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Tumor evolution in an ecological context: How genetic and microenvironmental factors shape the pathogenesis of pancreatic cancer

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ABSTRACT

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive cancer with a dismal prognosis and a growing global incidence. Despite its clinical relevance, the processes driving PDAC tumorigenesis and progression remain poorly understood, challenging traditional molecular models. Here, we address the biological and evolutionary mechanisms underpinning PDAC development and growth, integrating cellular and molecular aspects with an ecological perspective. This multidisciplinary approach offers broader insights into the analysis of PDAC pathogenesis, starting from precancerous lesions and moving through to the primary tumor and its metastatic spread. Indeed, cancer cells may be considered as existing within a dynamic ecological context and are influenced by evolutionary pressures similarly to individuals, populations, and species in nature. Genetic and epigenetic changes form the foundation for the emergence of intratumoral heterogeneity, which contributes to tumor progression, metastasis, and resistance to therapy. These processes in PDAC progression are governed by both clonal expansion and the ecological fitness of neoplastic cells within the tumor microenvironment, which represents their ecological niches. Hence, by integrating evolutionary principles into the study of PDAC, we have analyzed the conceptual advantages and potential applications of this approach on the understanding of the complex interactions between tumor cells and their environments. This research emphasizes the contribution of a holistic, evolutionary perspective to cancer biology and underlines the importance of considering genetic, cellular, and ecological factors in the management and development of treatments, and for guiding future research and therapeutic strategies.

1. Introduction

Cancer is a disease of multicellular organisms that can originate from different tissues. Neoplastic formation arises from one or a small number of cells that undergo a process, viewed as a form of somatic evolution, in which normal cells acquire mutations that confer a survival advantage, allowing them to proliferate more than their non-mutated counterparts (Swiatczak, 2021). In parallel with clonal expansion, cancer cells are subject to dynamic changes that shape their behavior and interactions, ranging from altered stress responses to shifts in communication with the surrounding microenvironment (Dasari et al., 2021).

It is worth noting that the onset of cancer is not the attack of an external agent; it does not come from outside, it's a cellular transformation driven by genetic mutations leading to uncontrolled growth and duplication, frequent genetic instability/mutation, and epigenetic dysregulation. These factors are responsible for a selection of genotypically and phenotypically different populations of cancer cells that create a heterogeneous neoplasia able to interact with the microenvironment and to create a tissue niche (Somarelli, 2021). The expansion of genetically different cancer cell clones defines intratumor

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heterogeneity, which is responsible for the evolution of the tumor through the various phases of progression, metastasis formation, and treatment resistance (Zhang and Wang, 2025). Applying an evolutionary framework to cancer biology may provide insights into the pathogenesis of cancer. One of the most influential statements in biology was made by Theodosius Dobzhansky in 1973, when he declared that "Nothing in biology makes sense except in the light of evolution" (Dobzhansky, 1973). Indeed, just as evolutionary principles drive the diversity and adaptation of species, they also govern the processes that shape cancer progression, including mutation accumulation, selective survival, and adaptation to the tissue niche where cancer cells live and grow (Attolini and Michor, 2009).

The pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal cancers, characterized by a heterogeneous genetic landscape and by a highly dense and spatially structured desmoplastic stroma (X. Li et al. 2024), representing the most common and aggressive type of pancreatic cancer. In general, the 5-year survival rate is just 13%, constituting, for the year 2025, the fourth leading cause of cancer-related death in the United States (Siegel et al., 2025). There are many reasons for its poor prognosis, including late-stage diagnosis of most patients, early metastasis formation, and primary resistance to all forms of therapies (Bärthel et al., 2023). The best treatment option is surgery with a five-year survival rate of 30%, but only a small proportion of patients is eligible at diagnosis (Neoptolemos et al., 2018). Both adjuvant and neo-adjuvant chemotherapy usually are not able to control disease progression for more than a few months. Over the past three decades, PDAC research has evolved through several discoveries that have enabled the identification of its driver mutations (Dominguez et al., 2024; Yao et al., 2020) and delineated the stepwise progression from precursor lesions to invasive carcinoma (Pedro and Wood, 2025). Nonetheless, in recent years, there have been no significant improvements in long-term overall survival, and this neoplasia was predicted to increase globally in its incidence (Hesami et al., 2024), becoming the second leading cause of cancer mortality within this decade (Rahib et al., 2014).

In this context, the ecological fitness of pancreatic cancer cells can be defined by their ability to survive, proliferate, and evolve within the tumor microenvironment (TME), which functions as an ecological system (Rumie Vittar et al., 2013). The success of cancer cells, analogous to the survival of species in an ecosystem, depends on their ability to adapt to harsh conditions, such as nutrient deprivation, low oxygen availability (hypoxia), and immune system attack, among others (Khalaf et al., 2021).

Compared to other solid tumors, due to its intrinsic characteristics, PDAC can be considered a good model for cancer ecology studies. Indeed, it exhibits a high degree of heterogeneity due to genetic and epigenetic factors, as well as to the strong influence of the microenvironment (Iovanna et al., 2025). Moreover, it is characterized by a distinctively harsh and spatially complex TME that challenges traditional molecular models. For this purpose, this type of cancer is anatomically characterized by dense stromal structures named desmoplasia, which generate distinct environmental niches characterized by marked spatial gradients of critical parameters such as oxygen, nutrient availability, pH, cytokines, and matrix stiffness (X. Li et al. 2024). The peculiarity is that this condition makes PDAC a niche-dependent tumor for the spatial segregation of these parameters, rather than in many other solid tumors. Furthermore, PDAC's immune coldness (Ullman et al., 2022) may be considered a spatial phenomenon arising from ecological exclusion: TME physically and functionally prevents T-cell infiltration, trapping immune cells in stromal zones and avoiding their direct contact with tumor cells (Kung et al., 2025). In these environmental niches, metabolic crosstalk further reinforces the ecological structure. Cancer cells and TME cells establish a network of resource flows among cell species, forming a symbiotic interaction (Thakur et al., 2025) that influences tumor fitness under hypoxia, nutrient scarcity, and therapy, allowing the survival of PDAC cells. These conditions shape the selection of specific clones, creating a heterogeneous cancer cell population. Considering the PDAC's characteristics, scientific approaches to this type of cancer show that they would benefit greatly from the application of ecological theories compared to other cancers. In light of this, the evolutionary dynamics of cancer progression involve a constant interaction between cancer cell features, ecological pressures, and the ever-changing environment of the TME (Somarelli and Johnson, 2024). Indeed, ecological interactions may explain why PDAC exhibits profound therapeutic resistance despite well-characterized genetics (Dujon et al., 2021). Thus, eco-evolutionary dynamics, considering multi-species interactions, spatial resource competition, and niche construction, can help to resolve the mechanistic gaps left by traditional molecular models.

The aim of this review is to analyze the contribution of applying an eco-evolutionary framework to PDAC, for which traditional strategies have so far failed to fully elucidate the underlying biological mechanisms or significantly improve patient prognosis. By exploiting its intrinsic characteristics within this perspective, we have examined the development and progression of the disease, from precancerous lesions to the primary tumor and metastatic dissemination, highlighting the main evolutionary processes that characterize the different stages of tumor progression. In parallel, we have discussed the conceptual advantages and potential applications of this approach for improving our understanding of PDAC biology and for guiding future studies and therapeutic strategies. Although the translational impact of this perspective remains to be fully established, it constitutes a promising and conceptually rich avenue of investigation, particularly for PDAC, that may yield clinically relevant insights in the future (Raja Arul et al., 2022; Sherman and Beatty, 2023; Somarelli and Johnson, 2024).

2. Somatic alterations drive pancreatic carcinogenesis in early stages of PDAC

From an evolutionary perspective, cancer development in a human host can be understood as a process of natural selection occurring within the individual organism (Aktipis and Nesse, 2013; Tabassum and Polyak, 2015). The Somatic Mutation Theory (SMT) of cancer, the most widely accepted model, proposes that cancer results from mutations that occur in somatic cells, rather than germ cells (Basu, 2018). The accumulation of multiple gene mutations in the same cell can act synergistically, promoting the establishment of an ancestral cancer cell with advantageous characteristics such as increased proliferation, evasion of cell death, or resistance to immune detection compared to the other non-mutated cells, leading to the development of a malignant tumor (Makohon-Moore and Iacobuzio-Donahue, 2016). Moreover, these mutations may be positively selected in cells (Vishwakarma and Piddini, 2020), analogous to the process of natural selection in evolutionary biology, where genetic alterations that confer a survival advantage are propagated within the tumor cell population (Fortunato et al., 2017). The evolutionary dynamics of these mutated cells follow a model similar to Darwinian selection in which a combination of step-by-step events must occur (Gatenby and Brown, 2020; Hamede et al., 2021). Indeed, in the Darwinian-like process of tumor evolution, the accumulation of somatic alterations leads to a clonal selection of cells with advantageous traits (Nesta et al., 2021). Furthermore, as the tumor expands, it experiences selective pressures (e.g., hypoxia, nutrient deprivation, immune system surveillance, and therapy-induced stress), which result in the survival of the fittest clones, those best adapted to the TME (Vishwakarma and Piddini, 2020). This evolutionary process mirrors ecological systems, where species with higher fitness, defined by traits that improve survival and reproductive success, dominate the environment (Bozic, 2022) (Fig. 1).

For instance, in the early stages of PDAC, specific hotspot mutations in driver genes such as Kirsten rat sarcoma virus (*KRAS)*, tumor protein p53 (*TP53)*, and Cyclin Dependent Kinase Inhibitor 2 A (*CDKN2A)* are commonly observed and are considered pivotal in the initiation and

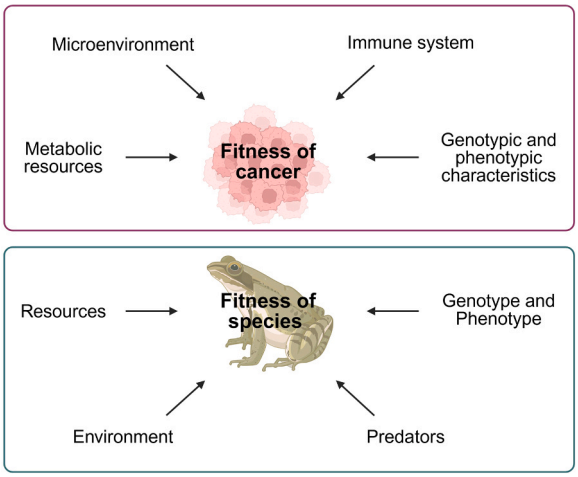


Fig. 1. Shared traits that affect the fitness of cancer cells and ecological species. The fitness of cancer cells is determined by a range of survival traits and the capacity to proliferate, mirroring the ecological systems in which the fitness of species is represented by traits that improve survival and reproductive success.

progression of pancreatic carcinogenesis (Sivapalan et al., 2022) (Fig. 2). *KRAS* mutations, in particular, occur in approximately 90% of PDAC cases and are recognized as early genetic events that drive aberrant cellular signaling pathways, contributing to uncontrolled cell proliferation, survival, and resistance to apoptosis (Cancer Genome Atlas Research Network, 2017).

