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Perspective

Disrupting Resistance: Enhancing Therapy in Pancreatic Ductal Adenocarcinoma

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DESCRIPTION

Pancreatic Ductal Adenocarcinoma (PDAC) is a highly aggressive malignancy characterized by poor prognosis and limited therapeutic options. As the most common type of pancreatic cancer, PDAC accounts for approximately 90% of pancreatic tumours and remains one of the leading causes of cancer-related mortality worldwide. The unique biological features of PDAC, including its dense stroma, late diagnosis, and resistance to conventional therapies, present significant barriers to effective treatment. Understanding these challenges is important for developing innovative therapeutic strategies. PDAC originates from the ductal epithelial cells of the pancreas and is often associated with risk factors such as smoking, obesity, diabetes, and genetic predisposition. The tumour microenvironment in PDAC is notably distinct due to its fibrotic stroma, which comprises a complex network of Extracellular Matrix (ECM) components, immune cells, and fibroblasts. This desmoplastic reaction not only contributes to tumour progression but also serves as a physical barrier to therapeutic agents.

Therapeutic resistance

PDAC exhibits inherent resistance to various treatment modalities, including surgery, chemotherapy, and radiation. Several factors contribute to this resistance:

Stromal composition: The dense stroma not only impedes drug delivery but also alters the tumour's metabolic environment. The presence of Cancer-Associated Fibroblasts (CAFs) can enhance tumour growth and provide protective signals that render cancer cells more resistant to therapy.

Genetic heterogeneity: PDAC is characterized by extensive genetic heterogeneity, leading to variations in response to treatment. Mutations in key oncogenes, such as *KRAS*, and tumor suppressor genes, such as *TP53* and *CDKN2A*, contribute to this complexity, making it challenging to design universal therapeutic approaches.

Cellular plasticity: PDAC cells exhibit significant plasticity, allowing them to adapt to therapeutic pressures. This adaptability can result in the emergence of drug-resistant clones, complicating treatment regimens and necessitating combination therapies to overcome resistance.

Current therapeutic approaches

Current treatment options for PDAC include surgical resection, chemotherapy, and radiation therapy. The most common chemotherapeutic regimen involves a combination of gemcitabine and nab-paclitaxel, which has shown modest improvements in survival.

Novel therapeutic strategies

To improve therapeutic efficacy against PDAC, researchers are exploring several innovative strategies:

Targeting the stroma: Approaches aimed at modifying the tumor microenvironment are gaining traction. Agents that inhibit the hedgehog signalling pathway or disrupt the interactions between cancer cells and CAFs have shown potential in preclinical models. These strategies aim to reduce the desmoplastic stroma, thereby enhancing drug delivery and sensitivity.

Immunotherapy: The potential of immunotherapy in PDAC is an area of active research. Immune checkpoint inhibitors, such as pembrolizumab, have demonstrated efficacy in other malignancies but have shown limited success in PDAC. Ongoing studies are investigating combinations of immune checkpoint inhibitors with other therapeutic agents, including chemotherapy and targeted therapies, to enhance immune responses.

Targeted therapies: Inhibitors of the *KRAS* pathway, such as sotorasib, have entered clinical trials, reflecting a growing interest in personalized medicine approaches for PDAC.

Nanoparticle-based delivery systems: Novel drug delivery systems, including nanoparticles, are being developed to improve the bioavailability of therapeutic agents. These systems can enhance the targeted delivery of drugs directly to tumor cells while minimizing systemic toxicity.

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CONCLUSION

PDAC remains one of the most challenging cancers to treat due to its aggressive nature and multiple barriers to therapeutic efficacy. Ongoing research efforts focused on understanding the tumour microenvironment, genetic heterogeneity, and cellular plasticity are important for developing effective treatment strategies. Advances in targeted therapies, immunotherapy, and innovative drug delivery systems hold potential for improving outcomes in patients with PDAC. As we continue to explain the complexities of this malignancy, the hope for enhanced therapeutic efficacy and better survival rates becomes increasingly attainable.