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Role of PIK3CA mutations in cancer progression and treatment

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Abstract

PIK3CA mutations play a crucial role in oncogenesis by activating the PI3K/AKT signaling pathway, driving uncontrolled cell growth and contributing to cancer progression. Common mutations, particularly in exons 9 and 20, are found in various cancers, including breast, colorectal, endometrial, and head and neck cancers. These mutations are associated with treatment resistance, influencing therapeutic strategies, particularly the use of PI3K inhibitors like alpelisib. PIK3CA mutation testing is vital for guiding treatment decisions, prognosis, and clinical trial eligibility, especially in HR-positive, HER2-negative breast cancer. The detection of PIK3CA mutations, though challenging due to tumor heterogeneity and low mutation frequency, is essential for precision oncology, offering targeted therapy opportunities and informing resistance mechanisms in diverse cancer types.

Keywords: PIK3CA Mutations; PI3K/AKT Signaling Pathway; Mutation Testing; Treatment Resistance

Introduction

PIK3CA mutations are significant in the context of cancer biology, as they drive uncontrolled cell growth through the activation of the PI3K/AKT signaling pathway. Understanding whether a tumor harbors a PIK3CA mutation can help guide treatment choices, particularly the use of targeted therapies aimed at inhibiting this pathway. However, the clinical implications can vary depending on the type of cancer and the presence of other mutations. The PIK3CA mutation refers to changes in the PIK3CA gene, which codes for a subunit of the enzyme phosphatidylinositol 3-kinase (PI3K). This enzyme is involved in the PI3K/AKT signaling pathway, which plays a crucial role in regulating cellular functions such as growth, survival, metabolism, and differentiation. The PIK3CA gene mutation leads to abnormal activation of this pathway, which can promote cell proliferation, survival, and increased metabolism, contributing to the development of various cancers. Common Mutations involve exons 9 and 20, with common hotspots being: E542K, E545K (both in exon 9) and H1047R (in exon 20) (Ligresti G, et al. 2009) [1]. PIK3CA mutations are found in many types of cancer, particularly breast cancer, colon cancer, and endometrial cancer (Zardavas D, et al. 2014; Wang H 2024) [2].

The PIK3CA mutation leads to the constitutive activation of the PI3K/AKT pathway, allowing tumors to bypass normal growth controls and develop resistance to programmed cell death (apoptosis). This mutation carries significant clinical implications, particularly in the context of targeted therapy. The presence of a PIK3CA mutation can influence treatment strategies, as drugs targeting the PI3K pathway, such as PI3K inhibitors like alpelisib, have been specifically developed for cancers harboring these mutations. Additionally, combination therapies aimed at downstream signaling targets, such as mTOR inhibitors, are being investigated to enhance treatment efficacy. PIK3CA mutations can also act as prognostic biomarkers in certain cancers, although their impact on prognosis varies depending on the type of cancer and the presence of other genetic alterations. For instance, in specific breast cancer subtypes, these mutations are associated with a more favorable prognosis (Yang, J. et al., 2019) [3], though their prognostic implications remain highly context-dependent across different cancers.

Impact of PIK3CA Mutations on Cancer Progression, Prognosis, and Treatment Resistance

PIK3CA mutations are common in hormone receptor-positive, HER2-negative breast cancers, often correlating with a more favorable prognosis when treated with endocrine therapy, though they can also be associated with resistance to treatment. In endometrial cancers, PIK3CA mutations occur frequently, particularly in those with microsatellite instability or type I estrogen-driven cancers. In colon cancer, PIK3CA mutations are typically found in advanced stages and are often linked to poor prognosis, with some cases showing resistance to EGFR inhibitors such as cetuximab (Zardavas D, et al. 2014) [4]. In head and neck squamous cell carcinoma (HNSCC), PIK3CA mutations are among the most frequently observed oncogenic alterations, occurring in approximately 10-20% of cases. Common hotspot mutations, such as E542K and E545K in the helical domain and H1047R in the kinase domain, lead to constitutive activation of PI3K signaling, promoting tumor growth and survival. These mutations are particularly prevalent in HPV-positive HNSCC, where they occur in 20–30% of cases compared to HPV-negative tumors. In HPV-positive tumors, PIK3CA mutations interact synergistically with viral oncoproteins like E6 and E7, driving oncogenesis by inhibiting tumor suppressors and enhancing PI3K signaling pathways (Qiu W, et al. 2006) [4]. The prognostic significance of PIK3CA mutations in HNSCC remains complex and context-dependent. In HPV-positive HNSCC, these mutations may be associated with favorable outcomes when treated with de-intensified therapies. Conversely, in HPV-negative tumors, their presence often correlates with worse outcomes. Additionally, PIK3CA mutations play a crucial role in tumor metabolism and angiogenesis by enhancing glucose uptake, lipid synthesis, and vascular growth, thereby supporting the metabolic demands of tumor cells and facilitating invasion and growth (Cochicho D, et al. 2022) [5].