In this context, the relationship between these mutations and

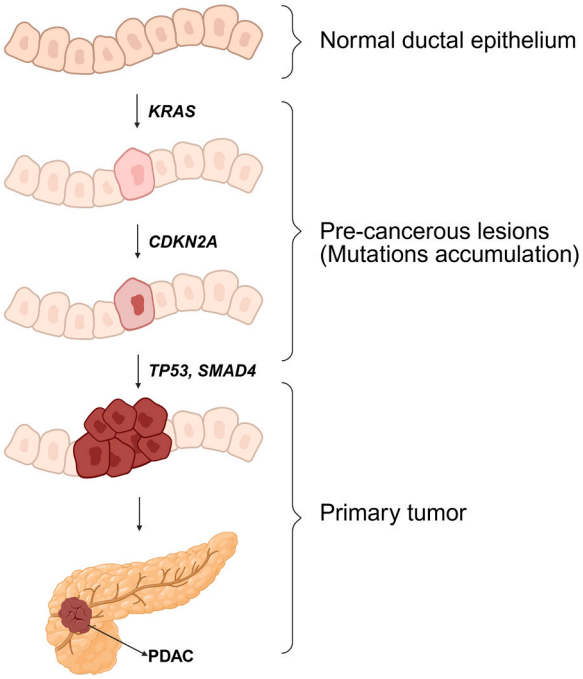


Fig. 2. Schematic representation of the development of pancreatic cancer pathogenesis. A normal ductal epithelial cell may accumulate driver mutations in key genes, including *KRAS*, *CDKN2A*, *TP53*, and *SMAD4*, that gradually induce its transformation into pre-cancerous lesions and then eventually into PDAC. The progression of pre-cancerous lesions can take place over many years as more genetic drivers accumulate, leading to increasing disorganization and an accumulation of cells exhibiting cytologic abnormalities (dysplasia). Malignant transformation occurs when these cells invade the surrounding pancreatic tissue.

immune evasion is also significant (Cheng and Vonderheide, 2023). The hotspot mutations that confer growth advantages to cancer cell fitness may simultaneously influence the tumor's interaction with the immune system, potentially impairing immune surveillance mechanisms (Gonzalez-Cárdenas and Treviño, 2024). This interplay between tumor cell survival and immune escape is critical for the advancement of PDAC from precursor lesions to invasive carcinoma (Argentiero et al., 2024).

Taken together, somatic mutation accumulation, particularly in mutation hotspots, accelerates the transformation of normal cells into malignant cells, paralleling evolutionary principles in which certain genetic changes confer survival advantages and lead to the dominance of mutated cells within a population.

3. Genetic alterations in precancerous lesions

Building upon these foundational genetic drivers, initiating mutations trigger early clonal diversification. In order to follow the transformation of a cell, it is crucial to consider tumor precursor lesions (Zamboni et al., 2013). The modification of key genes in a ductal pancreatic cell can convert a normal cell into a precancerous one, and further genomic changes can enhance its growth advantages, ultimately leading to the emergence of a new population of neoplastic cells that can progress to a clinical status identifiable as cancer (Gao, 2008). The different genetic backgrounds among the cells mainly contributed to the heterogeneity observed in precancerous lesions (Braxton et al., 2023). Hence, pancreatic precancerous lesions are divided into microscopic and macroscopic types. Microscopic lesions include pancreatic intraepithelial neoplasia (PanIN), the most common precursor to invasive PDAC. Macroscopic lesions include intraductal papillary mucinous neoplasm (IPMN) and mucinous cystic neoplasm (MCN). All lesions can be classified based on the morphological grade of dysplasia in their lining epithelium as low- or high-grade (Omori et al., 2023).

Pancreatic lesions share a high frequency of oncogene-mutated *KRAS,* indicating that this is an early event in the development of neoplasia, while mutations in other genes (*CDKN2A*, *TP53,* and SMAD Family Member 4 - *SMAD4*) are characteristic of more advanced lesions (Singhi and Wood, 2021) (Fig. 2). Based on these findings, *KRAS* mutations may be necessary for the initiation of PanIN lesions and for their progression to invasive cancer. In IPMN and MCN, mutations in *KRAS* are less frequent, respectively around 60,9% and 33–89% (Lee et al., 2016), and are not strictly associated with malignancy. Taken together, although *KRAS* mutations have a crucial role in the initiation of the neoplastic lesion, a combination of additional hits and somatic changes is required to alter different signaling pathways (Li et al., 2023). The next event to take into consideration is the loss of CDKN2A function, which was reported in the later stages of precancerous lesions (Singhi and Wood, 2021), in particular in wild-type-*KRAS* PanIN, suggesting the existence of an alternative mechanism involving *CDKN2A* but not *KRAS* mutations in the pathogenesis of pancreatic cancer (Kanda et al., 2012). Lastly, *TP53* mutations are considered a late event in the multistep progression of precursor lesions to PDAC (Qian et al., 2020). With p53 inactivation, precancerous cells lost their cell cycle regulation and programmed cell death, leading to uncontrolled proliferation and apoptosis (Chan-Seng-Yue et al., 2020). Similarly, *SMAD4* mutations occur in the late stage of PDAC in approximately 40–55% of patients, and this event is considered one of the final steps in the initiation of invasive PDAC (Singhi and Wood, 2021) (Fig. 2). Here, we are considering the most frequent alterations; several other genes commonly undergo mutations in PDAC with frequencies reported to be less than 10% in large-scale sequencing studies (Li et al., 2023).

Hence, PDAC arises from non-invasive precancerous lesions in which mutational events converge, causing the cells' transformation, which can improve their fitness and give them a selective advantage over non-tumor cells. Multiple genetic alterations in later-occurring driver genes were frequently localized to specific tumor clones, highlighting the possibility of convergent evolution in pancreatic tumorigenesis (Kuboki

et al., 2019) and suggesting that different genetic pathways can lead to the same outcome - the development of cancer (Pienta et al., 2020).

Moreover, precancerous lesions are a crucial area of research for the early detection of pancreatic cancer. The fitness of precancerous lesion cells that do not progress to aggressive cancer is a key point of interest: these cells maintain a balance in their genetic stability, avoiding excessive genetic divergence that would make them more aggressive (Lai and Zhang, 2025). They are very common in the population, as most patients have one or more pancreatic lesions at the time of death that usually do not develop into PDAC (Søreide et al., 2023). Indeed, they can coexist with normal cells and not invade nearby tissues or spread to distant organs, maintaining their fitness without progressing to malignancy or acquiring significant genetic changes, which suggests a form of evolutionary stasis, where the precancerous cells do not gain an advantage over normal cells. This observation raises an unresolved question: how do evolutionary forces shape the genetic differences between precancerous and non-tumor cell populations over time? Mathematical models have been proposed to better understand these dynamics, like the G-function theoretical modeling framework (Barua et al., 2018), which focuses on cancer cell speciation, diversification, and environmental adaptation (Bukkuri et al., 2023). Regarding precancerous conditions, an example of the modeling is the development of cervical intraepithelial neoplasia (CIN) grade 3 (CIN3), a precancerous lesion of the cervix (Cabrera-Becerril et al., 2017). The widely accepted model of CIN3 development posits a sequential progression from a normal state, through CIN grade 1 (CIN1) and CIN grade 2 (CIN2) stages, and finally to CIN3, thereby aiding in the early detection and treatment (Venkatas and Singh, 2020). To the best of our knowledge, a mathematical model for the development of pancreatic precancerous lesions is still lacking, but it could be a valuable resource for analyzing precancerous lesions and their progression to malignancy, which could aid in predicting carcinogenesis of pancreatic cancer. These models may offer insight into how ecological forces, such as competition for resources or cooperation between cell types, can drive the evolution of precancerous lesions and help predict the likelihood of a progression to malignancy, providing valuable information for potential early intervention.

While the fundamental biological drivers of PanIN and IPMN are well described, developing practical strategies for their interception has proven challenging, largely due to issues with detection, risk assessment, and low-risk intervention approaches. Detection strategies are restricted, primarily relying on the analysis of pancreatic juice for PanIN and the examination of cyst fluid for IPMN, for the detection of driver mutations (Pedro and Wood, 2025) in well-known key genes to monitor their temporal dynamics, the accumulation of mutations, and their evolutionary trajectories through the transformation into malignant cells. Moreover, imaging techniques can be used to understand their ecological landscape and the development of the lesion microenvironment. Although liquid biopsy of peripheral blood has not been extensively researched for precursor lesions, it does hold theoretical potential (Pedro and Wood, 2025). This approach may help in the monitoring of high-risk individuals with a family history of PDAC or oncogenic germline mutations. Furthermore, single-cell resolution with spatial omics may be useful to depict the cellular and ecological landscapes of early pancreatic lesions, revealing lesion transformation trajectories and microenvironmental remodeling. Indeed, spatial transcriptomics facilitated accurate mapping of lesion localizations and niche interactions, highlighting microenvironmental shifts that occur from normal pancreas to PanIN to PDAC. This includes fibroblast remodeling and T cell infiltration (Carpenter et al., 2023). In addition, a cellular atlas can be developed by analyzing single cells from PanIN, IPMN, and related PDAC. In a recent study, the analysis of over 35,000 cells derived from high-grade IPMNs and IPMN-derived PDAC indicates a lineage transition and epithelial subsets unique to PDAC. At the same time, a notable shift in the immune landscape was observed, from a pro-inflammatory state in IPMNs to an immunosuppressive one in PDAC, with M2 macrophages being the predominant type (J. Li et al., 2024). These results exhibit how transcriptional programs, cellular transformation and transitions, and microenvironment alteration are fundamental for PDAC initiation and heterogeneity (Qi et al., 2026). Taken together, based on PDAC characteristics, the analysis of pancreatic precancerous lesions' plasticity, clonal heterogeneity, dynamics, and immune remodeling processes may identify potential biomarkers that could aid in the detection of high-risk lesions, stratification of patients based on the evolutionary history of the tissue, and development of new targets for early therapeutic intervention.

4. Heterogeneity in primary tumor and metastases

Moving beyond the precancerous lesions, PDAC tumorigenesis and progression are quite peculiar (Rampias, 2020). Hence, transformed cells are subjected to genomic instability, chromosomal rearrangements, copy number alterations, and epigenetic changes, leading to rapid proliferation, invasion, and dissemination (Connor and Gallinger, 2022), which confer a competitive advantage over normal cells. Genotypic variations and phenotypic adaptations resulted in the emergence of distinct subpopulations within the tumor, each with different survival strategies (Whiting et al., 2024; Wu, 2012). As a result, the tumor ecosystem becomes increasingly complex, with certain clones gaining dominance over time (Rampias, 2020). Furthermore, particularly in PDAC, different TME characteristics can influence the success and the selection of cancer clones (DeGregori, 2018). Indeed, cancer progression can be influenced by interclonal competition leading to the selection of a single clone that may contribute to intratumor heterogeneity (Dentro et al., 2021). The presence of genetic subclones within a single tumor in a patient was first demonstrated in PDAC using karyotyping in 1998 (Gorunova et al., 1998) and subsequently using DNA sequencing (Campbell et al., 2010). The analysis of different sections of primary PDAC demonstrates the existence of spatially localized subclonal cell populations genetically evolved from the original parental tumor cells, resulting in the success of subclones exploiting available resources more efficiently under limiting conditions. To maintain this advantage, they adopt strategies that enable them to migrate and invade new sites, repeating this process whenever reachable nutrients become limiting. This is seen in the process of epithelial-mesenchymal transition (EMT), in which epithelial cells lose their properties and become mesenchymal cells, developing motility-invasive properties in a highly dynamic and plastic manner (Dardare et al., 2021). EMT plays an important role in cancer progression, as it can confer metastatic properties to tumor cells, enhancing invasion capabilities of surrounding tissues and distant organs (Luu, 2021). This process is tightly regulated by a complex network orchestrated by several intrinsic and extrinsic factors, including multiple transcription factors, post-translational control, epigenetic modifications, and noncoding RNA-mediated regulation (Yang et al., 2022). In summary, resource depletion can trigger migration and invasion in both ecological and cancer contexts, although the mechanisms and implications differ.

