Therapeutic Methods and Pancreatic Cancer Stem Cells

Hari Prasad Sonwani*

Department of Pharmacy, Apollo Group of Institution, Durg, India

Abstract

With 1-5% 5-year survival rates (6-month median survival duration) despite medication, pancreatic ductal adenocarcinoma (PDAC), one of the deadliest human malignancies, provides an unmet therapeutic challenge. PDAC accounts for 90% of all pancreatic malignancies and is the most prevalent histological subtype. It is a very aggressive and complex malignancy that manifests with early local invasion and metastasis and is resistant to the majority of treatments, all of which are thought to be factors in its incredibly bad prognosis. PDAC is characterized by molecular changes, including as mutations of the WNT, K-RAS, TP53, Hedgehog, transforming growth factor-, and NOTCH signaling pathways (90% of cases). Given that cancer stem cells play a significant role in medication resistance, the relapse or recurrence of numerous diseases, as well as tumor start and progression. They might make good targets for potent, cutting-edge medicinal strategies. Here, we examined contemporary treatment approaches that use chemotherapeutics and targeted medicines, non-coding RNAs (siRNA and miRNAs), immunotherapy, and natural substances to target pancreatic cancer stem cells.

Keywords: Pancreatic cancer; Cancer stem cells; Polyphenolic; microRNA; Targeted therapy; Immunotherapy; Drug resistance

Introduction

90% of PaCas are pancreatic ductal adenocarcinomas (PDAC), which are a significant histological subtype [1]. Although both the exocrine and endocrine cells of the pancreas can develop cancer, islet cell tumors (such as insulinomas, glucagonomas, and somatostatinomas) and neuroendocrine tumors (such as gastrinomas) are the more uncommon endocrine pancreas cancers. It is far more frequent for exocrine cells to generate PaCa, and almost all of these tumors are adenocarcinomas [2]. With currently accessible therapy, PDAC has a very poor prognosis, with 5-year survival rates of 1-5% (6-month median survival length) [3-5]. At the time of diagnosis, local metastasis affects 80–90% of PDAC patients. Since surgery is not an option for these patients, they get regular medical therapy utilizing chemotherapeutic drugs such gemcitabineor a mix of leucovorin [6] and 5-urouracil (5-FU). PDAC has a high mortality rate, which is due to the disease's aggressiveness, early local and distant metastases, inherent resistance to chemotherapy, and lack of effective treatments. Additionally, a significant role in the poor prognosis of PDAC is the lack of early diagnostic tests, which impede early treatment measures [4] (Figure 1).

weakening the HH signaling pathway showing that HH signaling is crucial for pancreatic CSC function.

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which is suggestive of the self-renewal of stem-like cells. Gemcitabine and rapamycin together have been observed to signi cantly reduce CSC survival, indicating that mTOR inhibitors may be particularly useful. in addition to conventional therapies to speci cally target CSCs [28].

Metformin the anti-diabetic medication metformin has been linked to the targeting of CSCs, particularly pancreatic CSCs. It does this by lowering the expression of self-renewal-associated genes such NANOG,

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pancreatic CSCs and cancer cells. MiR-21 and miR-221 are up-regulated in pancreatic CSCs and support critical biological processes in the development of cancer by encouraging cell migration, proliferation, and resistance to chemotherapy. Targeting CSCs to block miR-21 and miR-221 is maybe a treatment approach for PaCa.

Cluster of miR-17-92: Strong phenotypic variations observed in CSCs may also be explained by epigenetic processes. Chemoresistant CSCs exhibit down-regulation of the miR-17-92 cluster. e miR-17-92 cluster prevents NODAL/ACTIVIN/TGF-1 signaling, which encourages chemoresistance in CSCs. e loss of CSC characteristics and subsequent loss of in vivo tumorigenicity are caused by overexpression of miR-17-92.

