

Mechanisms of Tumor Progression and Drug Resistance in Pancreatic Cancer Models (PANC-1, MiaPaCa-2, and BxPC-3) – A Review

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Pancreatic cancer is one of the most lethal malignancies, accounting for approximately 3–4% of all cancers but nearly 7–8% of cancer-related deaths worldwide, with a 5-year survival rate of less than 12%. Its aggressive biology, early metastatic spread, and profound resistance to chemotherapy contribute to poor clinical outcomes. Due to these challenges, *in vitro* pancreatic cancer cell line models have become indispensable tools for elucidating molecular mechanisms underlying tumor progression and drug resistance. This review comprehensively evaluates three widely used pancreatic cancer cell lines PANC-1, MiaPaCa-2, and BxPC-3 highlighting their distinct molecular, phenotypic, and genetic characteristics and their relevance in anticancer drug discovery. PANC-1 cells, characterized by KRAS mutations and high mesenchymal marker expression, are extensively utilized to study epithelial–mesenchymal transition (EMT), migration, and invasiveness. MiaPaCa-2 cells exhibit enhanced glycolytic activity, stemness-associated markers, and pronounced chemoresistance, making them valuable for investigating cancer stem cell behavior and metabolic adaptations. In contrast, BxPC-3 cells, which are KRAS wild-type, serve as an important model for assessing drug sensitivity and therapeutic response mechanisms, particularly to gemcitabine and targeted agents. Comparative analyses across these models have significantly advanced understanding of key drug resistance pathways, including EMT-driven resistance, altered metabolic signaling, and survival pathway activation, and have facilitated preclinical screening of standard chemotherapeutics and emerging novel compounds. Furthermore, cross-model comparisons provide insights into tumor heterogeneity and support the identification of predictive biomarkers for therapeutic outcomes. Although conventional cell lines remain essential molecular tools, their inability to fully recapitulate the tumor microenvironment limits translational relevance. Therefore, integrating advanced systems such as organoids, patient-derived xenografts, and co-culture models is crucial to bridge the gap between preclinical research and clinical application and to improve therapeutic strategies for pancreatic cancer.

Keywords: Anticancer drug screening; BxPC-3; Drug resistance; MiaPaCa-2; Pancreatic cancer; PANC-1; Targeted therapy.

Pancreatic cancer is the 12th most common cancer worldwide and the seventh leading cause of cancer mortality.¹ Its poor prognosis is largely due to late-stage diagnosis, with a five-year survival rate below 10%, rapid metastasis, and resistance to conventional therapies. With an estimated 9.1 million disability-adjusted life years in 2017,² it represents a major global disease burden.³ The low treatment success rate is attributed to its aggressive clinical course, poor response to chemotherapy or radiotherapy, deep anatomical location, limited tissue accessibility, and absence of reliable screening methods.³ The lifetime cumulative risk is about 1 in 64.^t Modifiable risk factors include chronic pancreatitis, obesity, diabetes, smoking, and chemical exposures, while age, gender, family history, and genetic disorders are non-modifiable.^u Early-onset pancreatic cancer is increasingly reported among younger individuals,^v often associated with aggressive histology and poor prognosis.^w Surgery with adjuvant chemotherapy remains the standard for resectable pancreatic ductal adenocarcinoma (PDAC).^x However, most patients are diagnosed with advanced disease, and only 15–20% undergo surgery; even then, recurrence within a year is common.^y Gemcitabine, long considered the gold standard, improved survival compared with 5-fluorouracil (5-FU).^p More recently, gemcitabine plus nab-paclitaxel and the FOLFIRINOX regimen (5-FU, leucovorin, irinotecan, oxaliplatin)^{11,12} have become standard for metastatic disease. A modified FOLFIRINOX protocol as adjuvant therapy showed superior outcomes, with higher disease-free survival (21.6 vs. 12.8 months) and overall survival (54.4 vs. 35.0 months) compared with gemcitabine.¹³ Effective clinical care is still significantly hampered by inherent chemoresistance and the asymptomatic nature of early-stage illness, despite advancements in medical imaging and treatment protocols.¹⁴ In translational cancer research, cell lines are essential because they act as a link between fundamental laboratory results and practical uses. A controlled and repeatable platform for researching the cellular and molecular mechanisms of cancer genesis, progression, and response to treatment is provided by these *in vitro* models. Cell lines allow researchers to analyze the intricate signaling pathways that contribute to tumor growth, invasion, and medication

resistance in the setting of pancreatic cancer.¹⁵ They also facilitate high-throughput screening of novel compounds, genetic manipulations using CRISPR or RNA interference, and evaluation of combination therapies before progressing to *in vivo* studies. Moreover, pancreatic cancer cell lines reflect distinct genetic and phenotypic features of the disease, allowing for subtype-specific investigations. As a result, they are indispensable tools in identifying potential therapeutic targets, validating biomarkers, and accelerating the translation of benchside discoveries into effective clinical strategies. This review's objective is to examine the biological and molecular traits of these widely used pancreatic cancer cell lines, emphasising their value for researching tumor growth and treatment resistance. By doing so, we underscore their utility in preclinical drug screening, biomarker discovery, and development of targeted therapies aimed at improving patient outcomes.

MATERIALS AND METHODS

A literature search was performed in PubMed, Scopus, Web of Science, and Google Scholar for studies published between January 2000 and July 2025 on the molecular features, aggressiveness, and chemoresistance of pancreatic cancer cell lines. Keywords included “PANC-1,” “MiaPaCa-2,” “BxPC-3,” “pancreatic cancer cell lines,” “tumor aggressiveness,” “drug resistance,” “KRAS/MAPK,” “PI3K/AKT/mTOR,” “hypoxia,” “HIF-1 α ,” “VEGF,” “DNA damage repair,” “ATM/ATR,” and “BRCA.” Only peer-reviewed articles in English were included. To find further pertinent studies, the reference lists of the publications that were obtained were also examined. Studies focusing on molecular pathways, signaling differences, and resistance mechanisms in these cell lines were prioritized, while non-relevant, duplicate, or non-original research reports were excluded.

An Overview of Cell Lines for Pancreatic Cancer

PANC-1

The human pancreatic cancer cell line PANC-1 has been the subject of much research. It is produced from a primary pancreatic ductal adenocarcinoma (Fig.1). It harbors a KRAS

mutation, a hallmark of pancreatic cancer, which drives oncogenic signaling and contributes to its aggressive behavior. PANC-1 cells exhibit a predominantly mesenchymal phenotype, characterized by reduced cell–cell adhesion and enhanced migratory capacity, making them a valuable model for investigating epithelial-to-mesenchymal transition (EMT). The pancreatic ductal adenocarcinoma cell lines' genomic and phenotypic characteristics are used to assess how well they respond to peptide receptor radionuclide therapy and neuroendocrine chemotherapy. MIA PaCa 2, which is polymorphic, expresses the mesenchymal marker vimentin and the epithelial markers CK5.6, AE1/AE3, and E cadherin, according to immunohistochemistry and flow cytometry. Additionally, it exhibits neuroendocrine differentiation by expressing synaptophysin and chromogranin-A, as well as hormonal receptors (SSTR2 and NTR1), yet it is devoid of CD56. On the other hand, PANC 1, which exhibits pleomorphism, expresses vimentin, chromogranin-A, CD56, MNF 116, CK5.6, & SSTR2, but not NTR1, E cadherin, or synaptophysin. Both lines feature significant genetic alterations typical of pancreatic cancer, such as homozygous deletion of exons 1-3 of CDKN2A/

p16INK4A and KRAS and TP53 mutations, despite the fact that neither line shows microsatellite instability or SMAD4/DPC4 mutations. Importantly, both cell lines express SSTR2 receptors and show neuroendocrine development, which supports their utility as in vitro models for investigating targeted treatments based on somatostatin in pancreatic cancer.¹⁶Morphological and biochemical characterization of the PANC 1 cell line to determine whether it retains key features of differentiated human pancreatic ductal epithelium. The authors found that PANC 1 cells maintain epithelial-class intermediate filaments, exhibit basolateral localization of Na⁺/K⁺ ATPase, form complete tight junctions, and adopt a cuboidal morphology when cultured on collagen-coated supports or basement membrane substrates, mirroring ducts observed in situ.

Biochemically, PANC 1 cells express α glutamyl transpeptidase, carbonic anhydrase, and functional Na⁺/K⁺ ATPase activity assessed via [³H]ouabain binding resembling enzymatic profiles of native rat and human pancreatic ducts. Additionally, they synthesize and secrete high molecular weight sulfated proteins (ranging ~180/ kDa to 1/ MDa), with a predominant species of