The genetic heterogeneity of distant metastases reflects the intratumor clonal populations composing the primary PDAC (Yachida et al., 2010). In contrast, epigenetic and metabolic differences have been demonstrated when comparing paired primary PDAC and metastases. Epigenetic reprogramming and changes in chromatin modification were strongly associated with metastatic cells (Roe et al., 2017). Indeed, intratumoral heterogeneity in primary tumors is not only driven by genetic alterations but also by epigenetic dysregulation, gene expression variation, and post-transcriptional regulation (Guo et al., 2025). Recently, other studies on human PDAC samples in which single-cell multiomics (RNA-seq or single-nucleus RNA-seq) and spatial transcriptomics were performed confirmed the high heterogeneity and the coexistence of subclones with distinct expression signatures (Cui Zhou et al., 2022), and have fundamentally shifted our understanding of PDAC from a passive collection of mutated cells to an active ecosystem. In this context, there is an interaction between different subclones, in

which the one with a better fitness will try to take over, and between clones and the TME to ensure their survival. Translated to the current work, high-resolution spatial mapping demonstrates that specific PDAC clones actively secrete signaling molecules (e.g., transforming growth factor-beta TGF-β) to reshape their physical and immunological environment, polarizing macrophages and activating cancer-associated fibroblasts (CAFs) to build localized fibrotic tissue that excludes cytotoxic T-cells (Group Young Researchers in Inflammatory Carcinogenesis et al., 2021). It has also been reported that immunosuppression in PDAC arises from the complex interactions among dysfunctional T cells, tumor cells, and various components of the TME (Du et al., 2025; Qi et al., 2026; Yousuf et al., 2023). Single-cell multiomics and spatial transcriptomics were also applied to compare heterogeneity of primary tumor and metastases, revealing cellular programs that promote metastasis, but a clear explanation of how the different clones participate in this process is still missing (Qi et al., 2026; Yang et al., 2021). Collectively, these techniques are showing a great impact in PDAC studies due to the capacity to analyze multiple heterogeneous clones of the tumor and TME cell, and their interactions within a spatially localized niche.

Indeed, the process of resource depletion and its effects on migration and invasion are similarly observed in both ecological and cancer contexts (Gallaher et al., 2019). In ecology, the invasive species cane toad (*Rhinella marina*), introduced in the 1930s in Australia (Neinavaie et al., 2021), has rapidly depleted local resources and spread across nearby lands, often outcompeting native species for food and space. Similarly, the black rat (*Rattus rattus*) has caused significant ecological disruptions (Noorbakhsh et al., 2020). Introduced to various islands worldwide, this species has been responsible for the decimation of native bird populations and the alteration of plant communities. These same phenomena are evident in PDAC cells adapting by migrating and spreading to nearby tissues and organs, like the liver, forming new metastatic lesions, to exploit new environments (Carstens et al., 2021). These cells actively invade healthy tissues, like invasive species colonizing new territories. In both ecological and cancer contexts, competition for resources drives the expansion of populations, whether it's a rapidly growing invasive species or a fast-spreading tumor, demonstrating how limited resources act as a powerful force shaping behavior and growth (Fig. 3). In this context, nutrient depletion can generate dynamics consistent with disturbance-driven selection, in which the selective pressures acting on cancer cell populations in the tumor ecosystem are altered. These disturbances can eliminate less adaptable PDAC cells while favoring the survival and expansion of more plastic clones, often characterized by increased invasive potential. As in an ecological system affected by environmental disturbances, such processes may accelerate evolutionary dynamics within tumors and promote the emergence of more aggressive phenotypes, ultimately contributing to disease progression, cell migration, and metastasis formation (Cunningham et al., 2011; Gillies et al., 2012). In PDAC, disturbance in the desmoplastic TME caused by nutrient depletion, hypoxia, or therapeutic interventions can drive the selection of clones responsible for the early metastasis formation (Fig. 3) and therapy resistance.

This dynamic of resource competition and depletion, as it relates to cancer, may even suggest that the metastatic spread of tumors could be framed as an example of ecological failure. While metastasis enables the tumor cells to colonize distant organs, it often leads to the demise of the host, in particular in highly lethal tumors such as PDAC, raising the

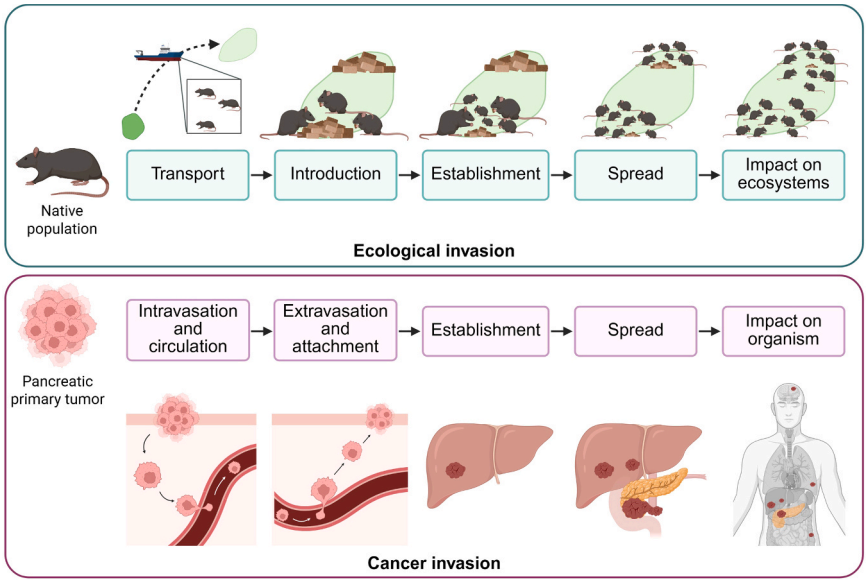


Fig. 3. Schematic representation comparing the steps of biological invasion of invasive species such as the black rat (*Rattus rattus*) in a new environment (Ecological invasion) and pancreatic cancer cells forming distant metastatic lesions in the liver and in other sites (Cancer invasion). Each step in the Cancer invasion closely mimics the respective one related to Ecological invasion. The native population of black rats and the pancreatic primary tumor cells represent the population before the invasion. The first step for both processes is defined by moving from the original site to a new site. The transport of invasive species in ecological invasion can usually be natural or mediated by human dispersal (for example, by boat). In cancer, this stage is represented by two phases, intravasation and circulation, in which a selected group of cancer cells infiltrates the blood or lymphatic vessels to travel to distant organs. The introduction phase in the ecological invasion closely parallels the extravasation and attachment step in cancer invasion marking the initiation of the new site. For the ecological invasion, it means the competition with native species for food and space. High food abundance is represented with big brown blocks. In cancer invasion, this phase is characterized by the process of extravasation and attachment of cancer cells at a new site, where they compete with native cells of the organ, in this case, liver cells, for nutrients. This step is followed by two common steps: establishment and spread. For ecological invasion, this involves the establishment and colonization of a new site, the depletion of local resources in one area, and the subsequent spread and invasion of new regions with more abundant food. For cancer invasion, division of cells using the nutrients of the new site grows a tumor mass with the development of a liver metastatic lesion, with consequences for the organ functions and the spreading into surrounding tissues, due to processes like colony formation, angiogenesis, proliferation, and dissemination. Finally, the results and consequences of the Ecological and Cancer invasion processes are the impact on the ecosystem and on the organism, respectively. The invaded ecosystem's health was disrupted; native animals, particularly birds, were decimated, and plant communities were altered. Similarly, the organism's health is definitely compromised by the metastatic spread and invasion into different sites and organs, altering their functions.

question of whether this could be considered an "*ecological failure*". As George Williams famously stated, "evolution has no eyes to the future", implying that evolutionary processes, though successful in the short term, may lead to outcomes that undermine long-term survival (Greaves, 2013). Negative impacts of successful individual behavior on population stability are well known in population and community ecology (Basset et al., 1997; Rosenzweig, 1971). In the context of PDAC, metastases are frequently fatal, with tumor cells ultimately contributing to the collapse of the host's biological system. This leads to a paradoxical outcome, in which the very evolutionary strategies that ensure the survival and spread of cancer cells can also result in the destruction of their host, rendering metastasis a tragic form of ecological failure within the cancer's broader evolutionary trajectory. Considering cancer cells as external agents, their negative effects on the host's biological systems and a positive influence on the biological host's population stability would have been expected; these potential relationships have not yet been addressed in the context of tumors' dynamics in human populations.

The use of an ecological perspective may be useful for PDAC early detection, progression, and biomarker development. Liquid biopsy from peripheral blood is considered an emerging diagnostic technique based on eco-evolutionary principles. Indeed, it allows the detection of molecular biomarkers such as circulating tumor cells, circulating tumor DNA, noncoding RNAs, and extracellular vesicles (Girolimetti et al., 2024; Wang et al., 2023) to follow the evolutionary trajectories and the ecological communication between cancer cells and the TME. This information may highlight the presence of PDAC, its development and progression to metastasis formation, and enable the formulation of precise and personalized treatment for the patient.

To better clarify the development of cancer ecology, the fundamental concepts, divided into classical foundations and recent advances, were summarized in Table 1, with the main references and their contribution.

5. Drawing parallels between ecological pressures and cancer progression

Based on characteristics examined during the development and progression of PDAC, from precancerous lesions to the primary tumor and metastatic dissemination, eco-evolutionary dynamics that consider multi-species interactions, spatial resource competition, and niche construction can help resolve the mechanistic gaps left by traditional molecular models. The *Hallmarks of Cancer*, proposed by Hanahan and Weinberg, may provide a framework for understanding the "ecological" nature of tumorigenesis. These hallmarks, which include sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and affording metabolic plasticity, among others, describe the capabilities that cancer cells acquire to survive and thrive in their ecological niche (Hanahan, 2022; Hanahan and Weinberg, 2011, 2000). From an ecological perspective, they can be seen as "strategies" that cancer cells employ to outcompete other cells and adapt to a changing environment, much like organisms in ecosystems adopt survival strategies to monopolize their niche space and to evolve in response to pressures. These ecological strategies may be applied to PDAC to improve the accuracy in describing its behavior, understand the biology, and guide future research and therapeutic approaches.

5.1. Ecological niche theory

The first ecological theory to take into consideration due to the intrinsic characteristics of PDAC and its TME, is the ecological niche theory. Originally developed to explain the coexistence of species

Table 1
Classical Foundations and Recent Advances (post year 2020) studies from early PDAC genetics and evolutionary concepts of cancer to single cell/spatial multiomics, tumor microenvironment, and eco-evolutionary perspectives. A selection of highly influential works that have contributed to the conceptual and technological development of the field is reported.