An RNA-binding protein called LIN28B controls how cells develop and di erentiate. Human primary PaCa tissues have a new CSC subpopulation that overexpresses both CD44 and LIN28B at the cell surface; this pancreatic CSC subpopulation proliferates quickly, demonstrates MDR, highly invasive ability, and high adherin levels. Consequently, pancreatic CSCs that are CD44+/LIN28B+ may be an e ective in vitro model, either to investigate cancer cell invasion, self-renewal, and metastasis, or to judge how well new PDAC treatments work. When cisplatin and gemcitabine hydrochloride were utilized as chemotherapy medicines, CD44+/LIN28B+ pancreatic CSCs were more resistant to growth inhibition, and In vivo, tumors formed quickly and easily. In these CD44+/LIN28B+ pancreatic CSCs, siRNA interference in endogenous LIN28b gene expression not only decreased their proliferative capacity but also inhibited the cell cycle since cyclin D1 expression was suppressed a er miRNA LET-7B expression was stimulated.

In PaCa cell lines, miR-1246 has been found to promote chemoresistance and CSC stemness. Cyclin-G2 (CCNG2) is a tumor suppressor gene that miR-1246 targets and regulates. Inhibition of CCNG2, which prevents CSCs from proliferating, invading, di erentiating, and becoming resistant to chemotherapy, may at least

carotenoids that has been the subject of the most research, has strong antioxidant properties because of its lengthy conjugated hydrocarbon chain. A natural pigment produced by plants and microbes, not by animals, lycopene is an acyclic isomer of -carotene. Carcinogenesis has been found to be prevented by lycopene. Lycopene has been shown to be e ective against xenogra tumors in several in vivo experiments because it produces apoptosis and inhibits cell-cycle progression in a variety of cancer cells.

Ca eic acid phenethyl ester (CAPE) and propolis: It is known that propolis, a sticky substance that bees gather from a variety of plant sources for their hives, has pharmacological action, including anticancer, antioxidant, and anti-in ammatory properties. Bioactive Activation of enzymes including xanthine oxidase, cyclo-oxygenase, and transcriptional factor NF-B has been demonstrated to be inhibited by propolis components like CAPE, which have been shown to have antioxidant and anti-in ammatory characteristics. CAPE is a powerful apoptosis-inducing drug and suppresses EMT in PaCa. Caspase-3/ caspase-7 activation and the creation of mitochondrial dysfunction may both contribute to its antiproliferative e ects. In PaCa cells, CAPE causes apoptosis a er autophagy is inhibited in both a caspase-dependent and caspase-independent manner. Apoptosis, cell cycle, self-renewal, progenitor generation, and the phenotype of CD44 cell markers were all a ected by CAPE, according to Coral et al.'s investigation into the e ect of CAPE on breast CSCs produced from aggressive triple-negative breast cancer cells. eir ndings overwhelmingly imply that CSCs a er CAPE treatment are brought into a less malignant condition and may terminally di erentiate their o spring, making them more chemosensitive.

Future considerations and the verdict

e CSC concept has signi cant clinical signi cance since it o ers the possibility to enhance therapy, maintain remission, or result in a full cure. It also o ers a beautiful model of carcinogenesis. A growing body of research demonstrates that CSC-targeted treatments work well in a preclinical context and have a noticeable survival advantage. Although further research is required to substantiate these claims, CSCs appear to be a potent target for more potent cancer therapy. A realistic approach to clinical translational may combine systems biology and bioinformatics approach to determine the best way to use all of the knowledge produced by the preclinical investigations. e preclinical studies have identi ed signal hubs, molecular mediators, and crossroads as being common to all of the molecular signaling pathways necessary for CSC survival and maintenance. ese results might serve as the basis for logically constructed molecular treatments that target CSCs. In order to be successful, future research should concentrate on identifying i) CSC-speci c pathways that can be pharmacologically targeted, ii) CSC-speci c surface markers for antibody therapy, iii) gene silencing approaches by siRNA or miRNA, and iv) natural products that promote the di erentiation of CSCs into progenitors that do not self-renew or that di erentiate only into normal tissue cells [17]. Although CSCs are a very exciting target for therapy, there are still a lot of uncertainties surrounding the CSC idea. Future target number one is to address the issue of clonal evolution, speci cally through the observation of CSCs both during the onset of cancer and a er treatment. Although CSCs may be a signi cant therapeutic target, it is yet unknown how to best reduce their capacity to advance, spread, and resist therapy in the host environment.

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