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Journal of Cell Signaling

Opinion Article

Targeting Hedgehog Signaling for Therapeutic Resistance in Pancreatic Cancer: A Path Worth Reconsidering

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DESCRIPTION

Pancreatic Ductal Adenocarcinoma (PDAC), the most common form of pancreatic cancer, remains one of the most lethal malignancies, with a five-year survival rate still in the single digits. Despite recent advances in chemotherapy and immunotherapy, therapeutic resistance remains a formidable barrier to long-term disease control. Among the various signaling pathways implicated in PDAC pathogenesis, the Hedgehog (Hh) signaling pathway stands out due to its multifaceted role in tumor progression, stroma modulation and, crucially, drug resistance. Hedgehog signaling, which plays a vital role in embryonic development and adult tissue homeostasis, is aberrantly activated in pancreatic cancer. The pathway is initiated by the binding of Hh ligands (e.g., Sonic Hedgehog or SHH) to the Patched receptor, relieving inhibition of the Smoothened (SMO) protein and activating downstream GLI transcription factors. In PDAC, however, Hh signaling is unique it is often paracrine, where tumor cells secrete Hh ligands that activate the pathway in surrounding stromal fibroblasts, leading to desmoplastic expansion and remodeling of the Tumor MicroEnvironment (TME).

Initial studies generated considerable excitement about targeting Hh signaling in PDAC. Preclinical models showed that SMO inhibitors like vismodegib and saridegib could deplete the dense fibrotic stroma and improve drug delivery. However, these findings did not translate into clinical success. Multiple clinical trials combining SMO inhibitors with chemotherapy showed no significant survival benefit and in some cases, paradoxical acceleration of tumor progression occurred. This unexpected outcome raised doubts about whether Hh signaling was a viable therapeutic target. Yet, dismissing the Hedgehog pathway entirely may be premature. The failure of early clinical approaches likely reflects an incomplete understanding of the pathway's role in PDAC rather than a fundamental flaw in targeting it. For one, stromal fibroblasts activated by Hh signaling are not uniformly tumor-promoting. Recent work has shown that some stromal components may actually restrain tumor aggressiveness. Hence, blanket depletion of the stroma by Hh inhibition may remove protective barriers and promote metastasis.

Moreover, non-canonical Hedgehog signaling, which bypasses SMO and directly activates GLI transcription factors, has been increasingly recognized in pancreatic cancer cells. These alternative routes mediated by oncogenic KRAS, TGF-β, or PI3K/AKT signalling may sustain GLI activity even in the absence of canonical ligand-receptor interaction. This raises a critical concern: SMO inhibitors may fail to fully suppress GLI-driven oncogenic programs, allowing cancer cells to maintain their resistant and aggressive phenotype. In this light, attention has shifted toward directly targeting GLI transcription factors, or the epigenetic and metabolic regulators that modulate their expression and activity. Agents like GANT61 (a GLI antagonist) or bromodomain inhibitors that indirectly suppress GLI function have shown promise in preclinical studies. These drugs, when combined with chemotherapy or immune checkpoint inhibitors, may enhance sensitivity and overcome resistance mechanisms. However, their clinical development remains in early stages, hampered by delivery challenges and toxicity concerns.

Another compelling rationale for reconsidering Hedgehog targeting lies in its contribution to cancer stem cell (CSC) maintenance. CSCs are believed to underlie tumor recurrence and resistance to standard therapies. Hedgehog signaling has been implicated in sustaining the stem-like properties of PDAC cells, especially under chemotherapeutic stress. Inhibiting this axis could help eradicate the resistant cell subpopulations that drive relapse, a critical step toward long-term remission. Additionally, the immunosuppressive nature of the Hh-modulated stroma presents another therapeutic opportunity. The dense matrix not only impedes drug penetration but also excludes cytotoxic T cells and antigen-presenting cells. Combining Hh pathway inhibition with immune modulation strategies may reprogram the TME into a more permissive state for immunotherapy, which has otherwise shown limited benefit in PDAC.

Therefore, the way forward may lie not in abandoning Hedgehog signaling as a therapeutic target, but in refining how and when it

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Received: 02-Feb-2025, Manuscript No. JCS-25-38272; **Editor assigned:** 05-Feb-2025, PreQC No. JCS-25-38272 (PQ); **Reviewed:** 19-Feb-2025, QC No. JCS-25-38272; **Revised:** 26-Feb-2025, Manuscript No. JCS-25-38272 (R); **Published:** 03-Mar-2025, DOI: 10.35248/2576-1471.25.10.391.

Citation: Michaels LE (2025). Targeting Hedgehog Signaling for Therapeutic Resistance in Pancreatic Cancer: A Path Worth Reconsidering. J Cell Signal.10:391.

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is targeted. Precision approaches that consider tumor stage, stromal composition and the presence of non-canonical signaling could help identify the subset of patients most likely to benefit. Importantly, newer inhibitors must address the limitations of previous agents by targeting downstream effectors and minimizing systemic side effects.

CONCLUSION

While early clinical failures dampened enthusiasm for Hedgehog pathway inhibition in pancreatic cancer, new mechanistic insights suggest this strategy still holds value-if applied with greater nuance. The pathway's role in mediating therapeutic resistance, sustaining cancer stemness and shaping the tumor microenvironment makes it an attractive, albeit complex, target. Future research should prioritize context-specific interventions, including combination therapies that integrate GLI inhibition, stromal modulation and immune activation. The path forward is not simple, but with deeper understanding and improved tools, targeting Hedgehog signaling could still be a key component in overcoming therapeutic resistance and improving outcomes in pancreatic cancer.