Categories		References	Main contribution
CLASSICAL FOUNDATIONS	**Early genetics of PDAC**	Gorunova et al., 1998	Cytogenetic analysis revealing intratumor chromosomal heterogeneity.
		Campbell et al., 2010	Characterization of genomic instability patterns in metastases.
		Kanda et al., 2012	Identification of somatic mutations in early PanIN lesions.
		Cancer Genome Atlas Research Network, 2017	Comprehensive integrated genomic characterization.
	Evolutionary concepts of cancer	Paget, 1889	Seed and soil hypothesis of metastasis.
		Dobzhansky, 1973	Established the central role of evolutionary theory in understanding biological systems, including cancer.
		Hanahan & Weinberg, 2000	Conceptual framework describing the hallmarks of cancer, integrating evolutionary principles.
		Fidler, 2003	Tumor microenvironment interactions in metastatic niches.
		Attolini & Michor, 2009	Mathematical and evolutionary models describing mutation accumulation and tumor progression.
		Gatenby et al., 2009	Concept of adaptive therapy in cancer treatment.
		Aktipis & Nesse, 2013	Evolutionary framework explaining cancer development through natural selection and adaptation.
RECENT ADVANCES (post-2020)	**Single-cell/spatial genomics**	Chan-Seng-Yue et al., 2020	Demonstrated that transcriptional phenotypes of PDAC are shaped by genomic evolutionary events.
		Raghavan et al., 2021	Single-cell analysis of microenvironment-driven cell states.
		Cui Zhou et al., 2022	Spatial genomics revealing microenvironment-dependent cell populations and resistance mechanisms.
		Li et al., 2024	Single-cell analysis of PDAC heterogeneity.
	Tumor microenvironment (TME) in PDAC	Ho et al., 2020	Overview of the clinical and biological role of the TME.
		Sherman & Beatty, 2023	Immune and stromal interactions driving progression.
		Li et al., 2024a	Characterization of the panoramic TME.
		Du et al., 2025	Identification of stromal cell populations contributing to desmoplastic and immunosuppressive niches.
	Eco-evolutionary perspectives	Somarelli, 2021	Interpretation of hallmarks of cancer as ecologically driven phenotypes.
		Dujon et al., 2021	Identified key research questions in the ecology and evolution of cancer.
		Raja Arul et al., 2022	Eco-evolutionary framework specifically applied to PDAC.
		Zhang et al., 2022	Clinical application of evolutionary modeling in adaptive therapy.
		Bukkuri et al., 2023	Modeling ecological and evolutionary dynamics of cancer systems.
		Lai & Zhang, 2025	Analysis of environmental drivers of malignant clonal selection in precancerous lesions.

interacting while exploiting the same resources under limiting conditions, this theory has emerged as a valuable conceptual framework for understanding the progression of cancer (Kareva, 2015). According to the Hutchinson's n-dimensional niche concepts, the niche is a property of individuals, populations, and species occurring in an ecosystem and of the ecosystem, as well (Hutchinson, 1957). Niche filtering is the process that allows ecosystem colonization by species whose niche is included in the ecosystem (Zobel, 1997). Niche width is a phenotypic property of individuals, evolving as a quantitative character of both individuals and populations (Roughgarden, 1972). By incorporating Hutchinson's multidimensional niche space (Colwell and Rangel, 2009; Hutchinson, 1957) and the resource-based mechanisms proposed by MacArthur (MacArthur and Pianka, 1966; Shapiro, 1985), this theory emphasizes the complex interplay of inter-species dynamics, such as competition, mutualism, and predation, within ecosystems, where each species occupies a defined niche shaped by both abiotic and biotic factors (Vandermeer, 1972). When applied to tumor biology, the TME can be viewed as a dynamic and evolving ecosystem, wherein multiple distinct cellular populations engage in interactions analogous to inter-species relationships observed in ecological systems (Ho et al., 2020; Laranga et al., 2020) (Fig. 4). Application of niche theory to cancer not only underscores the importance of cell-cell and cell-environment interactions but also provides a robust theoretical scaffold for interpreting tumor behavior through the lens of both inter- and intra-cellular evolutionary dynamics (Fidler, 2003; Kareva, 2015; Odling-Smee et al., 1996; Qian and Akçay, 2018). In cancer, particularly in PDAC, the TME is an active participant in tumor evolution. Stromal cells and extracellular matrix can exceed the epithelial tumor mass and profoundly shape cellular behavior, far more than in many other carcinomas. This creates a physical and functional ecosystem where cancer cells are embedded in a dense, reactive habitat. These processes underscore the dynamic and complex interactions between the various cell types within the TME, ranging from CAFs such as stellate cells and extracellular matrix (ECM) to various types of immune cells, like cytokines and endothelial cells, which participate in controlling tumor growth, invasion, and metastasis (Qian and Akçay, 2018; Tjomsland et al., 2011; Whatcott et al., 2015). This heterogeneity in the TME is also reflected in the diversity and dynamics of acellular components, including the ECM, cytokines, growth factors, and secreted ligands that modulate signaling pathways (Fig. 4). Indeed, its composition makes the TME a barrier for developing effective treatments for cancer cells (Bever et al., 2015; Raghavan et al., 2021). Based on this data, clinical studies have focused on the TME as a potential novel target for PDAC treatment. Clinical trials targeting TME components were performed, but, to date, no benefit for patients has been reported (Catenacci et al., 2015; Hingorani et al., 2018). These failures point to the fact that TME composition in PDAC is complex and heterogeneous, and the interactions between cancer cells and microenvironment components remain insufficiently understood. The TME can also influence pro-metastatic processes. The formation of a distant metastatic cell niche with a favorable microenvironment helps the colonization of distant organs. The most common sites of colonization for PDAC metastasis are the liver, the lungs, and the peritoneal sites; less frequently, PDAC cells can adapt to the brain, bones, or skin microenvironment (Pourshams et al., 2019) (Fig. 3). The metastatic cell niche may be the host organ's response to inflammatory signals from the primary tumor site, causing an increased presence of macrophages and neutrophils and deposition of ECM proteins, such as collagen and fibronectin (Truong and Pauklin, 2021). It was demonstrated that hepatocytes accumulate myeloid cells and fibrosis, increasing the possibility for the liver to undergo metastatic seeding and outgrowth from PDAC cells. In mice, hepatocytes show activation of the Signal transducer and activator of transcription 3

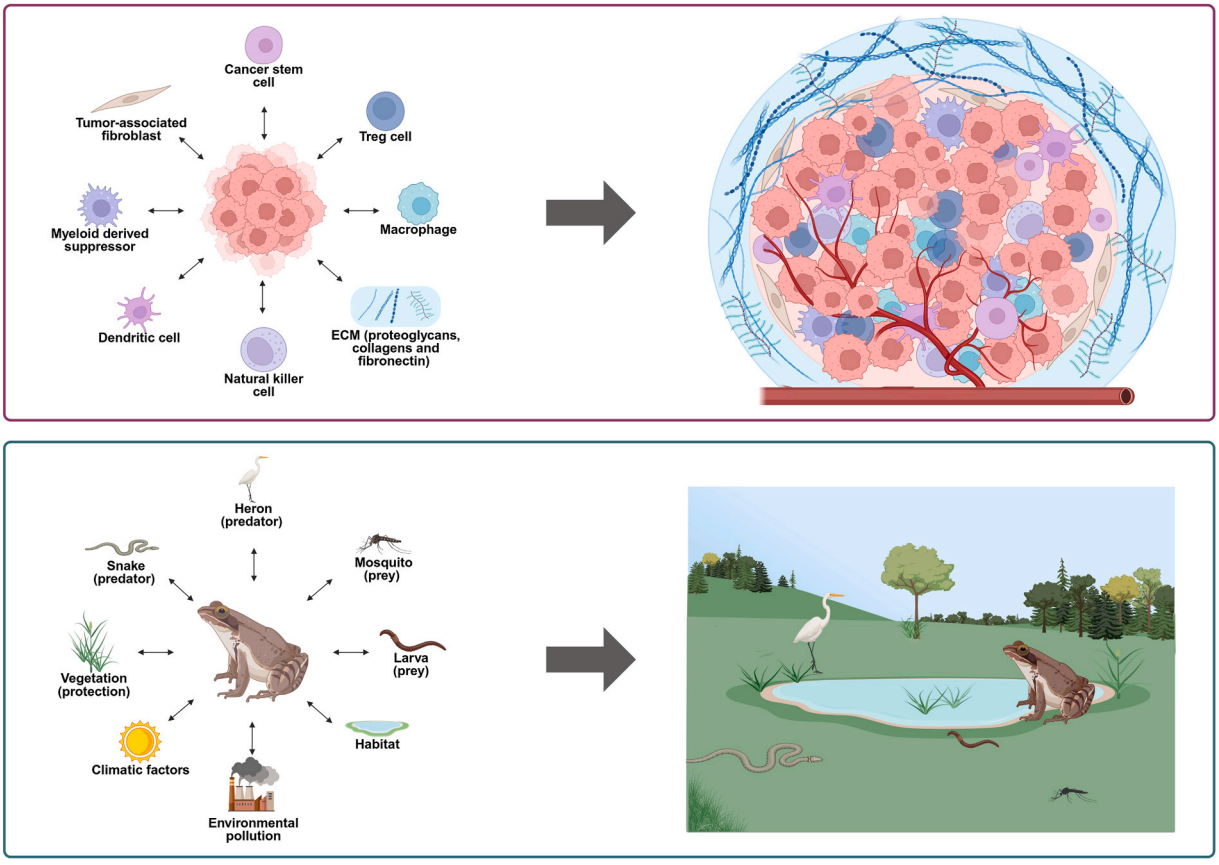


Fig. 4. The different components of the tumor microenvironment and of the ecological niche. Tumor cells contribute to and influence the formation of the TME, mimicking a species in its niche.

(STAT3) signaling and increased production of serum amyloid A1 and A2 during early pancreatic tumorigenesis in response to the release of Interleukin-6 (IL-6) into the circulation by non-malignant cells. Blocking the components of IL-6-STAT3-amyloid A1 and A2 signaling inhibits the pro-metastatic niche and liver metastasis (Lee et al., 2019).

5.2. Seed and soil hypothesis

From another perspective, Paget's "seed and soil" hypothesis offers a valuable lens for understanding the metastasis of PDAC (de Groot et al., 2017; Paget, 1889), which is consistent with the niche filtering process (Zobel, 1997). In this context, the cancer cells (the "seeds") must find a favorable "soil", an organ or tissue with a supportive microenvironment, i.e., the niche filter, that permits the establishment of secondary tumors when the "seed" is included in the "soil niche". Liver, lungs, and peritoneum represent PDAC "soil", possibly due to the abundance of factors like cytokines, chemokines, and immune cell populations that promote tumor cell survival and growth. For instance, the liver microenvironment contains abundant ECM components, such as laminin, and resident hepatic stellate cells that produce a pro-inflammatory milieu, which may facilitate the colonization of circulating PDAC cells. In addition, growth factors such as hepatocyte growth factor (HGF) and TGF-β are present at metastatic sites, creating a hospitable environment for the metastatic cells (Oronsky et al., 2023). Furthermore, it was demonstrated that extracellular vesicles play a role in helping tumor cells seed at pre-metastatic sites due to their cargo carried throughout the body, such as proteins, long non-coding RNAs, and microRNAs, that may have an impact on the tumor niche composition (Costa-Silva et al., 2015; Rana et al., 2013). This process mirrors how invasive species alter their new environments to ensure their survival and expansion. In PDAC, the stroma creates a "soil" that fosters tumor progression by providing growth factors and cytokines that support malignant cell proliferation and survival. This emphasizes that PDAC's propensity to metastasize is not solely determined by the cancer cells' intrinsic properties but also by the permissive characteristics of the surrounding tissue environments.

