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Correlating mRNA Expression between Neuroblastoma Cell Lines and Primary Tumors

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1. Abstract

1.1. Background: Numerous cell lines for neuroblastoma have been developed and are widely used to study biological processes of the cancer. The present study investigated the resemblance of these cell lines to neuroblastoma primary tumors in regards to gene expression. Moreover, the use of these cell lines in laboratories was evaluated.

1.2. Methods: RNA-sequencing data was retrieved from published datasets for 39 neuroblastoma cell lines and 160 primary neuroblastoma tumors. The most variable genes were used to calculate rank-based Spearman's correlation. PubMed was used to approximate the usage of cell lines.

1.3. Results: The observed median correlations ranged from 0.41 to 0.59. COG-N-557 showed the highest median correlation while NB-16 was the least correlated cell line. SH-SY5Y and SK-N-BE(2)-C subclones showed lower correlation than their parental cell lines. References to the lesser-correlated cell lines were found in the literature more often.

1.4. Discussion: Transcriptomic differences exist between neuroblastoma cell lines and primary tumors. Researchers should explore the transcriptomic relatedness and be mindful of differences thereof when selecting cell lines to study tumor biology.

2. Introduction

Neuroblastoma is neuroendocrine cancer arising in the developing sympathetic nervous system ultimately resulting in tumors in the adrenal glands and/or sympathetic ganglia [1]. To investigate the molecular biology of this cancer, cell lines are commonly used to model its tumors in vitro. From the inception of the first neuroblastoma cell line in the 1940s, the culturing of cell lines has become routine and has aided in studying pharmacological characteristics of tumors, such as drug sensitivity and resistance [2].

While many of these cell lines have been characterized on the genomic level, there has been no effort to analyze their transcriptomes and how they relate to those of primary neuroblastoma tumors. The present study aimed to analyze the correlation of the gene expression between tumors and cell lines of neuroblastoma.

3. Materials and Methods

RNA-sequencing data for 160 primary solid neuroblastoma tumors were taken from The Therapeutically Applicable Research to Generate Effective Treatments (TARGET) (https://ocg.cancer.gov/programs/target) of the National Cancer Institute (NCI) under the neuroblastoma database of Genotypes and Phenotypes (dbGAP) sub study ID phs000467. Published gene expression data for 39 neuroblastoma cell lines were downloaded from Gene Expression Omnibus under accession GSE89413, originally generated by Harenza et al [3].

The gene fragments per kilo base exons per million reads (FPKM) from both datasets were used and log-transformed. To account for intra-tumor heterogeneity and immune infiltrates, genes that were highly correlated with tumor purity scores ($R > -0.4$, adjusted p-value < 0.01) were removed. Purity scores (defined broadly as

the proportion of non-immune cells in the tissue sample) were calculated according to the ESTIMATE formula and pipeline by Yoshihara et al [4]. The top 5000 genes ranked by interquartile range (IQR) across primary tumor samples were selected to calculate rank-based Spearman correlations between cell lines and tumors, as these genes are likely biologically informative.

To estimate the frequency of use in laboratories, the name of each cell line was searched using PubMed search function (https://www.ncbi.nlm.nih.gov/pubmed/) on 15 July 2020 and the number of abstracts that mentioned the cell line name was recorded. Common punctuation alternatives were used to decrease likelihood of false-negative results.

4. Results

Median correlations ranged from 0.41 to 0.59. COG-N-557, SMS-KAN, and COG-N-573 showed the highest correlations while NB-16, CHP-212, and CK-N-AS were the least correlated (Figure 1).

PubMed citation analysis for the 39 cell lines revealed that the top 10 most correlated cell lines accounted for less than 15% of PubMed citations, while the least 10 correlated lines accumulated nearly 75% of PubMed citations.

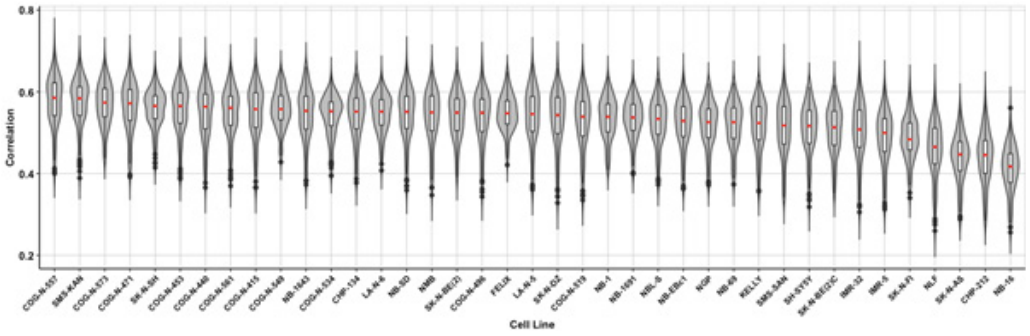

Figure 1: Violin plot of Spearman's correlations between neuroblastoma primary samples and cell lines. Median correlations range from 0.41 - 0.59. Overlaid boxplot represents upper and lower quartiles, with red line depicting the median.

5. Discussion/Conclusions

With numerous neuroblastoma cell lines developed, choosing optimal cell lines is a crucial aspect of experimental design. The results presented here show several cell lines display relatively less resemblance to primary tumors in regards to gene expression. The lack of comparable features in these cell lines may be attributed to acquired genomic damage or the heterogeneity of the TARGET tumor cohort and the disease itself.

It is interesting to note that within the top 10 most correlated cell lines, 8 were cell lines culture by the Children's Oncology Group (COG). Moreover, it should be pointed out that SK-N-BE(2)-C is a sub clone derived from SK-N-BE(2) [5]. SH-SY5Y is also a sub clone derived from parental line SK-N-SH [6]. According to the results, both these sub clones are less correlated than their respective parental cell lines. It is possible these changes are attributable to the sub culturing process. PubMed analysis revealed more abstracts referencing the lesser-correlated cell lines compared to the more strongly correlated lines. Of potential concern is SH-SY5Y, which has over 5000 PubMed citations. This may be explained by the fact that these cell lines are also commonly used for other diseases, such as Parkinson's disease [7].

Further experiments are warranted to elucidate any differences in gene expression that may affect the replicability of the disease process through these cell lines in vitro. Nonetheless, the hypothesis-generating data presented here lays the groundwork for further examination of neuroblastoma cell lines as tumor models.

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