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Commentary

Chromatin Remodeling Complexes in Lung Cancer: Targeting SWI/SNF Mutations

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DESCRIPTION

Mutations in SWI/SNF chromatin remodeling complexes are prevalent in lung cancer and create unique vulnerabilities that can be exploited for targeted therapy development. Lung cancer remains the leading cause of cancer-related deaths globally, with Non-Small Cell Lung Cancer (NSCLC) accounting for approximately 85% of cases. Recent genomic studies have revealed that components of the Switch/Sucrose Non-Fermentable (SWI/SNF) chromatin remodeling complex are frequently mutated in lung cancer, occurring in approximately 20% of NSCLC cases.

The SWI/SNF complex is a multi-subunit chromatin remodeling machinery that uses ATP hydrolysis to mobilize nucleosomes and regulate gene expression. Key components frequently altered in lung cancer include *SMARCA4* (*BRG1*), *SMARCA2* (*BRM*), *ARID1A*, and *ARID1B*. These mutations typically result in loss of function, leading to aberrant chromatin structure and gene expression patterns that promote tumorigenesis.

SMARCA4 mutations are particularly common in lung adenocarcinoma, occurring in approximately 15% of cases. Loss of *SMARCA4* function disrupts the normal chromatin landscape, leading to silencing of tumor suppressor genes and activation of oncogenic pathways. Tumors with *SMARCA4* deficiency show distinct transcriptional profiles characterized by reduced expression of cell cycle checkpoint genes and DNA repair factors. The synthetic lethality approach has emerged as a promising strategy for targeting SWI/SNF-deficient tumors. Cells with *SMARCA4* mutations show increased dependence on *SMARCA2*, creating a therapeutic vulnerability. *SMARCA2* degraders, such as Proteolysis-Targeting Chimeras (PROTACs), have demonstrated efficacy in preclinical models and are currently being evaluated in clinical trials.

Another synthetic lethal interaction involves the DNA repair machinery. SWI/SNF-deficient tumors exhibit impaired homologous recombination repair, making them sensitive to PARP inhibitors. This sensitivity extends beyond BRCA-mutated tumors, expanding the population of lung cancer patients who may benefit from PARP inhibitor therapy. The immune microenvironment in SWI/SNF-deficient lung cancers is also distinct. These tumors often show increased tumor mutational burden and neoantigen presentation, leading to enhanced immune infiltration. The combination of SWI/SNF targeting with immune checkpoint inhibitors has shown synergistic effects in preclinical models, suggesting potential for combination therapy approaches.

Epigenetic therapy represents another avenue for targeting SWI/SNF-deficient tumors. *EZH2* inhibitors have shown particular promise, as SWI/SNF loss leads to increased dependence on *PRC2*-mediated gene silencing. The selective *EZH2* inhibitor tazemetostat has demonstrated activity in SWI/SNF-deficient tumors and is being evaluated in lung cancer clinical trials.

The development of biomarkers for SWI/SNF deficiency is crucial for patient selection. Immunohistochemistry for *SMARCA4* protein expression provides a rapid and cost-effective screening method. However, comprehensive genomic profiling may be necessary to identify all relevant mutations and guide therapeutic decisions. Resistance mechanisms to SWI/SNF-targeted therapies are beginning to emerge. Secondary mutations that restore SWI/SNF function, activation of alternative chromatin remodeling complexes, and metabolic reprogramming have all been implicated in treatment resistance. Understanding these mechanisms is essential for developing next-generation therapies.

CONCLUSION

The heterogeneity of SWI/SNF mutations presents both challenges and opportunities. Different mutation patterns may confer distinct vulnerabilities, requiring personalized treatment approaches. The development of companion diagnostics that can accurately identify specific SWI/SNF alterations will be essential for optimizing treatment selection. Future research should focus on developing combination therapies that target multiple vulnerabilities simultaneously. The integration of SWI/SNF status into routine clinical practice will require standardized assays and clear treatment guidelines. As our understanding of chromatin remodeling in lung cancer continues to evolve, new therapeutic opportunities will undoubtedly emerge.

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