5.3. Evolutionary game theory

As the field has matured from qualitative ecological observations to quantitative science, another mathematical model has emerged as a useful tool. Recent quantitative oncology approaches, such as evolutionary game theory (EGT), have proven instrumental in modeling the frequency-dependent interactions between competing clonal populations (Dhanasekaran et al., 2025). By assigning payoff matrices to different cellular phenotypes (e.g., glycolytic vs. aerobic cells), EGT models can predict stable coexistence or the competitive exclusion of specific clones in PDAC. This is particularly relevant in PDAC due to the high heterogeneity of tumor cells and the cooperation of different clones. Therefore, this theory may result in new findings regarding how intercellular coexistence and competition happen between tumor-cell populations

5.4. Adaptive potential and metabolic plasticity

Biological diversity plays a crucial role in stabilizing ecosystems, which are constantly adapting to environmental changes. Different survival strategies among species are vital; without environmental compensatory mechanisms, such as adaptive shifts in individual niche position and/or niche breadth, species may face extinction (Lu et al., 2025; MacArthur and Levins, 1967). Maintaining biological diversity is essential for ensuring the stability and productivity of cellular ecosystems (Amend and Pienta, 2015). Tumors co-opt these principles, establishing heterogeneous populations and environments that maximize their adaptive potential. The metabolic plasticity of PDAC cells can dynamically reprogram their metabolism in response to environmental stress or therapeutic pressure, such as nutrient levels, oxygen availability, or treatment, ensuring they can fulfill their energy and biosynthetic requirements for survival, growth, and metastasis formation.

Compared with normal cells, tumor cells with high metabolic plasticity quickly adapt to utilize various bioenergetic resources, switching between glycolysis and oxidative phosphorylation or scavenging alternative fuels like lactate and lipids, whether sourced from the microenvironment or generated internally (Sebestyén et al., 2021). This capacity can be viewed in the light of the ecological trade-off between specialists and generalists: whereas specialists evolve for peak efficiency within a narrow niche, generalists maintain broad tolerances to persist across fluctuating habitats (Hausser and Alon, 2020). In complex organisms, normal differentiated cells typically behave as metabolic specialists: they are highly efficient but strictly dependent on specific substrates within a homeostatic niche. Conversely, cancer cells exhibit the trophic flexibility of aggressive generalists, allowing them to withstand severe conditions of nutrient and oxygen deprivation. Consequently, metabolic flexibility within tumor tissue ensures the survival of the tumor population "at all costs", like how invasive generalists outcompete native specialists in disturbed environments (Gillies et al., 2018).

Adaptation capacity also has important implications for therapeutic responses. An intensive treatment strategy may select clones based on their metabolic plasticity and the capacity to use alternative nutrient sources or metabolic pathways (Gatenby and Brown, 2020). When more subpopulations within a tumor depend on different metabolic pathways, targeting just one specific process might impact only a portion of the tumor, with the remaining cells that could potentially lead to a recurrence. From an eco-evolutionary perspective, such selective pressures may accelerate the emergence of therapy-resistant populations, highlighting the importance of considering metabolic heterogeneity and plasticity when designing therapeutic strategies (Gatenby et al., 2009). Hence, analyzing metabolic interactions at the single-cell level is becoming an important approach to understand how tumors manage nutrient uptake, reallocate metabolic resources, and utilize stromal elements to maintain growth even in challenging environmental conditions (Bärthel et al., 2023; Kaoutari et al., 2021). In a recent study on PDAC patients and cell, the authors integrated spatial transcriptomics, single-cells multiomics analyses and functional validation to demonstrate the spatial organization of metabolic heterogeneity focused on glycolysis and its correlation with hypoxia, vascular distribution, stromal density, and with clinical outcome, making metabolic heterogeneity a clinically significant prognostic indicator potentially resulting in personalized metabolic therapies (Chianese et al., 2026).

5.5. Eco-evolutionary feedback loops concept

Synthesizing the spatial heterogeneity and niche construction of PDAC leads directly to the concept of eco-evolutionary feedback loops, where the tumor and its microenvironment continuously shape one another (Luo, 2023): as PDAC cells genetically evolve to drive desmoplasia altering the ecology, the resulting fibrotic, hypoxic TME applies severe pressure back onto the tumor cells, selecting for metabolically plastic and highly invasive clones (Yang et al., 2025). Taken together, integrating metabolic profiling with ecological and evolutionary modeling may represent a promising path for the development of more personalized therapeutic strategies in PDAC, which makes a more precise characterization of the metabolic phenotypes, along with a deeper understanding of the metabolic dependencies, crucial.

5.6. Predator-prey model

Another ecological dynamic to take into consideration in cancer evolution is the traditional predator-prey model that could be directly related to the tumor immune escape (Barua et al., 2018). Indeed, PDAC cells, like organisms in an ecosystem, are engaged in complex interactions with the immune system, resembling a predator-prey

dynamic. The immune system, acting as a natural predator, seeks to eliminate tumor cells (the prey), while cancer cells evolve mechanisms to evade immune surveillance. This "arms race" allows tumor cells to actively suppress immune infiltration, constructing a more favorable niche for growth (Somarelli, 2021). Predator-prey dynamics between the immune system and the tumor cells could be applied to the pancreatic precancerous lesions in which a pro-inflammatory immune landscape is present. In the case of PDAC, when cancer cells are protected in the environmental niche, the predator may be trapped in the desmoplastic TME, preventing the prey and predator from direct contact (Kung et al., 2025) and favoring the immune escape.

5.7. Adaptive therapy and mathematical oncology

Mathematical modeling has also emerged as an indispensable tool in the field of oncology, providing valuable insights into the complex dynamics of cancer progression and treatment response. Models derived from the Lotka–Volterra equations, which characterize species-rich ecological communities, have been used to simulate and gain insights into tumor behavior under various treatment conditions (Belkhir et al., 2021).

These models have proven to be instrumental in the development of treatment approaches that leverage the principles of evolution to address the pervasive issue of drug resistance in cancer therapy (Gottesman et al., 2016). One of the key applications of mathematical modeling is in the realm of tumor dynamics, particularly in the context of adaptive therapy, an evolution-informed approach for managing tumors dynamically that has been proposed as an alternative strategy to conventional linear attempts based on tumor eradication (Gatenby et al., 2009). Instead of focusing on complete tumor eradication using maximal-dose treatments with the risk of creating a cellular chemoresistant subpopulation, adaptive therapeutic strategies aim at maintaining a balanced tumor ecosystem by preserving competition between drug-sensitive and resistant clones (Enriquez-Navas et al., 2016) within the tumor ecosystem. This approach may limit the expansion of highly plastic or resistant clones and delay disease progression. A small trial was performed on metastatic castration-resistant prostate cancer patients to understand the possible advantages of adaptive therapy with a treatment protocol based on a personalized and continuously updated mathematical model, compared to the standard of care for abiraterone treatment. The authors suggested that their approach prolonged time to progression and highlighted the benefits of a multidisciplinary approach in clinical trial design (Zhang et al., 2022, 2017). Hence, in cancer research, mathematical oncology enables the development of tumor dynamics models, treatment response, dose schedules, and timing, with the aim of designing effective treatment protocols with maximum therapy efficacy and minimum adverse effects (Jarrett et al., 2020). Additionally, mathematical models were employed to better understand the ecology of heterogeneous tumors, which could have implications for phenotypic plasticity, interactions between cancer and the immune system, and metastasis formation (Aguadé-Gorgorió et al., 2024).

Taken together, there is an increasing interest in applying mathematical models and methods from ecology in the field of cancer treatment, particularly through the concept of evolutionary-based adaptive dosing, which tailors drug dosages according to the level of tumor burden.

For PDAC, for which chemotherapy resistance is a major obstacle to a better patient's prognosis, new approaches in therapy management may be helpful. Nonetheless, there is still no solid evidence supporting the superiority of adaptive dosing over continuous dosing, and more standardized trials are necessary to draw conclusions. Mathematical oncology may be useful for personalized therapy, defined as an approach to medical treatment that customizes treatments according to the unique traits of each patient, including genetic factors such as the use of RAS inhibitors, which represents a great advance in the treatment of KRAS-driven PDAC. Unfortunately, the quick development of tumor resistance has diminished their therapeutic effectiveness. Therefore, in a recent study, a triple combination therapy was proposed to induce tumor regression and avoid resistance (Liaki et al., 2025). In this context, mathematical oncology may help in the design of novel combination therapy based on patients' tumor characteristics and mathematical models.

6. Conclusions

Integrating evolutionary and ecological perspectives into the study of PDAC tumorigenesis and progression offers an additional interdisciplinary perspective on a tumor for which, despite the great efforts made in recent years, advances in knowledge and management have been very limited. Evolutionary processes are fundamental to all stages of malignancy, ranging from the initial clonal outgrowth to the development of metastasis. To gain deeper insight into PDAC, it's essential to take into consideration, analyze, and quantify the cell population dynamics and evolutionary characteristics of neoplasms. Furthermore, the interactions between tumor cells and the microenvironment are not merely a series of random events but are governed by evolutionary principles, selective pressures, and dynamic interactions that mirror ecological processes. In this context, the heterogeneity of the TME could be a critical factor, underscoring the complexity of cancer as a disease and highlighting potential areas for therapeutic targeting that would focus not only on targeting tumor cells but also on altering the ecological dynamics within the TME.

6.1. Critical view section

Taken together, by recognizing cancer as an evolving system of interdependent "cell individuals" and "clone populations and species", we can obtain new insights into how tumors develop, grow, metastasize, and evade therapeutic interventions from ecological theories, as niche theory, decoding ecological patterns of biological diversity organization and maintenance into their underlying energetic, metabolic and behavioral mechanisms, affecting the relative performances of interacting phenotypes of same or different species (Basset and Rossi, 1987; Rossi, 1985; Roughgarden, 1972). Gaining a mechanistic and quantitative understanding of ecological factors controlling phenotypic and species performance under variable conditions and related short-term evolutionary dynamics can significantly enhance strategies for early detection, cancer prevention, diagnosis, and treatment, as well as the detection of PDAC progression-related biomarkers. However, translating this ecological model into standard clinical practice faces severe computational and practical hurdles. First, eco-evolutionary models are mathematically complex; parameterizing multi-scale models (from cellular gene networks to macroscopic tumor spread) requires vast amounts of data. Indeed, every patient exhibits distinct eco-evolutionary dynamics, necessitating a continuously updated personalized mathematical model (Zhang et al., 2022). Second, spatial heterogeneity inherently introduces potential risks of tumor sampling bias; a single biopsy rarely captures the full ecological diversity of a PDAC tumor, potentially leading to flawed algorithmic predictions (Grünwald et al., 2021). Finally, implementing evolution-based treatments, such as adaptive therapy, conflicts with established clinical trial endpoints and regulatory frameworks (Ingles Garces et al., 2023; West et al., 2019), which prioritize maximum tumor shrinkage over stable, long-term disease management and the use of maximum tolerated dose (Halbrook et al., 2023). Surmounting these challenges will require an interdisciplinary effort to align mathematical oncology with actual clinical standards and feasibility (West et al., 2023) to incorporate evolutionary biology into cancer research and take advantage of an eco-evolutionary approach for improving our understanding and management of PDAC.

6.2. Search strategy

This article provides a narrative review aimed at incorporating evolutionary principles into the study of PDAC, highlighting the complex interactions between tumor cells and their surrounding environment, and emphasizing the need for a holistic, evolutionary perspective in cancer analysis, treatment development, and management. The literature was collected through targeted searches on PubMed, Web of Science, Scopus, and Google Scholar, covering studies published up until March 2026. Various keywords and combinations of related terms were used: cancer ecology, pancreatic adenocarcinoma, tumor evolution, ecological fitness, niche construction, tumor microenvironment, and eco-evolutionary dynamics. Key recent peer-reviewed articles and foundational classical studies were selected based on their conceptual significance and contribution to the field, with the aim of assessing an integrated perspective. Both theoretical and experimental peer-reviewed articles addressing evolutionary, ecological, genetic, or microenvironmental aspects of PDAC or contributing conceptually to the eco-evolutionary framework applied to cancer were considered eligible and included in this narrative review.

