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Perspective

Genomic Co-Alterations in *FGFR2* Fusions and Rearrangements across Advanced Solid Tumors

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DESCRIPTION

Fibroblast Growth Factor Receptor 2 (*FGFR2*) fusions and rearrangements have emerged as significant oncogenic drivers in various advanced solid tumors, including cholangiocarcinoma, gastric cancer and breast cancer. *FGFR2*, a member of the fibroblast growth factor receptor family, plays a pivotal role in cell proliferation, differentiation and survival. Aberrations in *FGFR2*, such as gene fusions or rearrangements, can lead to constitutive activation of downstream signaling pathways, driving tumorigenesis and disease progression. However, *FGFR2* alterations rarely occur in isolation. Instead, they are often accompanied by genomic co-alterations that can significantly influence tumor behavior, treatment response and resistance mechanisms. This article describes the region of genomic co-alterations associated with *FGFR2* fusions/rearrangements and their clinical implications in advanced solid tumors.

FGFR2 fusions and rearrangements

FGFR2 fusions and rearrangements involve the fusion of the *FGFR2* gene with various partner genes, resulting in aberrant activation of *FGFR2* signaling. These alterations are frequently observed in intrahepatic cholangiocarcinoma, where they are present in approximately 10% to 15% of cases. *FGFR2* fusions can lead to ligand-independent dimerization and constitutive activation of the receptor, driving oncogenic signaling through pathways such as MAPK, PI3K-AKT and STAT.

Common fusion partners for *FGFR2* include genes such as *BICC1, AHCYL1* and *PPHLN1,* among others. The diversity of fusion partners contributes to the heterogeneity observed in *FGFR2*-driven tumors. While *FGFR2*-targeted therapies, such as selective Tyrosine Kinase Inhibitors (TKIs) like pemigatinib and futibatinib, have shown potential clinical efficacy, responses can vary significantly based on the presence of additional genomic co-alterations.

Genomic co-alterations in *FGFR2*-driven tumors

Genomic co-alterations refer to additional genetic changes that coexist with *FGFR2* fusions/rearrangements in the same tumor. These alterations can affect main oncogenic and tumor suppressor pathways, contributing to tumor aggressiveness, therapeutic resistance and clinical outcomes.

***KRAS* and *NRAS* mutations:** RAS pathway mutations are frequently observed alongside *FGFR2* fusions and can drive resistance to FGFR inhibitors. Mutations in *KRAS* or *NRAS* often result in constitutive MAPK pathway activation, bypassing *FGFR2* signaling and rendering *FGFR*-targeted therapies less effective.

***PIK3CA* mutations:** Alterations in the PI3K pathway, such as *PIK3CA* mutations, are another common co-alteration. These mutations can sustain downstream signaling independently of *FGFR2* activation, promoting cell survival and therapy resistance.

***TP53* mutations:** *TP53* is one of the most commonly mutated tumor suppressor genes and is often co-altered with *FGFR2* rearrangements. Mutations in *TP53* can drive genomic instability and enhance tumor progression, complicating treatment strategies.

ERBB pathway alterations: Co-occurring ERBB pathway mutations or amplifications, such as those affecting ERBB2 (HER2) and ERBB3, can contribute to therapeutic resistance and tumor heterogeneity, further complicating targeted treatment approaches.

Clinical implications of genomic co-alterations

The presence of genomic co-alterations in tumors with *FGFR2* fusions/rearrangements has significant clinical implications. First, these co-alterations can influence sensitivity and resistance to FGFR inhibitors. For example, *KRAS* or *PIK3CA* mutations may render FGFR inhibitors less effective, necessitating combination therapies targeting multiple pathways.

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Second, genomic co-alterations can serve as potential biomarkers for predicting treatment response. Patients with *FGFR2* fusions and a lack of additional co-alterations may experience more strong and durable responses to FGFR inhibitors.

Lastly, understanding the genomic region of *FGFR2*-driven tumors is essential for designing personalized treatment strategies. Comprehensive genomic profiling, including Next-Generation Sequencing (NGS), can identify both *FGFR2* fusions and associated co-alterations, allowing for customized therapeutic interventions.

Future directions and challenges

Despite significant progress in targeting *FGFR2* fusions, therapeutic resistance remains a major challenge. Acquired resistance mechanisms, including secondary *FGFR2* mutations and activation of bypass signaling pathways, highlight the need for novel therapeutic strategies.

Future research should focus on developing combination therapies that address both *FGFR2* signaling and co-altered pathways. Additionally, more clinical trials are needed to validate the efficacy of targeted therapies in patients with specific co-alteration profiles.

FGFR2 fusions and rearrangements play a critical role in driving tumorigenesis in several advanced solid tumors. However, their clinical behavior and therapeutic response are heavily influenced by genomic co-alterations. Identifying and understanding these co-alterations is essential for optimizing targeted therapies and overcoming resistance mechanisms. With advances in genomic profiling technologies and a growing understanding of *FGFR2* biology, more effective and personalized treatment strategies are on the horizon.