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Clinical and Preclinical Targeting of Oncogenic Pathways in PDAC: Focused Therapeutic Strategies for the Most Lethal Cancer

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Abstract

Pancreatic Ductal Adenocarcinoma is among the most lethal cancers, characterized by limited treatment options and poor prognosis. Its hallmark resistance to conventional therapies necessitates the exploration of targeted therapeutic approaches. Recent advances have significantly deepened our understanding of the oncogenic pathways driving PDAC development and progression. This article reviews clinical and preclinical strategies targeting these pathways, highlighting promising avenues for treating this deadly cancer.

Keywords: Cancer • Oncogenic pathways • Preclinical research

Introduction

Pancreatic Ductal Adenocarcinoma (PDAC) remains one of oncology's most challenging adversaries, with a five-year survival rate of less than 15%. Despite advancements in cancer treatment, PDAC continues to resist conventional chemotherapy and radiation therapy, necessitating the exploration of alternative therapeutic approaches. Targeted therapies directed against specific oncogenic pathways have emerged as a promising strategy to improve outcomes for PDAC patients. This article reviews the key oncogenic pathways implicated in PDAC and discusses the progress in clinical and preclinical targeting of these pathways [1].

Literature Review

PDAC is characterized by the dysregulation of multiple signaling pathways involved in cell proliferation, survival, invasion and metastasis. The most commonly implicated oncogenic pathways include KRAS, PI3K/AKT/mTOR, MAPK and TGF-β signaling. Mutations in the KRAS oncogene occur in nearly 90% of PDAC cases, making it a prime target for therapeutic intervention. The activation of the PI3K/AKT/mTOR pathway promotes tumor growth and survival, while aberrant MAPK signaling drives proliferation and invasion. TGF-β signaling plays a dual role in PDAC, functioning as both a tumor suppressor and a promoter of metastasis [2].

Discussion

Cancer encompasses a spectrum of diseases marked by varied genetic and molecular traits. Personalized medicine, evolving through clinical trials, customizes treatments based on patients' genetic profiles. Another avenue explores the tumor microenvironment, notably the stromal element pivotal in PDAC advancement and treatment resistance. Ongoing trials examine stroma-targeting drugs like hedgehog pathway inhibitors and focal adhesion kinase inhibitors alongside conventional chemotherapy to gauge their combined efficacy. These trials aim to uncover synergistic effects that could enhance treatment outcomes, potentially revolutionizing cancer care. By dissecting the intricate biology of tumors and their microenvironments, researchers strive to develop more precise and effective therapeutic strategies, offering hope for improved patient outcomes and quality of life. Research focusing on small molecule inhibitors and monoclonal antibodies targeting KRAS, the prevalent oncogene in PDAC, shows promise. Despite longstanding challenges due to KRAS's intricate biology and limited drug gable sites, recent advancements in targeted protein degradation and nucleotide-binding pocket inhibitors offer renewed optimism for effective KRAS suppression in PDAC. Alongside clinical trials, preclinical investigations have provided crucial insights into novel therapeutic avenues. Genetically Engineered Mouse Models (GEMMs) have been pivotal, allowing researchers to delve into specific oncogenic pathways, pinpoint potential targets and assess novel treatments before clinical trials [3,4].

This signifies that treatments can be finely tuned to match each individual's unique condition. For instance, certain breast cancer patients with specific genetic mutations may respond more favorably to hormone-based therapies rather than chemotherapy. Genomic insights also hold vital importance in early detection and prevention. Genetic screenings can pinpoint individuals at higher risk of particular diseases, enabling proactive interventions and lifestyle adjustments to mitigate those risks. Dedicated trials focus on early cancer detection and prevention. Screening and diagnostic techniques are advancing, becoming more sophisticated and less invasive and offering the potential to detect cancer at its earliest, most treatable stages. While progress in cancer clinical trials is promising, challenges persist. Participation rates, especially among underrepresented groups, require enhancement. Moreover, concerns linger regarding the affordability of novel treatments and ensuring fair access. Considering the diverse nature of PDAC and its intricate oncogenic pathways, combination therapies targeting multiple pathways are likely more effective than single-agent approaches. Additionally, personalized medicine and biomarker-driven therapy have opened avenues for tailored treatment strategies based on individual tumor molecular profiles. Biomarkers such as KRAS mutation status, DNA damage repair deficiencies and immune checkpoint expression can pinpoint patients most likely to benefit from specific targeted therapies [5,6].

Conclusion

To sum up, targeting oncogenic pathways stands out as a promising avenue for PDAC treatment. Clinical trials exploring agents aimed at crucial signaling pathways have yielded promising findings, despite hurdles in tackling tumor heterogeneity and resistance. Preclinical investigations persist in revealing new targets and strategies, fostering optimism for better PDAC

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outcomes ahead. Looking ahead, a multidisciplinary framework, merging clinical trials, preclinical studies and personalized medicine, will be pivotal in propelling PDAC therapeutics forward and enhancing patient well-bein.

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Conflict of Interest

No potential conflict of interest was reported by the authors.

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