Clinical and Preclinical Targeting of Oncogenic Pathways in PDAC: Targeted Therapeutic Approaches for the Deadliest Cancer

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Abstract

Pancreatic Ductal Adenocarcinoma (PDAC) stands as one of the most lethal forms of cancer with limited treatment options and poor prognosis. The hallmark of PDAC is its resistance to conventional therapies, urging the exploration of targeted therapeutic approaches. In recent years, significant progress has been made in understanding the oncogenic pathways driving PDAC development and progression. This article provides an overview of the clinical and preclinical strategies targeting these pathways, offering insights into promising avenues for the treatment of this deadly cancer.

Keywords: Pancreatic ductal adenocarcinoma • Oncogenic pathways • Preclinical research

Introduction

Pancreatic Ductal Adenocarcinoma (PDAC) remains a formidable challenge in oncology, with a five-year survival rate of less than 10%. Despite advancements in cancer treatment, PDAC continues to exhibit resistance to 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. In this article, we review the key oncogenic pathways implicated in PDAC and discuss 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. Among the most commonly implicated oncogenic pathways are the KRAS, PI3K/AKT/mTOR, MAPK, and TGF-β signaling pathways. Mutations in the KRAS oncogene occur in nearly 90% of PDAC cases, making it a prime target for therapeutic intervention. 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, acting as both a tumor suppressor and a promoter of metastasis [2].

Discussion

Cancer is not a singular disease but rather a collection of diseases with diverse genetic and molecular characteristics. Clinical trials have been instrumental in advancing the field of personalized medicine, where treatments are tailored to the genetic makeup of individual patients. Another approach involves targeting the tumor microenvironment, particularly the stromal component, which plays a crucial role in PDAC progression and resistance to therapy. Clinical trials evaluating stroma-targeting agents, such as hedgehog pathway inhibitors and focal adhesion kinase inhibitors, are underway to assess their efficacy in combination with standard chemotherapy regimens [3].

One promising avenue of research is the development of small molecule inhibitors and monoclonal antibodies targeting KRAS, the most frequently mutated oncogene in PDAC. Despite decades of effort, direct targeting of mutant KRAS has proven challenging due to its complex biology and lack of druggable binding sites. However, recent advances in targeted protein degradation and nucleotide-binding pocket inhibitors offer renewed hope for effective KRAS inhibition in PDAC. In addition to clinical trials, preclinical research has provided valuable insights into novel therapeutic targets and treatment strategies for PDAC. The development of Genetically Engineered Mouse Models (GEMMs) has enabled researchers to study the role of specific oncogenic pathways in PDAC initiation and progression. These models have been instrumental in identifying potential therapeutic targets and testing novel treatment approaches in preclinical settings [4].

This means that therapies can be designed to precisely match the individual's condition. For example, some breast cancer patients with specific genetic mutations may respond better to hormone-based therapies rather than chemotherapy. Genomic insights also play a crucial role in early detection and prevention. Genetic tests can identify individuals with a higher risk of developing specific diseases, allowing for proactive interventions and lifestyle modifications to mitigate that risk.

Some trials are dedicated to the early detection and prevention of cancer. Screening and diagnostic tests are becoming more sophisticated and less invasive, offering the potential to catch cancer at its earliest, most treatable stages. While advancements in cancer clinical trials are promising, there are challenges to overcome. Clinical trial participation rates, especially among underrepresented groups, need improvement. Additionally, the cost of novel treatments and ensuring equitable access are ongoing concerns. Given the heterogeneous nature of PDAC and the complexity of its oncogenic pathways, combination therapies targeting multiple pathways are likely to be more effective than single-agent approaches. Furthermore, the advent of personalized medicine and biomarker-driven therapy has paved the way for tailored treatment strategies based on the molecular profile of individual tumors. Biomarkers such as KRAS mutation status, DNA damage repair defects, and immune checkpoint expression can help identify patients who are most likely to benefit from specific targeted therapies [5,6].

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Conclusion

In conclusion, targeted therapeutic approaches aimed at inhibiting oncogenic pathways represent a promising strategy for the treatment of PDAC. Clinical trials investigating targeted agents directed against key signaling pathways have shown encouraging results, although challenges remain in overcoming tumor heterogeneity and resistance mechanisms. Preclinical research continues to uncover novel therapeutic targets and treatment strategies, offering hope for improved outcomes for PDAC patients in the future. Moving forward, a multidisciplinary approach integrating clinical trials, preclinical research, and personalized medicine will be essential for advancing the field of PDAC therapeutics and ultimately improving patient outcomes.

Acknowledgement

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Conflict of Interest

No potential conflict of interest was reported by the authors.

References

1. Fisher, Anita MR, A. Linn Murphree and Charles J. Gomer. "Clinical and preclinical photodynamic therapy." *Lasers Surg Med* 17 (1995): 2-31.

2. Obermeyer, Ziad and Ezekiel J. Emanuel. "Predicting the future-big data, machine learning, and clinical medicine." *N Engl J Med* 375 (2016): 1216.

3. Kurita, Geana P., Per Sjøgren, Ola Ekholm and Stein Kaasa, et al. "Prevalence and predictors of cognitive dysfunction in opioid-treated patients with cancer: A multinational study." *J Clin Oncol* 29 (2011): 1297-1303.

4. Klint, Åsa, Elisabeth Bondesson, Birgit H. Rasmussen and Carl Johan Fürst, et al. "Dying with unrelieved pain—prescription of opioids is not enough." *J Pain Symptom Manag* 59 (2019): 794-791.

5. Cheng, Wei-Yi, Tai-Hsien Ou Yang and Dimitris Anastassiou. "Development of a prognostic model for breast cancer survival in an open challenge environment." *Sci Transl Med* 5 (2013): 191ra50-191ra50.

6. Scarborough, Bethann M. and Cardinale B. Smith. "Optimal pain management for patients with cancer in the modern era." *CA: Cancer J Clin* 69 (2019): 192-196.

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