These mutations also contribute significantly to treatment resistance. Enhanced PI3K/AKT signaling promotes resistance to radiotherapy by improving DNA damage repair and reducing apoptosis, while also diminishing the efficacy of chemotherapy by supporting cellular survival pathways. Furthermore, PIK3CA mutations can create an immunosuppressive tumor microenvironment, limiting the effectiveness of immune checkpoint inhibitors (Dong C, et al. 2021) [6]. When PIK3CA inhibitors are used, tumors can sometimes develop resistance through secondary mutations or alternative signaling pathway activation. Mutations in PIK3CA can contribute to resistance against other therapies, such as hormone therapy in breast cancer. In colorectal cancer, PIK3CA mutations may indicate resistance to anti-EGFR therapies like cetuximab or panitumumab, guiding alternative treatment strategies. In breast cancer, these mutations help identify patients who may require combination treatments to overcome resistance to endocrine therapy (Wang Y, et al. 2025) [7]. In other cancers, such as ovarian and gastric cancers, PIK3CA mutations are also observed, where they can contribute to resistance against standard therapies, including hormone therapy in breast cancer. These insights highlight the diverse and significant roles of PIK3CA mutations across cancer types, influencing tumor progression, treatment resistance, and therapeutic opportunities (Samuels Y and Waldman T 2010) [8]. Despite these challenges, PIK3CA mutations represent a valuable therapeutic target. Drugs such as alpelisib and other PI3K inhibitors have shown promise in targeting PIK3CA-mutated tumors, particularly in clinical trials for HNSCC. Combination therapies, integrating PI3K inhibitors with radiation, chemotherapy, or immune checkpoint inhibitors, have demonstrated potential to improve treatment outcomes (Suleiman R, et al. 2024) [9].

Methods and Considerations for PIK3CA Mutation Testing

PIK3CA mutations can be detected using genetic testing methods, such as liquid biopsy techniques, quantitative polymerase chain reaction (qPCR), droplet digital PCR (ddPCR), allele-specific PCR (AS-PCR), melting curve analysis, next-generation sequencing (NGS), etc. (Board RE, et al. 2007; Filipenko ML, et al. 2016; Zeng Q, et al. 2017; Desriani, Al-Ahwani F. 2018; Oscorbin IP, et al. 2022; Nakai M, et al. 2022; Borkowska EM, et al 2021) [10-16]. The choice of sample plays a crucial role in PIK3CA mutation testing, as it can be performed on either tissue biopsy or liquid biopsy (ctDNA from blood). While liquid biopsies are less invasive, they may have lower sensitivity in detecting mutations. The clinical context further influences the relevance of a PIK3CA mutation, depending on the cancer type and stage. For instance, it is highly actionable in HR-positive, HER2-negative breast cancer but holds less clear significance in certain other tumor types (Seung, BJ and Sur, JH 2024) [17]. Patients with HR-positive, HER2-negative advanced breast cancer are tested for PIK3CA mutations to determine eligibility for alpelisib (a PI3K inhibitor) in combination with endocrine therapy. Approximately 40% of HR-positive breast cancers harbor actionable PIK3CA mutations, making testing crucial after progression on first-line endocrine therapy. In colorectal cancer, testing evaluates resistance to anti-EGFR therapies like cetuximab and panitumumab, as PIK3CA mutations, particularly in exon 20, may predict a lack of response. Testing is performed for metastatic or refractory colorectal cancer when planning targeted therapies or exploring clinical trials. In head and neck squamous cell carcinoma (HNSCC), PIK3CA mutations, which are common in HPV-positive cases, guide the use of investigational PI3K inhibitors and provide insights into prognosis and resistance mechanisms, particularly for recurrent or metastatic disease in clinical trial settings. For endometrial cancer, where PIK3CA mutations are frequently found, testing helps guide the use of PI3K/AKT/mTOR pathway inhibitors, often for advanced or recurrent cases when standard therapies have failed (Wilhoit T et al. 2020) [18].

