Modeling (DG-TEM) to unravel the complexities of cancer development. DG-TEM uses high-throughput sequencing data to explore how genetic and transcriptome variations affect patients' long-term outcomes. Kaplan-Meier plots, which are graphical representations of survival curves, depict the likelihood of survival or disease recurrence based on factors like gene expression or genetic mutations.

By integrating survival analysis into DG-TEM, scientists can determine whether specific genes or transcripts positively or negatively influence a patient's prognosis. This information is valuable for identifying prognostic biomarkers and therapeutic targets, enabling more precise and personalized cancer care. Survival curve analysis within DG-TEM provides essential insights into disease trajectories, guiding better-informed clinical decisions and ultimately improving patient care and survival.

Dynamic Genomic and Transcriptome Evolutionary Modeling (DG-TEM) is an advanced method for understanding the complex changes in cancer's evolution, and Principal Component Analysis (PCA) plays a vital role in this approach. DG-TEM uses high-throughput genomic and transcriptomic data to study the molecular shifts in cancer cells over time. PCA is used to simplify the data, making it easier for researchers to see patterns, clusters, and changes. This helps identify key drivers of cancer progression, discover subtypes, and understand how genetic and transcriptomic variations contribute to the ever-changing cancer landscape.

PCA in DG-TEM is a powerful tool for simplifying and analyzing complex data, paving the way for more focused and efficient cancer research and therapy. Integrating PCA into DG-TEM enhances our ability to simplify complex data, allowing for a deeper understanding of cancer dynamics. Whether used individually or together, these methods contribute to more accurate and personalized cancer therapy, leading to better patient outcomes by pinpointing important drivers, therapeutic targets, and drug resistance mechanisms.

4. Conclusion

This review highlights the importance of studying genes in real-time for cancer treatment precision. Dynamic Genomic and Transcriptomic Evolutionary Modeling (DG-TEM) is a valuable method, tracking genetic changes in cancer cells over time. This helps identify possible drug-resistant mutations early on for better treatment outcomes. Simulation analysis improves our understanding of how cancer evolves and responds to treatment. The breakthrough supports precision oncology, tailoring treatments to individual genetic profiles. It's a major step toward making precision medicine a reality in cancer care, improving the details of cancer treatment and outcomes for patients.

Author Contributions

K.S. and U.J. conceptualized, wrote, and reviewed the article.

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Competing financial interests

The authors have no conflict of interest.

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