Abbreviations

PDAC, pancreatic ductal adenocarcinoma; SMT, Somatic Mutation Theory; TME, tumor microenvironment; PanIN, pancreatic intraepithelial neoplasia; IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm; CIN, cervical intraepithelial neoplasia; CIN1, cervical intraepithelial neoplasia grade 1; CIN2, cervical intraepithelial neoplasia grade 2; CIN3, cervical intraepithelial neoplasia grade 3; EMT, epithelial-mesenchymal transition; ECM, extracellular matrix; STAT3, Signal transducer and activator of transcription 3; IL-6, Interleukin-6; KRAS, Kirsten rat sarcoma virus (gene); TP53, tumor protein p53 (gene); CDKN2A, Cyclin Dependent Kinase Inhibitor 2 A (gene); SMAD4, SMAD Family Member 4 (gene); CAF, Cancer-associated Fibroblast; EGT, evolutionary game theory; TGF-β, transforming growth factor-beta; HGF, hepatocyte growth factor.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

Aguadé-Gorgorió, G., Anderson, A.R.A., Solé, R., 2024. Modeling tumors as complex ecosystems. iScience 27, 110699. https://doi.org/10.1016/j.isci.2024.110699.

Aktipis, C.A., Nesse, R.M., 2013. Evolutionary foundations for cancer biology. Evol. Appl. 6, 144–159. https://doi.org/10.1111/eva.12034.

Amend, S.R., Pienta, K.J., 2015. Ecology meets cancer biology: the cancer swamp promotes the lethal cancer phenotype. Oncotarget 6, 9669–9678. https://doi.org/10.18632/oncotarget.3430.

Argentiero, A., Andriano, A., Caradonna, I.C., de Martino, G., Desantis, V., 2024. Decoding the intricate landscape of pancreatic cancer: insights into tumor biology, microenvironment, and therapeutic interventions. Cancers 16, 2438. https://doi.org/10.3390/cancers16132438.

Attolini, C.S.-O., Michor, F., 2009. Evolutionary theory of cancer. Ann. New Y Acad. Sci. 1168, 23–51. https://doi.org/10.1111/j.1749-6632.2009.04880.x.

Bärthel, S., Falcomatà, C., Rad, R., Theis, F.J., Saur, D., 2023. Single-cell profiling to explore pancreatic cancer heterogeneity, plasticity and response to therapy. Nat. Cancer 4, 454–467. https://doi.org/10.1038/s43018-023-00526-x.

Barua, S., Solis, L., Parra, E.R., Uraoka, N., Jiang, M., Wang, H., Rodriguez-Canales, J., Wistuba, I., Maitra, A., Sen, S., Rao, A., 2018. A functional spatial analysis platform for discovery of immunological interactions predictive of low-grade to high-grade transition of pancreatic intraductal papillary mucinous neoplasms. Cancer Inf. 17. https://doi.org/10.1177/1176935118782880.

Basset, A., DeAngelis, D.L., Diffendorfer, J.E., 1997. The effect of functional response on stability of a grazer population on a landscape. Ecol. Model. 101, 153–162. https://doi.org/10.1016/S0304-3800(97)01975-3.

Basset, A., Rossi, L., 1987. Relationships between trophic niche breadth and reproductive capabilities in a population of proasellus coxalis dollfus (Crustacea: Isopoda). Funct. Ecol. 1, 13. https://doi.org/10.2307/2389352.

Basu, A.K., 2018. DNA damage, mutagenesis and cancer. Int. J. Mol. Sci. 19, 970. https://doi.org/10.3390/ijms19040970.

Belkhir, S., Thomas, F., Roche, B., 2021. Darwinian approaches for cancer treatment: benefits of mathematical modeling. Cancers 13, 4448. https://doi.org/10.3390/cancers13174448.

Bever, K.M., Sugar, E.A., Bigelow, E., Sharma, R., Laheru, D., Wolfgang, C.L., Jaffee, E. M., Anders, R.A., De Jesus-Acosta, A., Zheng, L., 2015. The prognostic value of stroma in pancreatic cancer in patients receiving adjuvant therapy. HPB 17, 292–298. https://doi.org/10.1111/hpb.12334.

Bozic, I., 2022. Quantification of the selective advantage of driver mutations is dependent on the underlying model and stage of tumor evolution. Cancer Res. 82, 21–24. https://doi.org/10.1158/0008-5472.CAN-21-1064.

Braxton, A.M., Kiemen, A.L., Grahn, M.P., Forjaz, A., Babu, J.M., Zheng, L., Jiang, L., Cheng, H., Song, Q., Reichel, R., Graham, S., Damanakis, A.I., Fischer, C.G., Mou, S., Metz, C., Granger, J., Liu, X.-D., Bachmann, N., Almagro-Pérez, C., Jiang, A.C., Yoo, J., Kim, B., Du, S., Foster, E., Hsu, J.Y., Rivera, P.A., Chu, L.C., Liu, F., Niknafs, N., Fishman, E.K., Yuille, A., Roberts, N.J., Thompson, E.D., Scharpf, R.B., Cornish, T.C., Jiao, Y., Karchin, R., Hruban, R.H., Wu, P.-H., Wirtz, D., Wood, L.D., 2023. Three-dimensional genomic mapping of human pancreatic tissue reveals striking multifocality and genetic heterogeneity in precancerous lesions. https://doi.org/10.1101/2023.01.27.525553.

Bukkuri, A., Pienta, K.J., Hockett, I., Austin, R.H., Hammarlund, E.U., Amend, S.R., Brown, J.S., 2023. Modeling cancer's ecological and evolutionary dynamics. Med. Oncol. 40, 109. https://doi.org/10.1007/s12032-023-01968-0.

Cabrera-Becerril, A., Vargas-De-León, C., Hernández, S., Miramontes, P., Peralta, R., 2017. Modeling the dynamics of chromosomal alteration progression in cervical cancer: a computational model. PLoS One 12, e0180882. https://doi.org/10.1371/journal.pone.0180882.

Campbell, P.J., Yachida, S., Mudie, L.J., Stephens, P.J., Pleasance, E.D., Stebbings, L.A., Morsberger, L.A., Latimer, C., McLaren, S., Lin, M.-L., McBride, D.J., Varela, I., Nik-Zainal, S.A., Leroy, C., Jia, M., Menzies, A., Butler, A.P., Teague, J.W., Griffin, C.A., Burton, J., Swerdlow, H., Quail, M.A., Stratton, M.R., Iacobuzio-Donahue, C., Futreal, P.A., 2010. The patterns and dynamics of genomic instability in metastatic pancreatic cancer. Nature 467, 1109–1113. https://doi.org/10.1038/nature09460.

Cancer Genome Atlas Research Network, 2017. Integrated genomic characterization of pancreatic ductal adenocarcinoma. Cancer Cell 32, 185–203.e13. https://doi.org/10.1016/j.ccell.2017.07.007.

Carpenter, E.S., Elhossiny, A.M., Kadiyala, P., Li, J., McGue, J., Griffith, B.D., Zhang, Y., Edwards, J., Nelson, S., Lima, F., Donahue, K.L., Du, W., Bischoff, A.C., Alomari, D., Watkoske, H.R., Mattea, M., The, S., Espinoza, C.E., Barrett, M., Sonnenday, C.J., Olden, N., Chen, C.-T., Peterson, N., Gunchick, V., Sahai, V., Rao, A., Bednar, F., Shi, J., Frankel, T.L., Pasca di Magliano, M., 2023. Analysis of donor pancreata defines the transcriptomic signature and microenvironment of early neoplastic lesions. Cancer Discov. 13, 1324–1345. https://doi.org/10.1158/2159-8290.CD-23-0013.

Carstens, J.L., Yang, S., Correa De Sampaio, P., Zheng, X., Barua, S., McAndrews, K.M., Rao, A., Burks, J.K., Rhim, A.D., Kalluri, R., 2021. Stabilized epithelial phenotype of cancer cells in primary tumors leads to increased colonization of liver metastasis in pancreatic cancer. Cell Rep. 35, 108990. https://doi.org/10.1016/j.celrep.2021.108990.

Catenacci, D.V.T., Junttila, M.R., Karrison, T., Bahary, N., Horiba, M.N., Nattam, S.R., Marsh, R., Wallace, J., Kozloff, M., Rajdev, L., Cohen, D., Wade, J., Sleckman, B., Lenz, H.-J., Stiff, P., Kumar, P., Xu, P., Henderson, L., Takebe, N., Salgia, R., Wang, X., Stadler, W.M., de Sauvage, F.J., Kindler, H.L., 2015. Randomized phase ib/ii study of gemcitabine plus placebo or vismodegib, a hedgehog pathway inhibitor, in patients with metastatic pancreatic cancer. J. Clin. Oncol. 33, 4284–4292. https://doi.org/10.1200/JCO.2015.62.8719.

Chan-Seng-Yue, M., Kim, J.C., Wilson, G.W., Ng, K., Figueroa, E.F., O'Kane, G.M., Connor, A.A., Denroche, R.E., Grant, R.C., McLeod, J., Wilson, J.M., Jang, G.H., Zhang, A., Dodd, A., Liang, S.-B., Borgida, A., Chadwick, D., Kalimuthu, S., Lungu, I., Bartlett, J.M.S., Krzyzanowski, P.M., Sandhu, V., Tiriac, H., Froeling, F.E.M.,

Karasinska, J.M., Topham, J.T., Renouf, D.J., Schaeffer, D.F., Jones, S.J.M., Marra, M.A., Laskin, J., Chetty, R., Stein, L.D., Zogopoulos, G., Haibe-Kains, B., Campbell, P.J., Tuveson, D.A., Knox, J.J., Fischer, S.E., Gallinger, S., Notta, F., 2020. Transcription phenotypes of pancreatic cancer are driven by genomic events during tumor evolution. Nat. Genet 52, 231–240. https://doi.org/10.1038/s41588-019-0566-9.

Cheng, N.C., Vonderheide, R.H., 2023. Immune vulnerabilities of mutant KRAS in pancreatic cancer. Trends Cancer 9, 928–936. https://doi.org/10.1016/j.trecan.2023.07.004.

Chianese, U., Papulino, C., Saggese, G., Ali, A., Ciotola, M., Lonardo, E., Cortese, M., Favale, G., Di Mauro, A., La Gioia, D., Golino, V., Sommella, E., Campiglia, P., Franco, R., Ciardiello, F., De Vita, F., Carafa, V., Altucci, L., Benedetti, R., 2026. Glycolytic heterogeneity drives metabolic-targeted therapy in pancreatic ductal adenocarcinoma. Signal Transduct. Target Ther. 11, 25. https://doi.org/10.1038/s41392-025-02546-8.

Colwell, R.K., Rangel, T.F., 2009. Hutchinson's duality: the once and future niche. Proc. Natl. Acad. Sci. U. S. A. 106, 19651–19658. https://doi.org/10.1073/pnas.0901650106.

Connor, A.A., Gallinger, S., 2022. Pancreatic cancer evolution and heterogeneity: integrating omics and clinical data. Nat. Rev. Cancer 22, 131–142. https://doi.org/10.1038/s41568-021-00418-1.