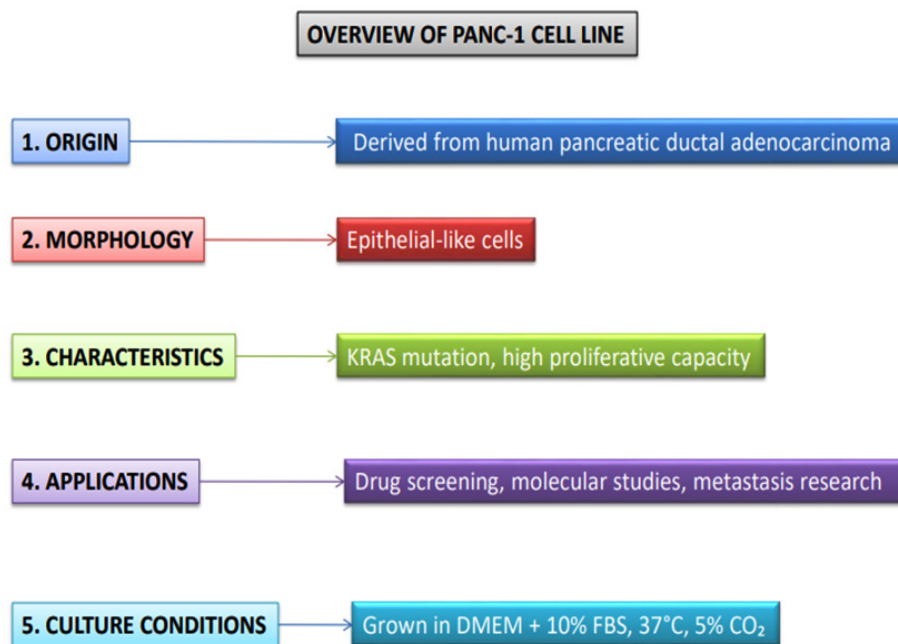


Fig.1. Overview of Pancreatic Cancer Cell Line – PANC-1

~660/ kDa, demonstrating secretory behavior consistent with ductal epithelium. Comparative analyses revealed that PANC 1 cells closely resemble other ductal-origin lines (e.g., MDCK), and differ markedly from mesenchymal-derived lines such as L cells, confirming their epithelial lineage. The findings suggest that PANC 1 retains several fundamental differentiated traits structural, enzymatic, and secretory making it a valuable model for investigating ductal secretion and epithelial function *in vitro*.¹⁷PANC 1 derivatives stably expressing either a dominant negative HRAS mutant (HRAS^{ΔS17N}), a constitutively active KRAS^{G12V}, or an EGFP control, then treated these cells with TGF β 1 and profiled gene expression changes across three independent experiments. Their findings revealed that activation state of RAS critically influenced TGF β 1-driven responses: Genes related to extracellular matrix remodelling, cell adhesion, and epithelial–mesenchymal transition (EMT) showed increased transcriptional activation in cells with active KRAS^{G12V} when compared to controls;

dominant negative HRAS mitigated these effects. In functional terms, this meant that constitutive KRAS activation potentiated TGF β 1 induced EMT-like features including upregulation of mesenchymal markers and motility related genes while HRAS inhibition reduced these phenotypic shifts. These results emphasize a cooperative interplay between oncogenic RAS signaling and TGF β 1 pathways in driving EMT and aggressive behavior in PANC 1 cells, providing mechanistic insight into how KRAS mutations promote tumor progression in pancreatic ductal adenocarcinoma.¹⁸ Along with EMT-type cells, a subpopulation of pancreatic cancer stem cells (CSCs) identified by markers like CD44, CD24, ESA, and CD133 are crucial for the development of metastatic pancreatic cancer and therapeutic resistance. CSCs possess defining features of self-renewal, multipotency, and high tumorigenicity, and are inherently more resilient to conventional chemoradiotherapy. EMT is typified by an overexpression of mesenchymal factors, which also encourage invasiveness, and a downregulation of epithelial markers such E

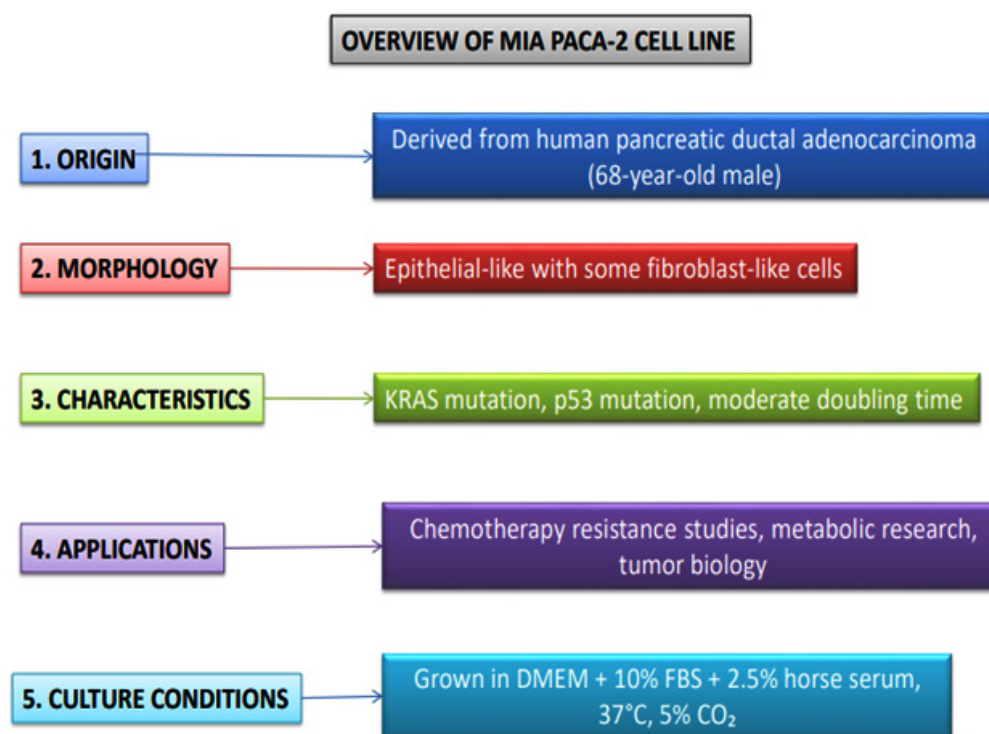


Fig. 2. Overview of Pancreatic Cancer Cell Line – MIA PaCa-2

cadherin (like vimentin, Zeb 1/Slug) also seems to give tumor cells stem-like characteristics, which supports a CSC phenotype. This dual CSC/EMT phenotype contributes significantly to both intrinsic and acquired chemoresistance as well as metastatic potential. Consequently, the authors argue that targeting CSCs and reversing EMT phenotypes are promising strategies to enhance drug sensitivity, suppress metastasis, and ultimately improve clinical outcomes in pancreatic ductal adenocarcinoma (PDAC).¹⁹ Due to their plasticity and expression of stemness-associated markers, PANC-1 cells are frequently used in studies exploring cancer stem cell properties and tumor heterogeneity. Furthermore, they display intrinsic resistance to chemotherapeutic agents like gemcitabine, positioning them as a robust model for evaluating mechanisms of drug resistance and testing novel therapeutic strategies aimed at overcoming treatment failure in pancreatic cancer.

MiaPaCa-2

MiaPaCa-2 is a human pancreatic ductal adenocarcinoma cell line widely utilized in cancer biology due to its well-characterized genetic and metabolic profile (Fig.2). Originating from a moderately differentiated pancreatic carcinoma,

MiaPaCa-2 cells harbor a KRAS mutation, which drives oncogenic signaling and contributes to their aggressive phenotype. One of the defining features of this cell line is its high glycolytic activity, making it an ideal model for studying the metabolic reprogramming commonly seen in pancreatic tumors. MiaPaCa-2 cells also exhibit significant mitochondrial dysfunction and oxidative stress, which has made them a valuable tool in research focusing on cancer cell metabolism, mitochondrial targeting, and apoptosis.

The functional influence on PDAC progression and the clinical importance of fibroblast activation protein- α (FAP) stromal expression. 98% of 48 PDAC specimens had stromal FAP expression, according to immunohistochemical examination; the expression varied in intensity from weak to strong and was not present in non-cancerous pancreatic tissue. Overall survival was considerably lower for patients with moderate to strong FAP expression (mean survival H³⁵² days) than for those with weak or negative expression (H⁴⁹⁷ days; $p = 0.006$). The scientists created human FAP-expressing NIH 3T3 fibroblast lines and cocultured them indirectly that is, without direct cell contact with MiaPaCa 2 pancreatic cancer cells

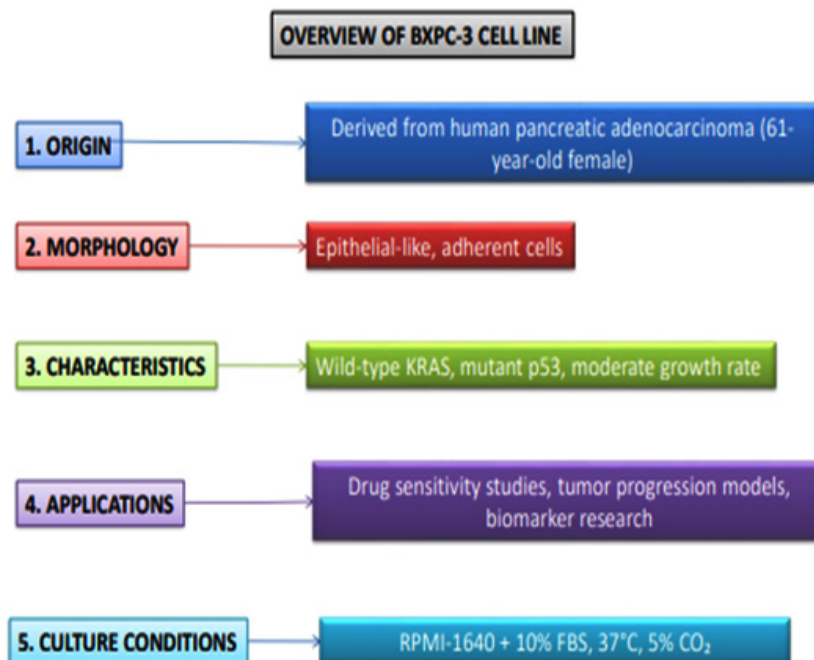


Fig. 3. Overview of Pancreatic Cancer Cell Line – BxPC-3

in order to investigate possible causes. As opposed to coculturing with fibroblasts that were control and did not express FAP, coculture with fibroblasts that expressed FAP markedly increased the invasiveness of MiaPaCa 2. Additionally, by encouraging the phosphorylation of the retinoblastoma (Rb) protein, FAP-expressing fibroblasts sped up the cell cycle progression of MiaPaCa 2 cells, causing them to transition from G₀/G₁ to S/G₂/M phases. Together, these findings imply that stromal FAP expression is a negative prognostic indicator in PDAC and functionally contributes to tumor aggressiveness by enhancing cancer cell invasion and proliferation through paracrine stromal–epithelial interactions.²⁰ In MiaPaCa 2 human pancreatic adenocarcinoma cells, the anticancer activity and underlying molecular mechanisms of Tan IIA, a bioactive chemical produced from *Salvia miltiorrhiza*. Tan IIA treatment markedly reduced the expression of EGFR, IGF1R, VEGFR, Ras, Raf, MEK, ERK, PI3K, AKT, and mTOR, while also affecting PTEN. Molecular analyses revealed that Tan IIA inhibits the Ras/Raf/MEK/

