Identification of Bone Metastasis Genetic Biomarkers in Lung Cancer: EGFR, CDKN2B, and CCDC6 Drive Bone Tropism and Survival Outcomes

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INTRODUCTION: Bone metastases (BM) are a major cause of morbidity and mortality in cancer patients, often leading to decreased survival and reduced quality of life. Despite their clinical significance, the genetic drivers and molecular mechanisms underlying bone metastasis in non-small cell lung cancer (NSCLC) remain poorly understood. Identifying key genetic alterations associated with BM could provide critical insights for prognostic stratification and the development of targeted therapies. This study aims to uncover genomic predictors of bone metastasis in NSCLC by analyzing large-scale clinical sequencing data.

METHODS:

We analyzed a comprehensive dataset of 25,000 metastatic cancer patients from the cBioPortal database (Nguyen et al., Cell 2022), focusing exclusively on samples derived from metastatic sites. Patients were stratified into two primary cohorts: those with bone metastasis (BM, n=4,006) and those without (No-BM, n=6,137). A secondary analysis was conducted within NSCLC patients, comparing BM (n=971) and No-BM (n=791) subgroups. Additionally, NSCLC-BM cases were compared to breast and prostate cancer BM cohorts to identify NSCLC-specific alterations. Statistical significance was determined using a threshold of $P < 0.05$. To assess the clinical relevance of identified genes, survival analysis was performed on over 11,000 patients across 22 independent lung cancer studies.

RESULTS:

Among 59 genetic alterations enriched in the pan-cancer BM cohort, three were significantly elevated in NSCLC-BM compared to NSCLC-No-BM: EGFR, CDKN2B, and CCDC6. Notably, none of these alterations overlapped with BM-associated mutations in breast or prostate cancer, suggesting NSCLC-specific mechanisms of bone tropism. Survival analysis revealed distinct prognostic implications: EGFR alterations correlated with improved overall survival (OS), CCDC6 alterations were associated with worse OS, and CDKN2B alterations had no significant impact on survival.

DISCUSSION AND CONCLUSION: This study identifies EGFR, CCDC6, and CDKN2B as potential genetic signatures of bone metastasis in NSCLC, with divergent effects on patient outcomes. The NSCLC-specific nature of these alterations highlights unique molecular pathways driving bone metastasis in lung cancer compared to other malignancies.