Costa-Silva, B., Aiello, N.M., Ocean, A.J., Singh, S., Zhang, H., Thakur, B.K., Becker, A., Hoshino, A., Mark, M.T., Molina, H., Xiang, J., Zhang, T., Theilen, T.-M., García-Santos, G., Williams, C., Ararso, Y., Huang, Y., Rodrigues, G., Shen, T.-L., Labori, K. J., Lothe, I.M.B., Kure, E.H., Hernandez, J., Doussot, A., Ebbesen, S.H., Grandgenett, P.M., Hollingsworth, M.A., Jain, M., Mallya, K., Batra, S.K., Jarnagin, W.R., Schwartz, R.E., Matei, I., Peinado, H., Stanger, B.Z., Bromberg, J., Lyden, D., 2015. Pancreatic cancer exosomes initiate pre-metastatic niche formation in the liver. Nat. Cell Biol. 17, 816–826. https://doi.org/10.1038/ncb3169.

Cui Zhou, D., Jayasinghe, R.G., Chen, S., Herndon, J.M., Iglesia, M.D., Navale, P., Wendl, M.C., Caravan, W., Sato, K., Storrs, E., Mo, C.-K., Liu, J., Southard-Smith, A. N., Wu, Y., Naser Al Deen, N., Baer, J.M., Fulton, R.S., Wyczalkowski, M.A., Liu, R., Fronick, C.C., Fulton, L.A., Shinkle, A., Thammavong, L., Zhu, H., Sun, H., Wang, L.-B., Li, Y., Zuo, C., McMichael, J.F., Davies, S.R., Appelbaum, E.L., Robbins, K.J., Chasnoff, S.E., Yang, X., Reeb, A.N., Oh, C., Serasanambati, M., Lal, P., Varghese, R., Mashl, J.R., Ponce, J., Terekhanova, N.V., Yao, L., Wang, F., Chen, L., Schnaubelt, M., Lu, R.J.-H., Schwarz, J.K., Puram, S.V., Kim, A.H., Song, S.-K., Shoghi, K.I., Lau, K.S., Ju, T., Chen, K., Chatterjee, D., Hawkins, W.G., Zhang, H., Achilefu, S., Chheda, M.G., Oh, S.T., Gillanders, W.E., Chen, F., DeNardo, D.G., Fields, R.C., Ding, L., 2022. Spatially restricted drivers and transitional cell populations cooperate with the microenvironment in untreated and chemo-resistant pancreatic cancer. Nat. Genet 54, 1390–1405. https://doi.org/10.1038/s41588-022-01157-1.

Cunningham, J.J., Gatenby, R.A., Brown, J.S., 2011. Evolutionary dynamics in cancer therapy. Mol. Pharm. 8, 2094–2100. https://doi.org/10.1021/mp2002279.

Dardare, J., Witz, A., Merlin, J.-L., Bochnakian, A., Toussaint, P., Gilson, P., Harlé, A., 2021. Epithelial to mesenchymal transition in patients with pancreatic ductal adenocarcinoma: state-of-the-art and therapeutic opportunities. Pharm. 14, 740. https://doi.org/10.3390/ph14080740.

Dasari, K., Somarelli, J.A., Kumar, S., Townsend, J.P., 2021. The somatic molecular evolution of cancer: Mutation, selection, and epistasis. Prog. Biophys. Mol. Biol. 165, 56–65. https://doi.org/10.1016/j.pbiomolbio.2021.08.003.

de Groot, A.E., Roy, S., Brown, J.S., Pienta, K.J., Amend, S.R., 2017. Revisiting seed and soil: examining the primary tumor and cancer cell foraging in metastasis. Mol. Cancer Res. 15, 361–370. https://doi.org/10.1158/1541-7786.MCR-16-0436.

DeGregori, J., 2018. Adaptive Oncogenesis: A New Understanding of How Cancer Evolves inside Us. Harvard University Press, Cambridge, Massachusetts.

Dentro, S.C., Leshchiner, I., Haase, K., Tarabichi, M., Wintersinger, J., Deshwar, A.G., Yu, K., Rubanova, Y., Macintyre, G., Demeulemeester, J., Vázquez-García, I., Kleinheinz, K., Livitz, D.G., Malikic, S., Donmez, N., Sengupta, S., Anur, P., Jolly, C., Cmero, M., Rosebrock, D., Schumacher, S.E., Fan, Y., Fittall, M., Drews, R.M., Yao, X., Watkins, T.B.K., Lee, J., Schlesner, M., Zhu, H., Adams, D.J., McGranahan, N., Swanton, C., Getz, G., Boutros, P.C., Imielinski, M., Beroukhim, R., Sahinalp, S.C., Ji, Y., Peifer, M., Martincorena, I., Markowetz, F., Mustonen, V., Yuan, K., Gerstung, M., Spellman, P.T., Wang, W., Morris, Q.D., Wedge, D.C., Van Loo, P., PCAWG Evolution and Heterogeneity Working Group and the PCAWG Consortium, 2021. Characterizing genetic intra-tumor heterogeneity across 2,658 human cancer genomes. Cell 184, 2239–2254.e39. https://doi.org/10.1016/j.cell.2021.03.009.

Dhanasekaran, S., Silambarasan, D., Vivek Karthick, P., Sudhakar, K., 2025. Enhancing pancreatic cancer classification through dynamic weighted ensemble: a game theory approach. Comput. Methods Biomech. Biomed. Eng. 28, 145–169. https://doi.org/10.1080/10255842.2023.2281277.

Dobzhansky, T., 1973. Nothing in biology makes sense except in the light of evolution. Am. Biol. Teach. 35, 125–129. https://doi.org/10.2307/4444260.

Dominguez, A.A., Perz, M.T., Xu, Y., Cedillo, L.G., Huang, O.D., McIntyre, C.A., Vudatha, V., Trevino, J.G., Liu, J., Wang, P., 2024. Unveiling the promise: navigating clinical trials 1978–2024 for PDAC. Cancers 16, 3564. https://doi.org/10.3390/cancers16213564.

Du, Y., Zhao, Y., Li, J., Wang, J., You, S., Zhang, Y., Zhang, L., Yang, J., Alinejad-Rokny, H., Cheng, S., Shao, C., Zou, D., Ye, Y., 2025. PLXDC1+ Tumor-associated pancreatic stellate cells promote desmoplastic and immunosuppressive niche in pancreatic ductal adenocarcinoma. Adv. Sci. 12, e2415756. https://doi.org/10.1002/advs.202415756.

Dujon, A.M., Aktipis, A., Alix-Panabières, C., Amend, S.R., Boddy, A.M., Brown, J.S., Capp, J.-P., DeGregori, J., Ewald, P., Gatenby, R., Gerlinger, M., Giraudeau, M., Hamede, R.K., Hansen, E., Kareva, I., Maley, C.C., Marusyk, A., McGranahan, N., Metzger, M.J., Nedelcu, A.M., Noble, R., Nunney, L., Pienta, K.J., Polyak, K., Pujol, P., Read, A.F., Roche, B., Sebens, S., Solary, E., Staňková, K., Swain Ewald, H., Thomas, F., Ujvari, B., 2021. Identifying key questions in the ecology and evolution of cancer. Evol. Appl. 14, 877–892. https://doi.org/10.1111/eva.13190.

Enriquez-Navas, P.M., Kam, Y., Das, T., Hassan, S., Silva, A., Foroutan, P., Ruiz, E., Martinez, G., Minton, S., Gillies, R.J., Gatenby, R.A., 2016. Exploiting evolutionary principles to prolong tumor control in preclinical models of breast cancer. Sci. Transl. Med 8, 327ra24. https://doi.org/10.1126/scitranslmed.aad7842.

Fidler, I.J., 2003. The pathogenesis of cancer metastasis: the "seed and soil" hypothesis revisited. Nat. Rev. Cancer 3, 453–458. https://doi.org/10.1038/nrc1098.

Fortunato, A., Boddy, A., Mallo, D., Aktipis, A., Maley, C.C., Pepper, J.W., 2017. Natural selection in cancer biology: from molecular snowflakes to trait hallmarks. Cold Spring Harb. Perspect. Med 7, a029652. https://doi.org/10.1101/cshperspect.a029652.

Gallaher, J.A., Brown, J.S., Anderson, A.R.A., 2019. The impact of proliferation-migration tradeoffs on phenotypic evolution in cancer. Sci. Rep. 9, 2425. https://doi.org/10.1038/s41598-019-39636-x.

Gao, J.-X., 2008. Cancer stem cells: the lessons from pre-cancerous stem cells. J. Cell Mol. Med. 12, 67–96. https://doi.org/10.1111/j.1582-4934.2007.00170.x.

Gatenby, R.A., Brown, J.S., 2020. The evolution and ecology of resistance in cancer therapy. Cold Spring Harb. Perspect. Med 10, a040972. https://doi.org/10.1101/cshperspect.a040972.

Gatenby, R.A., Silva, A.S., Gillies, R.J., Frieden, B.R., 2009. Adaptive therapy. Cancer Res 69, 4894–4903. https://doi.org/10.1158/0008-5472.CAN-08-3658.

Gillies, R.J., Brown, J.S., Anderson, A.R.A., Gatenby, R.A., 2018. Eco-evolutionary causes and consequences of temporal changes in intratumoural blood flow. Nat. Rev. Cancer 18, 576–585. https://doi.org/10.1038/s41568-018-0030-7.

Gillies, R.J., Verduzco, D., Gatenby, R.A., 2012. Evolutionary dynamics of carcinogenesis and why targeted therapy does not work. Nat. Rev. Cancer 12, 487–493. https://doi.org/10.1038/nrc3298.

Girolimetti, G., Pelisenco, I.A., Eusebi, L.H., Ricci, C., Cavina, B., Kurelac, I., Verri, T., Calcagnile, M., Alifano, P., Salvi, A., Bucci, C., Guerra, F., 2024. Dysregulation of a subset of circulating and vesicle-associated mirna in pancreatic cancer. Noncoding RNA 10, 29. https://doi.org/10.3390/ncrna10030029.

Gonzalez-Cárdenas, M., Treviño, V., 2024. The impact of mutational hotspots on cancer survival. Cancers 16, 1072. https://doi.org/10.3390/cancers16051072.

Gorunova, L., Höglund, M., Andrén-Sandberg, A., Dawiskiba, S., Jin, Y., Mitelman, F., Johansson, B., 1998. Cytogenetic analysis of pancreatic carcinomas: intratumor heterogeneity and nonrandom pattern of chromosome aberrations. Genes Chromosomes Cancer 23, 81–99. https://doi.org/10.1002/(sici)1098-2264(199810)23:2/253C81::aid-gcc1/253E3.0.co;2-0.

Gottesman, M.M., Lavi, O., Hall, M.D., Gillet, J.-P., 2016. Toward a better understanding of the complexity of cancer drug resistance. Annu Rev. Pharm. Toxicol. 56, 85–102. https://doi.org/10.1146/annurev-pharmtox-010715-103111.

Greaves, M., 2013. Cancer stem cells as "units of selection.". Evol. Appl. 6, 102–108. https://doi.org/10.1111/eva.12017.

Group Young Researchers in Inflammatory Carcinogenesis, Wandmacher, A.M., Mehdorn, A.-S., Sebens, S., 2021. The heterogeneity of the tumor microenvironment as essential determinant of development, progression and therapy response of pancreatic cancer. Cancers 13, 4932. https://doi.org/10.3390/cancers13194932.

Grünwald, B.T., Devisme, A., Andrieux, G., Vyas, F., Aliar, K., McCloskey, C.W., Macklin, A., Jang, G.H., Denroche, R., Romero, J.M., Bavi, P., Bronsert, P., Notta, F., O'Kane, G., Wilson, J., Knox, J., Tamblyn, L., Udaskin, M., Radulovich, N., Fischer, S. E., Boerries, M., Gallinger, S., Kislinger, T., Khokha, R., 2021. Spatially confined sub-tumor microenvironments in pancreatic cancer. Cell 184, 5577–5592.e18. https://doi.org/10.1016/j.cell.2021.09.022.