ERK and PI3K/AKT/mTOR pathways, key drivers of pancreatic cancer survival and proliferation. As a result, MiaPaCa 2 cells exposed to Tan IIA exhibited marked reductions in growth and viability, indicating that targeting these parallel kinase cascades may be an effective strategy for suppressing tumor aggressiveness in this model.²¹ A novel strategy to impair oncogenic KRAS signaling in pancreatic cancer by targeting lipid metabolism, specifically focusing on phosphatidylserine (PS) remodeling. They show that the enzyme LPCAT3, responsible for generating unsaturated PS species essential for KRAS nanocluster formation at the plasma membrane, is a key dependency in KRAS mutant pancreatic cancer cells such as MiaPaCa 2. Silencing LPCAT3 via siRNA or CRISPR, as well as using small-molecule inhibitors (HTS3/HTS4), led to depletion of unsaturated PS, mislocalization of mutant KRAS from the membrane, disruption of KRAS nanoclustering, and suppression of MAPK signaling. This resulted in significantly reduced proliferation and colony-forming ability in KRAS-dependent tumor cells, with minimal

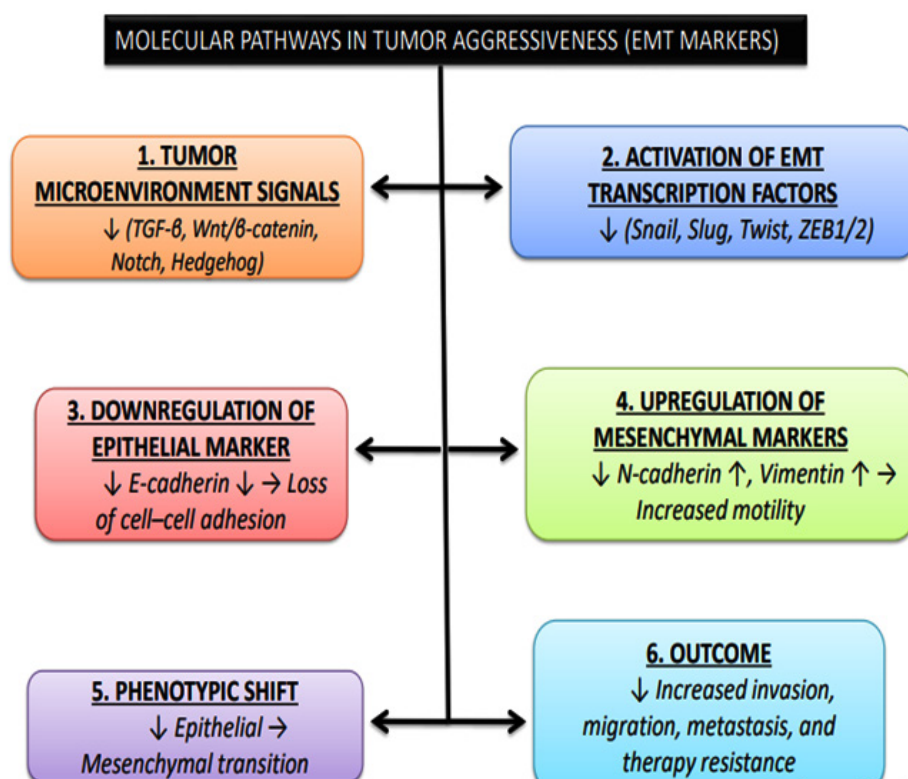


Fig. 4. Molecular Pathways in Aggressiveness – EMT in BxPC-3 / MIA PaCa-2

SOX2, NANOG, AND OCT4 SHOW OVERLAPPING EXPRESSION ACROSS STEM CELL TYPES

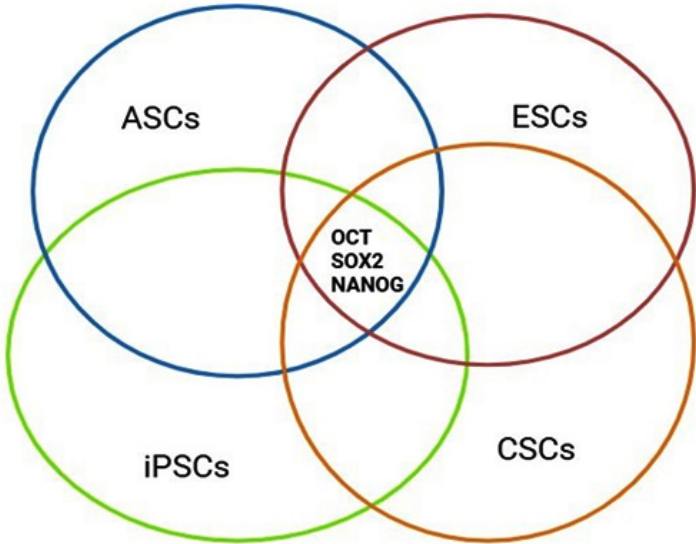


Fig. 5. SOX2, NANOG, and OCT4 show overlapping expression across all four stem cell types : embryonic stem cells (ESCs), adult stem cells (ASCs), induced pluripotent stem cells (iPSCs), and cancer stem cells (CSCs)

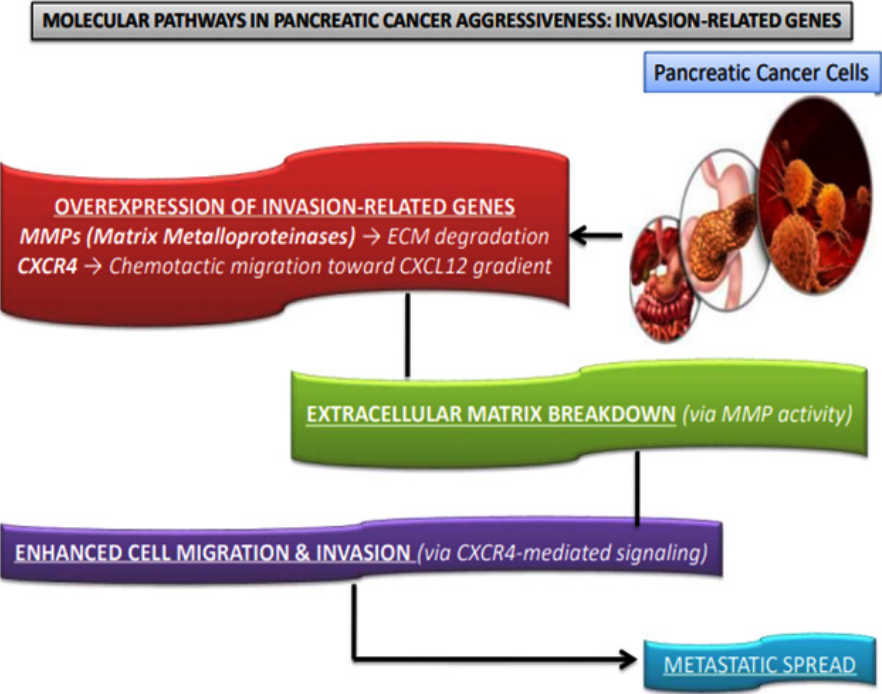


Fig. 6. Molecular Pathways in Pancreatic Cancer Aggressiveness: Invasion-related Genes

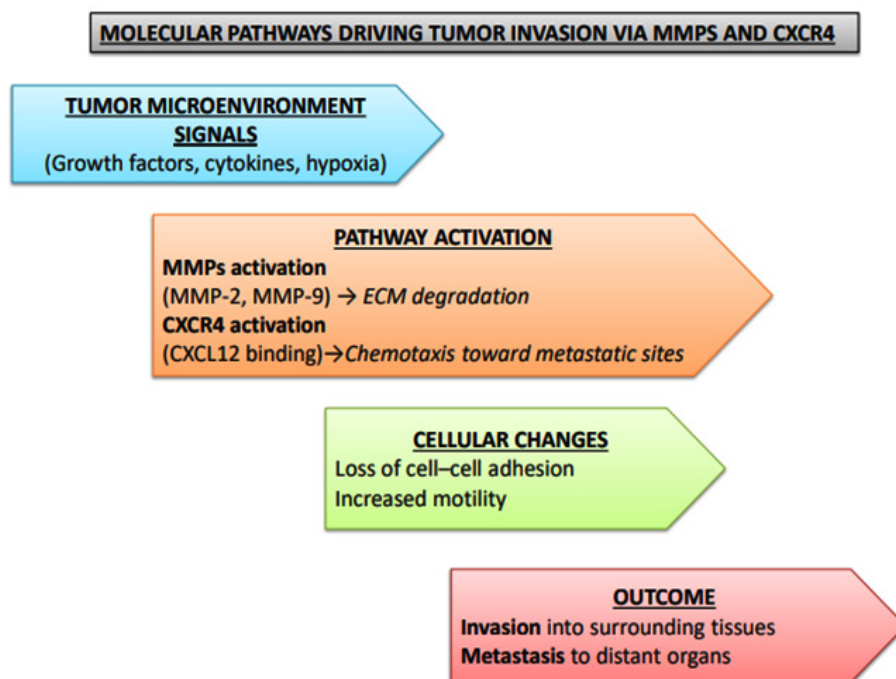


Fig. 7. Molecular Pathways Driving Tumour Invasion via MMPs and CXCR4

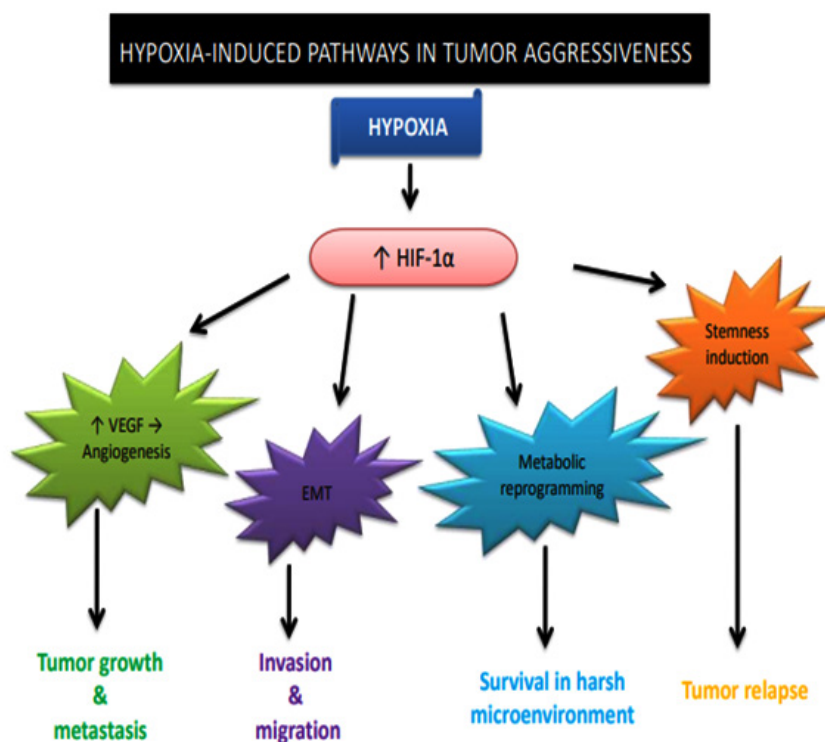


Fig. 8. Hypoxia Pathways Driving Cancer Aggressiveness

effects in KRAS wild-type cells. These findings highlight LPCAT3 inhibition as a potential pan-KRAS-targeting therapeutic approach that bypasses allele-specific resistance mechanisms and disrupts KRAS-driven tumorigenesis by perturbing essential lipid-mediated nanoscale architecture on the plasma membrane.²²Through a variety of ways, it has been demonstrated that the naturally occurring anthraquinone compound aloe emodin has strong anticancer effects on the human pancreatic adenocarcinoma cell lines. Cell viability

and colony formation were significantly reduced as a result of the treatment, with MiaPaCa-2 cells showing higher sensitivity than PANC-1. Aloe emodin caused chromatin condensation, membrane blebbing, and cell shrinkage all of which are obvious morphological changes associated with apoptosis. Both early and late apoptotic cell populations significantly increased, according to flow cytometry data, and there was a noticeable buildup of cells in the sub-G1 phase, which suggests apoptotic DNA fragmentation. Importantly, aloe

Table 1. Molecular Pathways Involved in Aggressiveness: KRAS/MAPK vs PI3K/AKT/mTOR

Feature	KRAS/MAPK Pathway	PI3K/AKT/mTOR Pathway
Primary Role	Proliferation, differentiation, migration	Survival, metabolism, growth
Upstream Trigger	KRAS mutation/EGFR activation	PI3K activation/PTEN loss
Key Steps	KRAS → RAF → MEK → ERK → Gene transcription	PI3K → PIP3 → AKT → mTOR → Protein synthesis
Effect in Aggressive Cell Lines	↑ EMT, ↑ invasion potential	↑ Anti-apoptotic signaling, ↑ metabolic adaptation
Observed Difference Between Cell Lines	Cell line A: Higher ERK phosphorylation; Cell line B: Lower ERK	Cell line A: Moderate AKT activity; Cell line B: Strong AKT & mTOR activation

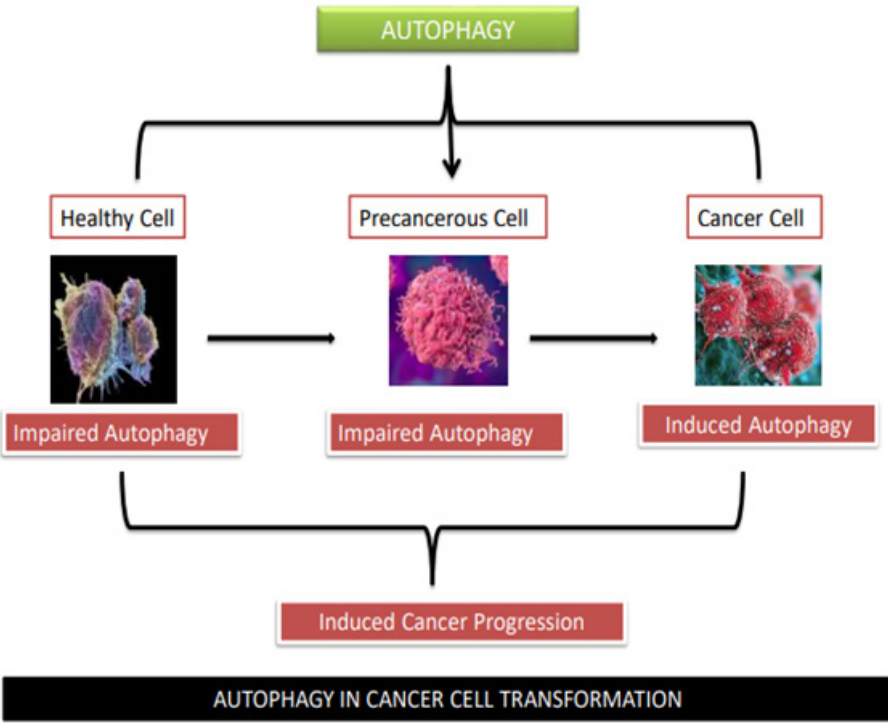


Fig. 9. Role of autophagy and apoptosis evasion

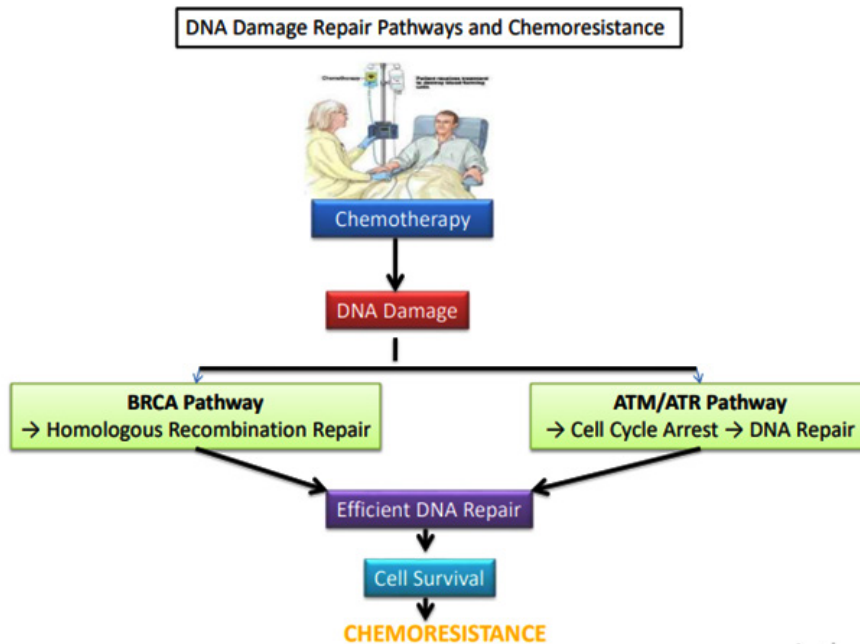


Fig.10. DNA Damage Repair–Mediated Chemoresistance

emodin disrupted the mitochondrial membrane potential ($\Delta\psi$), indicating activation of the intrinsic apoptotic mechanism. Aloe emodin increased autophagy and promoted apoptosis, as evidenced by increased LC3-II expression. The dual activation of apoptotic and autophagic pathways, combined with cell cycle arrest and mitochondrial dysfunction, highlights aloe emodin's multi-targeted anticancer potential, especially against KRAS-mutated pancreatic cancer cells.²³ Because of their sensitivity to metabolic inhibitors and pro-apoptotic stimuli, MiaPaCa-2 cells are frequently employed in preclinical studies aimed at developing therapies that exploit cancer-specific metabolic vulnerabilities.

BxPC-3

BxPC-3 was established from a moderately differentiated adenocarcinoma (Fig.3). It stands out from many previous pancreatic cancer models because it has KRAS wild-type. In contrast to more mesenchymal or stem-like cell lines like PANC-1 or MiaPaCa-2, it has a well-defined epithelial phenotype, tight cell–cell junctions, and significant E-cadherin expression. BxPC-3 is an important model for studying KRAS-independent signalling pathways and assessing the effectiveness

of targeted treatments that might not depend on the RAS/MAPK axis because it lacks KRAS mutations. BxPC-3 is widely used by researchers to investigate receptor tyrosine kinase signalling (EGFR, HER2), alternative oncogenic drivers, and the cellular response to chemotherapeutics in situations when KRAS is not present. Exposure of human CD14⁺ monocyte derived dendritic cells (DCs) to conditioned media from the highly metastatic pancreatic cancer cell line BxPC 3 (BxCM) resulted in impaired DC differentiation, maturation, and antigen-presentation capacity and increased microRNA 146a (miR 146a). Specifically, DCs treated with BxCM failed to fully differentiate or effectively stimulate antigen-specific T cell responses key functions required for effective immunity. Importantly, inhibition of miR 146a expression partially reversed these functional impairments, suggesting that elevated miR 146a plays a central role in mediating BxCM-induced DC dysfunction, likely through downregulation of the SMAD4 signaling pathway. These results identify miR 146a as a critical suppressive factor induced by KRAS independent stromal signaling, highlighting how BxPC 3 tumors can orchestrate immunosuppressive microenvironments through

Table 2. Comparative Characteristics of Commonly Used Pancreatic Cancer Cell Lines

Cell Line	Origin	KRAS Status	Doubling Time (in vitro)	EMT / Phenotype	Drug Resistance Highlights
PANC-1	Primary pancreatic ductal adenocarcinoma	KRAS-mutant (e.g., G12D)	~52 h	Partial EMT; mesenchymal traits (↑ vimentin, ↓ E-cadherin)	Intrinsic gemcitabine resistance (low hENT1, survival pathway activation); used to study EMT- and stemness-linked resistance. ⁷⁵
MiaPaCa-2	Pancreatic carcinoma patient derived (metastasis)	KRAS-mutant (e.g., G12C)	~40 h	Mesenchymal-like; high plasticity, glycolytic	Resistant to gemcitabine; shows metabolism-, stemness-, and apoptosis-related resistance mechanisms. ⁷⁶
BxPC-3	Moderately differentiated pancreatic adenocarcinoma	KRAS wild-type	~48-60 h	Epithelial phenotype (high E-cadherin, tight junctions)	Initially gemcitabine-sensitive; develops resistance via EMT, CXCR4/CXCR7 signaling, and anti-apoptotic pathways. ⁷⁷

miRNA-mediated reprogramming of DCs.²⁴ With an IC₅₀ of approximately 19.3/ µg/mL and up to ~90/ % inhibition at 32/ µg/mL, oridonin, a diterpenoid derived from *Rabdosia rubescens*, effectively inhibited cellular growth in a dose-dependent manner, according to MTT studies. In addition to its cytotoxic effects, oridonin greatly decreased the secretion of pro-inflammatory cytokines, including IL 1 α , IL 6, and IL 33, dose-dependent reductions were verified by ELISA (e.g., IL 1 α declined from approximately 14.40 to approximately 11.17 pg/mL; IL 6 decreased from approximately 4.45 to approximately 3.95; IL 33 decreased similarly). At the molecular level, the therapy increased the expression of Smad4 while suppressing TGF β 1, BMP 2, and several Smad proteins. Important nuclear transcription factors and inflammatory mediators, including AP 1, RelA (and phosphorylated RelA), NF- κ B1, STAT3, and phosphorylated STAT3, were similarly downregulated. Furthermore, after receiving oridonin, the expression of tumor-associated hallmark proteins such MMP 2, VEGF, and survivin was reduced. Taken together, these findings indicate that oridonin exerts anticancer effects in BxPC 3 cells through dual mechanisms inhibition of inflammation-associated cytokines and disruption of transcription factor networks effectively targeting cancer hallmarks like growth, angiogenesis, invasion, and metastasis in a KRAS wild type epithelial pancreatic cancer context.²⁵ The role of Response Gene to Complement 32 (RGC 32) in TGF-induced epithelial mesenchymal transition (EMT) and the migration of the human pancreatic cancer cell line BxPC 3. Their immunohistochemical examination of tumor samples showed that in patients with pancreatic cancer, greater TNM stage and lymph node metastases were substantially connected with abnormal E cadherin localisation and increased RGC 32 expression. Exposure to TGF β caused a dose- and time-dependent rise in RGC 32 in cultivated BxPC 3 cells, along with the EMT hallmarks of vimentin overexpression and E cadherin downregulation. Significantly, in transwell tests, siRNA-mediated reduction of RGC 32 decreased migratory capacity and significantly hampered TGF β -induced EMT alterations. However, since BxPC 3 cells lack functioning Smad4, overexpression of RGC 32

alone was enough to induce EMT marker changes and improve cell migration even in the absence of exogenous TGF β . This suggests that RGC 32 can initiate EMT via a KRAS independent, Smad independent mechanism. According to these findings, RGC 32 is a new gene that promotes metastases in pancreatic cancer by boosting TGF- β -induced EMT and making BxPC 3 cells of the KRAS wild type more aggressive.²⁶ No matter if a KRAS mutation is present or not, in vivo serial passage of human pancreatic cancer cell lines in orthotopic animal models could enrich aggressive metastatic phenotypes. They extracted tumour from critically ill mice, serially re-implanted derived cells for up to six passages, and orthotopically implanted 10⁶ BxPC 3 RFP (KRAS wild-type) or PANC 1 GFP (KRAS-mutant) cells into the pancreas tail of naked animals. By the sixth passage (P6 for BxPC 3, P5 for PANC 1), both cell lines gave rise to significantly more aggressive tumours, characterized by accelerated primary growth, dramatically shortened median survival (from ~127/ days to ~52/ days in BxPC 3; from ~124/ days to ~42/ days in PANC 1), and metastasis detectable as early as three weeks post-implantation (versus ~14/ weeks in parental lines). This study compellingly demonstrates that serial in vivo selection yields highly metastatic variants irrespective of KRAS mutation, making these derivatives powerful models to study the molecular basis of aggressive pancreatic cancer and to rigorously test potential therapeutic interventions.²⁷ The KRAS signalling system is modulated in pancreatic ductal adenocarcinoma models, including KRAS mutant (MiaPaCa 2, PaCa 44) and KRAS wild type (BxPC 3) cell lines, as well as in vivo xenograft models, by treatment with both standard paclitaxel and the investigational taxane SB T 1216.

According to their findings, the baseline expression of genes linked to KRAS downstream branches, including PI3K/PDK1/AKT, RalGEF, and RIN1/ABL, differed significantly between cell lines based on the presence or absence of KRAS mutations. Nevertheless, taxanes consistently led to downregulation of the KRAS signalling pathway at the mRNA and protein levels, even in the absence of a KRAS mutation. There was no correlation between KRAS mutational status and differential sensitivity to taxane treatment, suggesting that

taxanes act through mechanisms beyond KRAS-dependent pathways. Importantly, the study concluded that despite effective suppression of KRAS-related pathway expression, no predictive biomarkers for taxane activity or targets to sensitize PDAC models were identified via KRAS pathway profiling.²⁸ A novel PET imaging strategy using zirconium-89-labeled transferrin ($[^{89}\text{Zr}]\text{Zr Tf}$) to noninvasively assess oncogenic signaling and target engagement in PDAC. The study used the MYC-induced expression of the transferrin receptor (TfR) as a quantifiable biomarker because KRAS mutations are seen in more than 90% of PDAC cases and drive downstream pathways including ERK and MYC. In both genetically engineered mouse models and human PDAC xenografts, high uptake of $[^{89}\text{Zr}]\text{Zr Tf}$ was observed in tumours with active KRAS signaling. This uptake significantly decreased upon treatment with JQ1 (a BRD4 inhibitor) or SCH772984 (an ERK inhibitor), indicating reduced MYC and TfR expression. Notably, KRAS-mutant xenografts such as Capan-2 and Suit-2 showed strong tracer signals and sensitivity to inhibition, while KRAS wild-type models like BxPC-3 exhibited low-to-moderate uptake that was unaffected by these inhibitors. Immuno histochemical analyses confirmed that PET tracer accumulation correlated with TfR and MYC protein levels in the tumours. These findings demonstrate that $[^{89}\text{Zr}]\text{Zr Tf}$ PET imaging can serve as a functional tool for evaluating KRAS–MYC pathway activity and therapeutic responses, offering a promising approach for precision oncology in pancreatic cancer.²⁹ This cell line is thus particularly valuable for developing and testing therapeutic strategies that may benefit the subset of pancreatic cancer patients lacking KRAS mutations.

Molecular Pathways Involved In Aggressiveness EMT markers

When epithelial cells lose their polarity and cell-cell adhesion properties and develop mesenchymal traits that improve their migratory and invasive capacities two crucial elements of cancer growth and metastasis a fundamental biological process known as the epithelial–mesenchymal transition (EMT) takes place (Fig.4). This transition is indicated by a noticeable alteration in molecular markers. The development of embryos and the maintenance of proper tissue architecture

depend on calcium-dependent cell adhesion molecules known as cadherins. Additionally, they support the preservation of various tissues' epithelial structure.³⁰ Since some carcinomas have been found to have an aggressive and undifferentiated character due to lack of E-cadherin expression, including pancreatic carcinoma, it is well known that E-cadherin contributes to tumour progression and metastasis.³¹ Another adhesion molecule, N-cadherin (neural cadherin), is linked to an increased propensity for invasion in cancer. E-cadherin, a hallmark epithelial marker responsible for maintaining intercellular adhesion, is typically downregulated during EMT, contributing to the loss of epithelial integrity. Conversely, N-cadherin, a mesenchymal cadherin, is upregulated, promoting increased cell motility and invasiveness, a phenomenon often referred to as the “cadherin switch.” Vimentin, an intermediate filament protein, is another key mesenchymal marker that becomes highly expressed in cells undergoing EMT, further supporting changes in cell shape, structural flexibility, and metastatic potential. Dynamic cell mobility and tissue patterning depend on adhesion changes regulated by growth factors. E-cadherin expression is modulated by such signals; for example, TGF- α induces epithelial-to-fibroblastic transition with reduced E-cadherin,³² while FGF-1 and FGF-2 enhance E-cadherin-mediated adhesion and reduce cancer cell invasion.³³ Furthermore, FGF receptor stimulation may promote N-cadherin-dependent motility, although the mechanism governing cadherin expression is unknown.³⁴ The large number of nerves inside and surrounding the organ is most likely one of the primary causes of pancreatic cancer spreading along the neural bands. The adhesion molecules that determine the cancer cells' affinity for the neural band may also have an impact on the cancer cells' motility. One study found no connection between neural invasion and the expression of neural cell adhesion molecules.³⁵ N-cadherin, normally abundant in neuronal and mesenchymal tissues, is closely linked to pancreatic cancer invasiveness and neural invasion.³⁶ In aggressive, drug-resistant cell lines like PANC-1 and MiaPaCa-2, reduced E-cadherin with elevated N-cadherin and Vimentin marks EMT activation.

Stemness (SOX2, OCT4, NANOG)

The ability of stem cells (SCs) to self-renew and generate progeny that can follow a variety of differentiation paths is one of their traditional definitions.³⁷ There are now four types of SCs recognised.³⁸ The first two, known as somatic and embryonic stem cells, are biologically present at various periods of life. Since ESCs are the most researched SCs, the information gleaned from their study has influenced research on other SC types. ASCs, postnatal derivatives of ESCs, retain expression of key transcription factors OCT4, KLF4, and SOX2. In pancreatic cancer, stemness is defined by the expression of OCT4, SOX2, and NANOG, which maintain CSC self-renewal and pluripotency, contributing to tumorigenicity, metastasis, and therapy resistance. These markers are elevated in aggressive PDAC lines like PANC-1 and MiaPaCa-2. Recent studies highlight nine transcription factors essential for maintaining pluripotency in mouse cells—OCT4, NANOG, SOX2, Dppa4, Dppa5, Sall4, Utf1, Rex2, and Rif1.³⁹ OCT4, NANOG, and SOX2 are highly expressed in the ICM during early embryogenesis, sustaining ESC pluripotency.⁴⁰ All stem cell types share these core pluripotency genes, while c-MYC, a key oncogene, exhibits greater variability but regulates many stem cell properties.⁴¹ These genes control transcription factors, surface markers, ABC transporters, and enzymes that define stem cell behavior.⁴² Although CSC regulation is well studied across cancers, few publications address SOX2, OCT4, and NANOG in pancreatic cancer, with 24, 27, and 20 studies found in PubMed, respectively. Elevated OCT4 and NANOG correlate with early carcinogenesis and poor prognosis,^{43,44} while OCT4 also mediates metastasis and multidrug resistance. Cells positive for NANOG, OCT4, and SOX2 show enhanced growth, invasion, and drug resistance.^{45,46} OCT4 helps to maintain pluripotency and supports the long-term survival of CSCs, whereas SOX2 is essential for maintaining the undifferentiated state and accelerating tumour growth. NANOG supports the transcriptional network that maintains the stem-like phenotype by acting downstream of SOX2 and OCT4. The coordinated overexpression of these stemness markers in pancreatic cancer cells not only drives tumour heterogeneity and relapse but also presents promising targets for therapeutic

intervention aimed at eliminating CSC populations and improving patient outcomes.

Invasion-related genes (MMPs, CXCR4)

Invasive genes, like matrix metalloproteinases (MMPs) and The promotion of pancreatic cancer cell invasion and metastasis depends on C-X-C chemokine receptor type 4. MMPs, especially MMP-2 and MMP-9, are enzymes that break down extracellular matrix components, which helps tumour cells invade neighbouring tissues and spread (Fig.6). Their overexpression in pancreatic ductal adenocarcinoma (PDAC) is often linked to poor prognosis, lymph node involvement, and advanced tumour stage. Similarly, in response to its ligand CXCL12 (SDF-1), the chemokine receptor CXCR4 promotes directed cell migration. In PDAC cell lines, high CXCR4 expression facilitates chemotactic migration towards distant organs and encourages the formation of metastatic lesions. In pancreatic ductal adenocarcinoma (PDAC), the CXCL12 (SDF 1 α)/CXCR4 chemotactic axis is essential for promoting perineural invasion (PNI).

Analysis of 78 human PDAC specimens showed that elevated CXCR4 expression strongly correlated with PNI occurrence, suggesting its clinical relevance. generated by peripheral nerves CXCL12 exhibited paracrine activity in both in vitro and in vivo models, facilitating the migration and invasion of cancer cells that were positive for CXCR4 and encouraging the formation of dorsal root ganglia in the direction of tumour cells. Importantly, pharmacologic or genetic inhibition of CXCR4 signaling significantly suppressed tumour invasion and halted sciatic nerve extension in orthotopic mouse models, underscoring its therapeutic potential for preventing PNI. These findings position the CXCL12 CXCR4 pathway as a critical mediator of nerve tropism and invasion in pancreatic cancer, highlighting it as a promising target to curtail local neuroinvasion and disease progression.⁴⁷ In vitro, pancreatic cancer cell lines, including KRAS wild type BxPC 3 and KRAS-mutant MiaPaCa 2/PANC 1, showed markedly reduced proliferation, colony formation, and invasion when the stromal derived factor 1 α (SDF 1/CXCL12)–CXCR4 axis was blocked by shRNA or pharmacological inhibition. Importantly, CXCR4 inhibition resulted in a downregulation of canonical Wnt/ β catenin signalling, as seen by

decreased expression of mesenchymal markers including vimentin and Slug, as well as decreased TOPflash reporter activity and Wnt target gene expression. These findings imply that because CXCR4 regulates the Wnt/ β catenin pathway, which in turn encourages EMT and invasive behaviour, it may be a suitable therapeutic target for halting the progression of pancreatic cancer.⁴⁸ According to recent studies, CXCR7 (also called ACKR3) and CXCR4 often co-express in pancreatic cancer tissues and cell lines. They also work together to transmit CXCL12-driven signalling that improves the behaviour of tumour cells. Upon binding CXCL12 or CXCL11, CXCR7 can activate MAPK/ERK pathways via β -arrestin-dependent mechanisms, while CXCR4 primarily transduces G α i-mediated signals that activate KRAS and MAPK/ERK; both receptors together amplify downstream proliferative and migratory outputs. Functionally, this co expression appears to promote EMT and directional metastasis, with CXCR7 enhancing CXCR4 signaling fidelity by shaping the CXCL12 gradient through ligand sequestration thereby influencing cell motility and invasion along defined pathways. The mechanistic insights strongly support the interpretation that CXCR7 assists CXCR4 in modulating TGF β induced EMT, mesenchymal transition, and tissue directed metastatic spread in pancreatic cancer models expressing both receptors.⁴⁹ The elevated expression of MMPs and CXCR4 is primarily responsible for the aggressive nature of pancreatic cancer, making them essential molecular targets for anti-metastatic therapies (Fig. 7).

Hypoxia pathways (HIF-1 α , VEGF)

Solid tumours, such as pancreatic cancer, are characterised by hypoxia, which greatly increases the tumour's aggressiveness, resistance to treatment, and potential for metastasis (Fig. 8). Low oxygen levels cause the hypoxia-inducible factor 1- α (HIF-1 α) to stabilise and migrate to the nucleus, where it initiates the transcription of several target genes involved in hypoxia adaptation. One of its primary downstream targets is vascular endothelial growth factor (VEGF), a potent angiogenic agent that promotes the formation of new blood vessels to support the oxygen-depleted tumour. In pancreatic cancer cell lines, upregulation of HIF-1 α and VEGF has been connected to increased angiogenesis, epithelial-mesenchymal

transition (EMT), and stemness, all of which have been connected to invasion and metastasis. To further improve tumour survival and progression, the hypoxic microenvironment also interacts with additional oncogenic signaling pathways, including RAS/RAF/MEK/ERK and PI3K/AKT/mTOR. Hypoxia resulting from rapid tumour growth and dense desmoplastic stroma is a key driver of angiogenesis in pancreatic ductal adenocarcinoma (PDAC). Stabilization of HIF 1 α under low oxygen conditions triggers transcriptional upregulation of VEGF and other pro angiogenic genes, fostering the formation of an abnormal, leaky vascular network that paradoxically fails to relieve hypoxia but promotes tumour aggressiveness. Elevated HIF 1 α expression in PDAC has been correlated with regions of fibrosis and high microvessel density, further associating hypoxia with enhanced local invasion, metastatic spread, and poor prognosis. While early anti angiogenic strategies targeting VEGF or its receptors (e.g. with tyrosine kinase inhibitors or VEGFR antibodies) demonstrated preclinical efficacy, clinical trials have yielded disappointing results when used alone highlighting the need for combination regimens (e.g. VEGF blockade plus MMP inhibitors or chemotherapy) to effectively disrupt this complex, hypoxia-driven angiogenic network.⁵⁰ Hypoxia-inducible factor 1 (HIF 1), and particularly its α subunit, is an essential mediator that links tumour hypoxia to VEGF production and angiogenesis in human pancreatic ductal adenocarcinoma models and tissue samples. In human pancreatic cancer samples, elevated HIF 1 α protein localized to tumour cell nuclei and strongly correlated with increased VEGF mRNA in the same cancer cells, indicating coordinated activation under hypoxic conditions. Several human pancreatic cancer cell lines were exposed to low oxygen conditions in vitro, which resulted in high HIF 1 DNA-binding activity at the VEGF promoter and increased amounts of VEGF mRNA and protein. Cells with high constitutive HIF 1 α also produced higher baseline VEGF, even under normoxia. These results establish HIF 1 α as the molecular switch that activates VEGF-driven neoangiogenesis, thus connecting intratumoural hypoxia with abnormal vascularization and aggressive tumour behavior in pancreatic cancer.⁵¹ Therefore, targeting hypoxia-driven pathways particularly HIF-1 α and VEGF

remains a promising therapeutic approach in overcoming the aggressive nature of pancreatic ductal adenocarcinoma.

KRAS/MAPK and PI3K/AKT/mTOR signaling differences between the cell lines

Commonly utilised cell lines have very different signalling characteristics in pancreatic cancer research, especially in the KRAS/MAPK and PI3K/AKT/mTOR pathways (Table 1).

MiaPaCa-2 and PANC-1 cells both have activating KRAS mutations. These mutations promote carcinogenic characteristics such migration, proliferation, and resistance to apoptosis and result in constitutive activation of the KRAS/MAPK cascade (RAS–RAF–MEK–ERK). These cell lines are also good models for testing dual-targeted treatments that try to block both pathways at once since they show strong PI3K/AKT/mTOR pathway activity. In contrast, BxPC-3 cells are KRAS wild-type and maintain an epithelial phenotype, relying on alternative mechanisms such as receptor tyrosine kinases for MAPK activation. Their PI3K/AKT/mTOR signaling is less constitutively active, positioning BxPC-3 as a valuable model for studying KRAS-independent therapeutic strategies.⁵² These differences highlight the importance of selecting appropriate cell lines based on their distinct molecular characteristics when designing experiments focused on pancreatic cancer signaling and drug resistance. Pharmacologic inhibition of the KRAS–MAPK pathway in pancreatic ductal adenocarcinoma (PDAC) causes HER2 to compensate, which is driven by the phosphatase DUSP6 being broken down by proteasomes. Under MAPK blockade, the loss of DUSP6 destabilizes the negative regulation of HER2, resulting in rapid HER2 phosphorylation and signaling reactivation. Leveraging this understanding, the researchers show that combining ERK pathway inhibitors (e.g., ulixertinib or trametinib) with trastuzumab deruxtecan an anti HER2 antibody–drug conjugate elicits sustained and complete tumour regression in multiple patient-derived xenograft models of PDAC, without significant toxicity. Notably, even KRAS inhibitors led to similar HER2 activation, further supporting the combination approach. These results identify a rational therapeutic strategy dual targeting of KRAS/MAPK and HER2 to overcome adaptive resistance and improve treatment efficacy

in pancreatic cancer.⁵³ These differences highlight the importance of selecting appropriate cell lines based on their distinct molecular characteristics when designing experiments focused on pancreatic cancer signaling and drug resistance.

Chemoresistance Mechanisms In Each Cell Line Common drugs: Gemcitabine, 5-FU, Oxaliplatin, Paclitaxel

The multiple processes behind the well-known chemoresistance of pancreatic ductal adenocarcinoma (PDAC) to chemotherapy. Different chemoresistance profiles to common treatment drugs like gemcitabine, 5-fluorouracil (5-FU), oxaliplatin, and paclitaxel are shown by pancreatic cancer cell lines. Patients with advanced and metastatic PC respond effectively to gemcitabine and other treatment drugs, although their effectiveness is significantly reduced when chemoresistance to gemcitabine develops. Compared to other chemotherapy drugs, gemcitabine is without a doubt more effective against pancreatic cancer cells. Most studies on chemoresistance in advanced pancreatic cancer focus on gemcitabine, as data on other drugs remain limited. The mechanisms underlying gemcitabine resistance are not fully understood but are linked to transcription factors, signaling pathways, and enzymes involved in nucleoside metabolism.⁵⁴ EMT plays a key role, where upregulation of Snail, Twist, and Zeb1 and loss of E-cadherin enhance invasiveness and reduce gemcitabine uptake by downregulating nucleoside transporters. Additionally, cancer stem cells (CSCs) contribute to resistance through self-renewal and drug efflux capacity. As a result, CSCs are able to withstand standard treatments. Dysregulated non-coding RNAs (including miR-29c, miR-210, and lncRNAs) that promote autophagy, DNA repair, and survival signaling enable these CSCs. Stromal-derived factors like SDF-1 α are secreted by the tumour microenvironment, particularly by pancreatic stellate cells. These factors interact with cancer cells' CXCR4 and trigger downstream signalling pathways (including PI3K/AKT and ERK) that strengthen drug resistance. A key role is also played by hypoxia, which is mediated by HIF-1 α activation and supports EMT and stemness features by encouraging angiogenesis and metabolic adaptability. Furthermore, the intracellular activation of gemcitabine is restricted by changes in

drug transporter and metabolic enzyme expression, such as reduced expression of human equilibrative nucleoside transporter 1 and deoxycytidine kinase, whereas increased expression of ATP-binding cassette transporters results in enhanced drug efflux, including MDR1.⁵⁵ MiaPaCa-2, which harbors a mutant KRAS gene and displays high glycolytic activity, often resists gemcitabine due to overexpression of RRM1, reduced nucleoside transporter (hENT1) expression, and enhanced activity of survival pathways like PI3K/AKT and NF- κ B. It also demonstrates resistance to 5-FU and oxaliplatin via increased drug efflux (ABCC1/ MRP1) and DNA repair mechanisms, alongside enhanced autophagy and stemness (SOX2, OCT4) contributing to cell survival under treatment stress. In contrast, BxPC-3, a KRAS wild-type line, shows relatively higher sensitivity to gemcitabine but acquires resistance through EMT activation and upregulation of N-cadherin and Vimentin, leading to a more invasive phenotype. Oxaliplatin resistance, on the other hand, involves increased synthesis of DNA damage response elements and anti-apoptotic proteins (Bcl-2, survivin), paclitaxel resistance in BxPC-3 is associated with α -tubulin isotype switching and activation of MAPK/ERK signalling.⁵⁶ Both lines demonstrate altered hypoxia responses (HIF-1 α , VEGF), which further facilitate chemoresistance by promoting angiogenesis and metabolic adaptation. The poor response of PDAC to chemotherapeutic drugs including gemcitabine, 5-FU, oxaliplatin, and paclitaxel is a result of these coupled processes.⁵⁷ Designing successful combination tactics to overcome medication resistance in pancreatic cancer requires an understanding of these pathways.

Overexpression of efflux transporters (e.g., MDR1/P-gp, MRP1)

The upregulation of efflux transporters, such as multidrug resistance-associated protein 1 (MRP1) and P-glycoprotein (P-gp, encoded by the MDR1 gene), mediates chemoresistance in pancreatic cancer. By vigorously pumping a variety of chemotherapeutic medications out of cancer cells, these ATP-binding cassette (ABC) transporters lessen intracellular drug accumulation and its lethal effects. Elevated P-gp and MRP1 expression has been linked to poor response to popular chemotherapeutic drugs, including gemcitabine, 5-fluorouracil, paclitaxel, and

oxaliplatin, in pancreatic ductal adenocarcinoma (PDAC). This overexpression is often driven by genetic and epigenetic changes and is further exacerbated by microenvironmental factors such as hypoxia and inflammatory cytokines. Moreover, cancer stem cell populations within pancreatic tumours tend to express high levels of these efflux proteins, contributing to their intrinsic resistance and the likelihood of relapse following treatment. In human pancreatic cancer specimens, the first systematic immunohistochemical investigation of MDR1/P-glycoprotein (P-gp) and MRP-1 expression showed that 93.3% of tumours express MDR1/P-gp, whereas 31% co-express MRP-1 and MDR1, and a small minority (~6.7%) lack both expressions. Most tumours displayed moderate to strong staining intensity and broad distribution within tumour cells. These high expression rates suggest that MDR1/P-gp, and to a lesser extent MRP-1, are frequently present in pancreatic cancer and may significantly contribute to clinical chemoresistance though a direct causal link remains to be confirmed. The study underscores the importance of considering efflux pump expression when designing chemotherapy regimens or evaluating inhibitors targeting drug resistance mechanisms in pancreatic cancer.⁵⁸ All things considered, focussing on these efflux transporters offers a viable way to get past medication resistance and enhance treatment results for individuals with pancreatic cancer.

Role of autophagy and apoptosis evasion

Pancreatic cancer cells rely on autophagy and apoptosis evasion for survival, growth, and resistance to treatment (Fig.9). Autophagy, a cellular degradation process, helps cancer cells withstand metabolic stress and nutrient deprivation by recycling damaged organelles and proteins. In pancreatic ductal adenocarcinoma (PDAC), autophagy is often upregulated and acts as a survival mechanism, enabling tumour cells to adapt to the hypoxic and nutrient-poor tumour microenvironment. By halting drug-induced cell death, this pathway not only encourages tumour growth but also builds resistance to chemotherapeutic drugs like gemcitabine. PDAC is a complex aetiology that includes gene mutation, chemical exposure, and inflammatory induction. These mechanisms mediate pancreatic carcinogenesis, and a malfunction in autophagy

can either promote or hinder it.⁵⁹Inflammation is one of the most significant extrinsic variables in the development of pancreatic tumours. Autophagy controls inflammation in the early stages of pancreatic cancer in a complex way. Acinar-ductal metaplasia (ADM), a pathogenic change that arises when oncogenic signalling is triggered (e.g., gene mutation and inflammation), is the precursor to PanIN. In cells of the pancreatic epithelium (Pdx1-Cre;atg7^{fl/fl}), conditional deletion of Atg7 causes severe acinar cell degeneration.⁶⁰This is followed by the development of ADM due to mitochondrial malfunction, ER stress, and decreased protein synthesis.⁶⁰Pancreatic cancer may emerge as a result of ATG7-mediated inflammatory regulation. By controlling cell death signals, pancreatic Atg7 deletion (Pdx1-Cre;atg7^{fl/fl}) also causes inflammation and fibrosis in mice. Autophagy increases TBK1 (TANK binding kinase 1)-mediated dysplasia, which aids in the carcinogenesis of KRAS-driven pancreatic cancer.^{62,63}Enhanced autophagy reduces TBK1-mediated inflammation in mice, so autophagy inhibition or Atg5 deletion (Pdx1-Cre;atg5^{fl/fl}) exacerbates pancreatitis and dysplasia.⁶³Thus, autophagy has dual roles in inflammation-driven pancreatic carcinogenesis. HMGB1, a DNA-binding protein and DAMP, promotes autophagy via multiple mechanisms.⁶⁴Pancreatic Hmgb1 knockout (Pdx1-Cre;hmgb1^{fl/fl}) accelerates inflammatory damage, KRAS activation, and tumourigenesis more than Atg7 deletion.⁶⁵Simultaneously, pancreatic cancer cells evade apoptosis the programmed cell death mechanism through the dysregulation of various pro- and anti-apoptotic signaling pathways. Despite accumulating genetic damage or being exposed to cytotoxic therapies, Because pro-apoptotic factors like Bax, p53, and caspases are downregulated or mutated, Even when anti-apoptotic proteins like Bcl-2 and Bcl-xL are overexpressed, these cells can still stop cell death. The simultaneous activation of autophagy and suppression of apoptosis thus creates a protective advantage for pancreatic cancer cells, fostering aggressive tumour behavior, resistance to therapy, and poor clinical outcomes. One possible tactic to improve therapy effectiveness and get past resistance in pancreatic cancer is to target these pathways with particular inhibitors or combination medicines.

DNA damage repair pathways (ATM/ATR, BRCA)

The growth of tumours and resistance to treatment in pancreatic cancer are significantly influenced by the dysregulation of DNA damage repair (DDR) pathways, especially those involving the ATM/ATR and BRCA genes (Fig.10). The DNA damage response depends on the ataxia-telangiectasia mutant and ATM and Rad3-related kinases, which identify replication stress and DNA double-strand breaks, respectively, and trigger downstream effectors such CHK1 and CHK2 to stop the cell cycle and promote repair. Geographically, the incidence of PDAC varies significantly, with high-income countries having the highest frequency.⁶⁶There are many known risk factors, both inherited and non-inherited, some of which could explain these differences, despite the fact that the causes of PDAC are intricate and multifaceted. Obesity, smoking, alcohol consumption, diabetes mellitus, chronic pancreatitis, and perhaps *Helicobacter pylori* infection are non-inherited risk factors.⁶⁷Several genes are linked to increased PDAC susceptibility.⁶⁸Germline DDR mutations (ATM, BRCA1, BRCA2, MLH1, MSH2, PALB2, PMS2, STK11) and traditional cancer risk genes (CDKN2A, TP53) are commonly inherited.⁶⁹Some inherited cancer predisposition syndromes feature monoallelic, dominantly inherited mutations (e.g., BRCA1/2) that elevate PDAC and other cancer risks.⁷⁰Mutations or functional deficiencies in ATM are observed in a subset of pancreatic ductal adenocarcinoma (PDAC) cases, leading to genomic instability and aggressive tumour phenotypes. Similarly, BRCA1 and BRCA2, key mediators of homologous recombination repair, are frequently mutated in hereditary and sporadic pancreatic cancers. Loss of BRCA function impairs high-fidelity DNA repair, making tumour cells more dependent on alternative, error-prone pathways, thereby promoting mutagenesis. While such deficiencies can enhance tumour aggressiveness, they also create therapeutic vulnerabilities particularly to platinum-based chemotherapy and PARP inhibitors through synthetic lethality. However, activation of compensatory DDR pathways, such as ATM/ATR signaling in BRCA-deficient cells, can confer resistance to these therapies, highlighting the complex interplay of

DDR mechanisms in pancreatic cancer and the need for tailored combination strategies.

miRNAs and non-coding RNAs influencing resistance

Through their effects on gene expression networks related to drug metabolism, apoptosis, epithelial–mesenchymal transition (EMT), and DNA repair, In pancreatic cancer, chemoresistance is regulated by microRNAs (miRNAs) and other non-coding RNAs (ncRNAs). Tumour suppressors or oncogenic miRNAs (oncomiRs) are two possible functions of dysregulated miRNAs. For instance, by targeting tumour suppressor genes like PTEN and PDCD4, miR-21, which is commonly overexpressed in pancreatic ductal adenocarcinoma (PDAC), increases resistance to gemcitabine while improving cell survival and lowering apoptosis. Similarly, miR-155 and miR-221 have been linked to resistance by modulating pathways like NF- κ B and PI3K/AKT. On the other hand, by promoting EMT and suppressing pro-apoptotic signaling, downregulation of tumour-suppressive miRNAs like miR-34a and miR-200 family lowers susceptibility to chemotherapeutics. A longer mRNA-like transcript is processed into the mature, active 19–24 nucleotide miRNA (Fig. 1). Most initial transcripts are transcribed by RNA polymerase II.^{71,72} The pri-miRNA may contain pre-miRNA hairpins for multiple miRNAs, some clustered within related genes.⁷³ Transcription can be driven by a distal host gene promoter or a proximal miRNA promoter.^{71,72} After nuclear cleavage by the DROSHA-containing microprocessor complex, pre-miRNA is exported to the cytoplasm via XPO5.⁷² The final mature RNA molecule is put into the miRNA-induced silencing complex (miRISC), which contains ARGONAUTE, and becomes functionally active after being cleaved by another RNase III DICER in the cytoplasm. Through its binding to partially complementary regions, usually on the 3' UTR, miRNA guides miRISC to target mRNAs, reducing protein production via mRNA degradation, cleavage, or translational inhibition through interactions with mRNA-bound complexes like CCR4-NOT and eIF4A-G.^{71,72} The seed region, which consists of the second to eighth nucleotides of the miRNA, is typically responsible for miRNA binding to the mRNA. This allows tens or even hundreds of mRNAs to interact with a single miRNA. The

amount of protein synthesis reduction for each target gene depends on the number of binding sites, binding affinity, and relative abundance of miRNA to target mRNA.⁷⁴ By serving as molecular sponges for miRNAs or by directly interacting with signalling proteins, Treatment resistance in PDAC is also influenced by circular RNAs and long non-coding RNAs. For example, by activating the Wnt/ β -catenin and AKT pathways, lncRNA HOTAIR and lncRNA PVT1 increase resistance to gemcitabine. Certain circRNAs, like circHIPK3, sequester tumour-suppressive miRNAs, indirectly activating pro-survival genes. Collectively, the dysregulation of these ncRNAs alters multiple signaling cascades, enabling pancreatic cancer cells to evade cytotoxicity. One promising therapeutic approach to combat chemoresistance in PDAC is to target certain miRNAs or lncRNA–miRNA interactions.

Comparative Analysis

Three commonly utilised human pancreatic cancer cell lines, each exhibiting distinct biological and molecular traits. PANC-1 and MiaPaCa-2, both harboring KRAS mutations, display mesenchymal-like phenotypes and higher drug resistance, with longer doubling times for PANC-1. In contrast, BxPC-3 is KRAS wild-type, more epithelial in nature, and generally more drug-sensitive. These differences make them valuable models for studying pancreatic cancer heterogeneity, drug responses, and specific pathways in tumour biology (Table 2).

Applications in Drug Screening

Cell lines serve as indispensable platforms for evaluating new therapeutic agents in pancreatic cancer research. Their unique genetic profiles such as variations in KRAS, TP53, SMAD4, and CDKN2A allow researchers to capture the heterogeneity of pancreatic tumours, making them ideal for *high-throughput screening* (HTS) platforms where thousands of compounds can be rapidly tested for cytotoxicity, apoptosis induction, and signaling pathway modulation.⁷⁸ Both natural products, such as plant-derived flavonoids and marine metabolites, and synthetic molecules, including kinase inhibitors and chemotherapeutic analogs, have been extensively screened using these models.⁷⁹ Combination therapy approaches, such as pairing standard agents like gemcitabine with novel targeted inhibitors, are frequently

assessed in these cell lines to explore synergistic effects and overcome intrinsic or acquired drug resistance.⁸⁰To better replicate the in vivo tumour microenvironment, these cell lines are increasingly cultured in *3D spheroid* and organoid systems. They offer improved drug penetration profiles, nutrition gradients, and cell–matrix and cell–cell interactions, making them more accurate predictors of therapeutic outcomes.⁸¹Additionally, advanced molecular tools such as CRISPR/Cas9 genome editing and siRNA knockdown are employed to selectively silence or modify genes of interest. This facilitates the validation of novel drug targets, identification of resistance-conferring pathways, and elucidation of mechanisms underlying variable drug responses.⁸²Collectively, these applications position cell lines as critical preclinical models for streamlining the drug discovery pipeline and translating laboratory findings into effective therapeutic strategies for pancreatic cancer.

Limitations And Future Perspectives

While cell lines have significantly advanced our understanding of pancreatic cancer biology and drug resistance mechanisms, they are not without limitations. A primary drawback lies in their reliance on conventional 2D monolayer culture systems, which fail to accurately mimic the complex architecture, extracellular matrix interactions, and heterogeneous tumour microenvironment of in vivo pancreatic tumours.⁸³This oversimplification can lead to discrepancies in drug sensitivity and therapeutic response compared to clinical outcomes. To address these shortcomings, *co-culture systems* which integrate pancreatic cancer cells with stromal, immune, and endothelial components have emerged as powerful tools to recreate more physiologically relevant interactions. Similarly, *organoid models* derived from these lines or from patient samples can preserve tumour heterogeneity, genetic mutations, and spatial organization, providing a more accurate platform for translational research.⁸⁴Beyond in vitro methods, researchers may now examine tumour growth, metastasis, and medication resistance under more clinically relevant circumstances thanks to patient-derived xenografts (PDXs) using these cells in immunodeficient mice. These models bridge the gap between cell culture and patient trials, offering valuable insights into tumour

behavior in a living organism.⁸⁵Looking ahead, the integration of these well-characterized pancreatic cancer cell lines into *personalized therapy models* is a promising avenue. By combining genomic profiling, drug response data, and advanced culture systems such as microfluidic chips and AI-driven analytics, researchers can tailor treatment strategies to individual patient profiles.⁸⁶This multi-platform approach holds potential for improving drug discovery, refining therapeutic regimens, and ultimately enhancing clinical outcomes in pancreatic cancer management.

CONCLUSION

PANC-1, MiaPaCa-2, and BxPC-3 serve as cornerstone models in pancreatic cancer research, offering complementary insights into tumour heterogeneity, signaling pathways, and phenotypic variations. Their distinct molecular profiles and drug sensitivity patterns provide a robust foundation for dissecting the mechanisms underlying chemoresistance, particularly in the context of KRAS-driven and KRAS-independent pathways. However, given the complexity of pancreatic cancer biology, integrating these traditional cell line models with advanced platforms such as AI-driven predictive analytics, organ-on-chip systems, and patient-derived organoids will enhance translational relevance, accelerate drug discovery, and improve therapeutic precision.

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