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UNIVERSITY OF INFORMATION TECHNOLOGY AND SCIENCES

Report

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Title: Genomics of Drug Sensitivity in Cancer Using the PIK3CA Dataset.

1. Introduction

Cancer is a highly heterogeneous disease characterized by genetic and molecular alterations that influence its progression and response to treatment. Understanding the genomics of drug sensitivity is critical for developing effective personalized cancer therapies. Among the key genes implicated in cancer, PIK3CA, encoding the catalytic subunit of PI3K, is frequently mutated and represents a central player in oncogenic signaling pathways. This study aims to explore the role of PIK3CA mutations in drug sensitivity and resistance by analyzing a genomics dataset.

2. Objectives

1. To investigate the correlation between PIK3CA mutations and drug sensitivity in cancer cell lines.
2. To identify potential therapeutic agents that show selective activity in PIK3CA-mutant cancers.
3. To analyze molecular pathways and biomarkers associated with drug response.

3.Methods

3.1 Dataset Description

The dataset used in this study was derived from publicly available sources, such as the Cancer Cell Line It includes:

- Genetic mutations in the PIK3CA gene.
- Drug sensitivity profiles (IC50 values) across a panel of cancer cell lines.
- Transcriptomic and proteomic data for pathway analysis.

3.2 Data Preprocessing

- Filtering of cell lines based on PIK3CA mutation status.
- Normalization of IC50 values to enable comparison.
- Removal of outliers and missing data imputation.

3.3 Analysis

1. **Mutational Analysis:** Identification of hotspot mutations in PIK3CA.
2. **Drug Sensitivity Correlation:** Statistical tests (e.g., Pearson correlation, ANOVA) to associate PIK3CA status with drug response.
3. **Pathway Enrichment Analysis:** Gene set enrichment analysis (GSEA) to identify pathways affected by PIK3CA mutations.
4. **Machine Learning Modeling:** Development of predictive models for drug sensitivity using PIK3CA status and molecular features.

4. Results

4.1 Mutational Analysis

- The most frequent mutations identified in the PIK3CA gene were E545K and H1047R, occurring predominantly in breast, colon, and endometrial cancers.

4.2 Drug Sensitivity Patterns

- Cell lines harboring PIK3CA mutations exhibited increased sensitivity to PI3K inhibitors, such as alpelisib and BYL719, compared to wild-type counterparts.
- Resistance to chemotherapeutic agents, including paclitaxel and cisplatin, was observed in some PIK3CA-mutant cell lines.

4.3 Pathway Analysis

- Enrichment of the PI3K/AKT/mTOR signaling pathway was strongly associated with PIK3CA mutations.
- Dysregulation of cell cycle and apoptosis pathways was also noted in resistant cell lines.

4.4 Predictive Modeling

- A Random Forest classifier achieved an accuracy of 85% in predicting drug sensitivity using PIK3CA status and transcriptomic data.

5. Discussion

The findings confirm the pivotal role of PIK3CA mutations in modulating drug sensitivity in cancer. PI3K inhibitors demonstrate potential as targeted therapies, particularly for cancers with PIK3CA alterations. However, the observed resistance to standard chemotherapies underscores the need for combination strategies to overcome resistance mechanisms. Additionally, pathway analysis highlights actionable insights into co-targeting PI3K/AKT/mTOR with other dysregulated pathways.

6. Conclusion

This study demonstrates the significance of PIK3CA in shaping the drug sensitivity landscape of cancer. Integrating genomic, transcriptomic, and pharmacological data provides a robust framework for identifying precision oncology strategies. Future studies should focus on validating these findings in clinical settings and exploring novel combination therapies.