Guo, J.A., Gong, D., Evans, K., Takahashi, K., Jambhale, A.D., Shiau, C., Yu, P., Wang, S., Wu, W.W., Chugh, S., Kapner, K.S., Dilly, J., Zhao, D., Chen, P., Smith, E.L., Mancias, J.D., Vazquez, F., Singh, H., Hwang, W.L., Aguirre, A.J., 2025. Integrative genomic identification of therapeutic targets for pancreatic cancer. Cell Rep. 44, 116191. https://doi.org/10.1016/j.celrep.2025.116191.

Halbrook, C.J., Lyssiotis, C.A., Pasca di Magliano, M., Maitra, A., 2023. Pancreatic cancer: Advances and challenges. Cell 186, 1729–1754. https://doi.org/10.1016/j.cell.2023.02.014.

Hamede, R., Madsen, T., McCallum, H., Storfer, A., Hohenlohe, P.A., Siddle, H., Kaufman, J., Giraudeau, M., Jones, M., Thomas, F., Ujvari, B., 2021. Darwin, the devil, and the management of transmissible cancers. Conserv Biol. 35, 748–751. https://doi.org/10.1111/cobi.13644.

Hanahan, D., 2022. Hallmarks of cancer: new dimensions. Cancer Discov. 12, 31–46. https://doi.org/10.1158/2159-8290.CD-21-1059.

Hanahan, D., Weinberg, R.A., 2011. Hallmarks of cancer: the next generation. Cell 144, 646–674. https://doi.org/10.1016/j.cell.2011.02.013.

Hanahan, D., Weinberg, R.A., 2000. The hallmarks of cancer. Cell 100, 57–70. https://doi.org/10.1016/S0092-8674(00)81683-9.

Hausser, J., Alon, U., 2020. Tumour heterogeneity and the evolutionary trade-offs of cancer. Nat. Rev. Cancer 20, 247–257. https://doi.org/10.1038/s41568-020-0241-6.

Hesami, Z., Olfatifar, M., Sadeghi, A., Zali, M.R., Mohammadi-Yeganeh, S., Habibi, M.A., Ghadir, M.R., Houri, H., 2024. Global trend in pancreatic cancer prevalence rates through 2040: an illness-death modeling study. Cancer Med. 13, e70318. https://doi.org/10.1002/cam4.70318.

Hingorani, S.R., Zheng, L., Bullock, A.J., Seery, T.E., Harris, W.P., Sigal, D.S., Braiteh, F., Ritch, P.S., Zalupski, M.M., Bahary, N., Oberstein, P.E., Wang-Gillam, A., Wu, W., Chondros, D., Jiang, P., Khelifa, S., Pu, J., Aldrich, C., Hendifar, A.E., 2018. HALO 202: Randomized phase ii study of pegph20 plus nab-paclitaxel/gemcitabine versus

nab-paclitaxel/gemcitabine in patients with untreated, metastatic pancreatic ductal adenocarcinoma. J. Clin. Oncol. 36, 359–366. https://doi.org/10.1200/JCO.2017.74.9564.
Ho, W.J., Jaffee, E.M., Zheng, L., 2020. The tumour microenvironment in pancreatic cancer — clinical challenges and opportunities. Nat. Rev. Clin. Oncol. 17, 527–540. https://doi.org/10.1038/s41571-020-0363-5.
Hutchinson, G.E., 1957. Concluding remarks. Cold Spring Harb. Symp. Quant. Biol. 22, 415–427. https://doi.org/10.1101/SQB.1957.022.01.039.
Ingles Garces, A.H., Porta, N., Graham, T.A., Banerji, U., 2023. Clinical trial designs for evaluating and exploiting cancer evolution. Cancer Treat. Rev. 118, 102583. https://doi.org/10.1016/j.ctrv.2023.102583.
Iovanna, J., Fraunhoffer, N., Urrutia, R., Dusetti, N., 2025. Understanding the heterogeneity of pancreatic ductal adenocarcinoma. Transl. Oncol. 60, 102479. https://doi.org/10.1016/j.tranon.2025.102479.
Jarrett, A.M., Faghihi, D., Ii, D.A.H., Lima, E.A.B.F., Virostko, J., Biros, G., Patt, D., Yankeelov, T.E., 2020. Optimal control theory for personalized therapeutic regimens in oncology: background, history, challenges, and opportunities. J. Clin. Med. 9, 1314. https://doi.org/10.3390/jcm9051314.
Kanda, M., Matthaei, H., Wu, J., Hong, S.-M., Yu, J., Borges, M., Hruban, R.H., Maitra, A., Kinzler, K., Vogelstein, B., Goggins, M., 2012. Presence of somatic mutations in most early-stage pancreatic intraepithelial neoplasia. Gastroenterology 142, 730–733.e9. https://doi.org/10.1053/j.gastro.2011.12.042.
Kaoutari, A.E., Fraunhoffer, N.A., Hoare, O., Teyssedou, C., Soubeyran, P., Gayet, O., Roques, J., Lomberk, G., Urrutia, R., Dusetti, N., Iovanna, J., 2021. Metabolomic profiling of pancreatic adenocarcinoma reveals key features driving clinical outcome and drug resistance. EBioMedicine 66, 103332. https://doi.org/10.1016/j.ebiom.2021.103332.
Kareva, I., 2015. Cancer ecology: niche construction, keystone species, ecological succession, and ergodic theory. Biol. Theory 10, 283–288. https://doi.org/10.1007/s13752-015-0226-y.
Khalaf, K., Hana, D., Chou, J.T.-T., Singh, C., Mackiewicz, A., Kaczmarek, M., 2021. Aspects of the TUmor Microenvironment Involved in Immune Resistance and Drug Resistance. Front Immunol. 12, 656364. https://doi.org/10.3389/fimmu.2021.656364.
Kuboki, Y., Fischer, C.G., Guthrie, V.B., Huang, W., Yu, J., Chianchiano, P., Hosoda, W., Zhang, H., Zheng, L., Shao, X., Thompson, E.D., Waters, K., Poling, J., He, J., Weiss, M.J., Wolfgang, C.L., Goggins, M.G., Hruban, R.H., Roberts, N.J., Karchin, R., Wood, L.D., 2019. Single-cell sequencing defines genetic heterogeneity in pancreatic cancer precursor lesions. J. Pathol. 247, 347–356. https://doi.org/10.1002/path.5194.
Kung, H.-C., Zheng, K.W., Zimmerman, J.W., Zheng, L., 2025. The tumour microenvironment in pancreatic cancer - new clinical challenges, but more opportunities. Nat. Rev. Clin. Oncol. 22, 969–995. https://doi.org/10.1038/s41571-025-01077-z.
Lai, Y., Zhang, S., 2025. Environmental drivers of malignant clonal selection in precancerous lesion evolution. Cell Prolif. 58, e70011. https://doi.org/10.1111/cpr.70011.
Laranga, R., Duchi, S., Ibrahim, T., Guerrieri, A.N., Donati, D.M., Lucarelli, E., 2020. Trends in bone metastasis modeling. Cancers 12, 2315. https://doi.org/10.3390/cancers12082315.
Lee, J.-H., Kim, Y., Choi, J.-W., Kim, Y.-S., 2016. KRAS, GNAS, and RNF43 mutations in intraductal papillary mucinous neoplasm of the pancreas: a meta-analysis. Springerplus 5, 1172. https://doi.org/10.1186/s40064-016-2847-4.
Lee, J.W., Stone, M.L., Porrett, P.M., Thomas, S.K., Komar, C.A., Li, J.H., Delman, D., Graham, K., Gladney, W.L., Hua, X., Black, T.A., Chien, A.L., Majmundar, K.S., Thompson, J.C., Yee, S.S., O'Hara, M.H., Aggarwal, C., Xin, D., Shaked, A., Gao, M., Liu, D., Borad, M.J., Ramanathan, R.K., Carpenter, E.L., Ji, A., de Beer, M.C., de Beer, F.C., Webb, N.R., Beatty, G.L., 2019. Hepatocytes direct the formation of a pro-metastatic niche in the liver. Nature 567, 249–252. https://doi.org/10.1038/s41586-019-1004-y.
Li, J., Wei, T., Ma, K., Zhang, J., Lu, J., Zhao, J., Huang, J., Zeng, T., Xie, Y., Liang, Y., Li, X., Zhang, Q., Liang, T., 2024. Single-cell RNA sequencing highlights epithelial and microenvironmental heterogeneity in malignant progression of pancreatic ductal adenocarcinoma. Cancer Lett. 584, 216607. https://doi.org/10.1016/j.canlet.2024.216607.
Li, O., Li, L., Sheng, Y., Ke, K., Wu, J., Mou, Y., Liu, M., Jin, W., 2023. Biological characteristics of pancreatic ductal adenocarcinoma: initiation to malignancy, intracellular to extracellular. Cancer Lett. 574, 216391. https://doi.org/10.1016/j.canlet.2023.216391.
Li, X., Hou, W., Xiao, C., Yang, H., Zhao, C., Cao, D., 2024. Panoramic tumor microenvironment in pancreatic ductal adenocarcinoma. Cell Oncol 47, 1561–1578. https://doi.org/10.1007/s13402-024-00970-6.
Liaki, V., Barrambana, S., Kostopoulou, M., Lechuga, C.G., Zamorano-Dominguez, E., Acosta, D., Morales-Cacho, L., Álvarez, R., Sun, P., Rosas-Perez, B., Barrero, R., Jiménez-Parrado, S., López-García, A., San Roman, M., López-Gil, J.C., Drosten, M., Sainz, B., Musteanu, M., Caleiras, E., Dusetti, N., Poli, V., Sánchez-Bueno, F., Guerra, C., Barbacid, M., 2025. A targeted combination therapy achieves effective pancreatic cancer regression and prevents tumor resistance. Proc. Natl. Acad. Sci. USA 122, e2523039122. https://doi.org/10.1073/pnas.2523039122.
Lu, M., Yanco, S.W., Carlson, B.S., Winner, K., Cohen, J.M., Ellis-Soto, D., Sharma, S., Rogers, W., Jetz, W., 2025. A theoretical framework for scaling ecological niches from individuals to species. Proc. Natl. Acad. Sci. U. S. A. 122, e2425582122. https://doi.org/10.1073/pnas.2425582122.
Luo, W., 2023. Nasopharyngeal carcinoma ecology theory: cancer as multidimensional spatiotemporal "unity of ecology and evolution" pathological ecosystem. Theranostics 13, 1607–1631. https://doi.org/10.7150/thno.82690.
Luu, T., 2021. Epithelial-mesenchymal transition and its regulation mechanisms in pancreatic cancer. Front Oncol. 11, 646399. https://doi.org/10.3389/fonc.2021.646399.
MacArthur, R., Levins, R., 1967. The limiting similarity, convergence, and divergence of coexisting species. Am. Nat. 101, 377–385. https://doi.org/10.1086/282505.
MacArthur, R.H., Pianka, E.R., 1966. On optimal use of a patchy environment. Am. Nat. 100, 603–609. https://doi.org/10.1086/282454.
Makohon-Moore, A., Iacobuzio-Donahue, C.A., 2016. Pancreatic cancer biology and genetics from an evolutionary perspective. Nat. Rev. Cancer 16, 553–565. https://doi.org/10.1038/nrc.2016.66.
Neinavaie, F., Ibrahim-Hashim, A., Kramer, A.M., Brown, J.S., Richards, C.L., 2021. The genomic processes of biological invasions: from invasive species to cancer metastases and back again. