Structural and Functional Analysis of ALK and NPM Genes at Translocation Breakpoints: Investigating Polymorphic CD30 and p53 in Silico

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Abstract

Chromosomal translocations between the anaplastic lymphoma kinase (ALK) and nucleophosmin (NPM) genes are known to play a key role in cancer development. The translocation t(2;5)(p23;q35) leads to the formation of the NPM–ALK fusion gene, which causes continuous activation of kinase activity and abnormal signaling through the JAK/STAT, PI3K/AKT, and MAPK pathways. Such uncontrolled signaling promotes tumor growth and survival in cancers like anaplastic large-cell lymphoma (ALCL) and non-small cell lung cancer (NSCLC). Additionally, genetic changes in CD30 (TNFRSF8) and p53 (TP53) are linked with tumor progression, therapy resistance, and defective apoptosis.

Materials and Methods: The study was conducted using an in silico approach to explore the structural and functional effects of ALK–NPM translocations. Genomic information was collected from NCBI, Ensembl, and UCSC Genome Browser to locate breakpoints of these genes. Protein structures were obtained from the Protein Data Bank (PDB) and analyzed using PyMOL and Chimera to observe changes in protein configuration. STRING-DB was used to create protein–protein interaction networks, while KEGG and DAVID were applied for pathway and gene ontology analysis. Mutation and translocation frequencies were compared using COSMIC and TCGA datasets. Statistical evaluations were carried out in R/Bioconductor.

Results: The computational analysis indicated that the NPM–ALK fusion protein remains active without external stimulation, resulting in constant cell growth signals. Pathway analysis through KEGG confirmed that ALK is involved in key cancer-related signaling systems, including MAPK/ERK and PI3K–AKT pathways. CD30 was found to be associated with the NF-κB pathway, enhancing tumor cell survival, while mutations in p53, such as R72P, were linked to reduced apoptosis and poor treatment response. Interaction analysis showed strong connections among ALK, NPM, STAT3, and MYC, confirming their combined role in tumor formation.

Discussion and Conclusion: This study highlights how ALK–NPM translocations and variations in CD30 and p53 genes together contribute to lymphoma progression. The findings suggest that targeting ALK with inhibitors like crizotinib or alectinib, along with CD30-directed therapies such as brentuximab vedotin, may improve treatment outcomes. By combining structural and pathway analysis, this research provides new understanding of the molecular mechanisms behind ALK-driven cancers. The results support the use of precision medicine to design better therapeutic approaches and patient-specific treatments.

Keywords

ALK-NPM Transloaction, Lymphoma, CD30, P53 Polymorphism, in silico Analysis.