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Patients with PIK3CA-related overgrowth spectrum (PROS) disorders, such as CLOVES syndrome or macrodactyly, undergo testing to confirm the diagnosis and guide targeted therapies for symptom control when clinical symptoms suggest a PROS disorder. For cancers of unknown primary (CUP), testing aids tumor profiling and identifies actionable mutations for targeted therapy, especially for advanced or metastatic CUP where standard treatments are ineffective. Patients exploring clinical trial options may require evidence of a PIK3CA mutation to determine eligibility for novel PI3K/AKT/mTOR pathway inhibitors, particularly for recurrent or metastatic disease or cancers with limited standard treatment options. Lastly, in rare or advanced cancers like ovarian cancer or glioblastoma, testing identifies actionable PIK3CA mutations relevant to PI3K pathway activation, often when conventional therapies have failed and molecular profiling is needed to guide treatment (Keppler-Noreuil KM, et al. 2015) [19].

Testing methodology is another key factor, with the choice of technology, such as NGS or PCR, affecting the test's sensitivity, specificity, and cost. NGS provides comprehensive insights but is more resource-intensive. The presence of co-mutations can also alter the clinical significance of PIK3CA mutations, as other mutations (e.g., in TP53 or KRAS) may influence prognosis and treatment response (Lin XY, et al. 2023) [20]. Resistance development remains a challenge, as tumors with actionable mutations may develop resistance to PI3K inhibitors, necessitating ongoing monitoring and potential therapy adjustments. Variant classification adds complexity, as not all PIK3CA mutations share the same clinical significance; while "hotspot" mutations (e.g., E542K, E545K, H1047R) are well-characterized, other variants may have uncertain significance. Lastly, regulatory approvals determine the availability of FDA-approved drugs targeting PIK3CA mutations, which vary by cancer type. For contexts where approvals are lacking, participation in clinical trials may be the only viable option (Tufail M, et al. 2024) [21].

Limitations of PIK3CA Mutation Testing

Tumor heterogeneity poses a challenge, as a PIK3CA mutation may not be present in all cancer cells, and testing a single biopsy could miss mutations in other parts of the tumor. Low mutant allele frequency (MAF) can further complicate detection, especially in cases of low tumor purity or circulating tumor DNA (ctDNA) analysis, where mutations may be present at low levels, affecting sensitivity (Sivakumar S, et al. 2023) [22]. False negatives are another concern, as testing methods with lower sensitivity, such as Sanger sequencing, may miss low-frequency mutations, making advanced methods like next-generation sequencing (NGS) preferable, albeit more expensive. False positives can also arise due to technical errors, particularly in ultra-sensitive techniques like droplet digital PCR. The predictive utility of PIK3CA testing may be limited in some cancers; while it is highly predictive for treatment selection in HR-positive breast cancer, its role in cancers like colorectal or endometrial cancer remains less clear and under investigation. Moreover, PIK3CA-specific tests do not comprehensively detect other alterations in the PI3K/AKT/mTOR pathway, such as mutations in PTEN, AKT1, or amplification of PIK3CA. The cost and accessibility of comprehensive genomic testing add another layer of difficulty, as it can be expensive and may not be covered by all insurance plans. Lastly, the presence of secondary mutations or pathway cross-talk, such as with the MAPK pathway, may limit the efficacy of PI3K-targeted therapies despite the detection of a PIK3CA mutation.

Summary

PIK3CA mutations drive cancer progression by activating the PI3K/AKT pathway, contributing to tumor growth and resistance to treatments. These mutations are common in cancers like breast, colorectal, and head and neck. Testing for PIK3CA mutations helps guide targeted therapies, such as PI3K inhibitors, and is important for prognosis and clinical trial eligibility. Despite detection challenges, such testing plays a key role in precision oncology, offering insights for personalized treatment strategies and overcoming resistance.

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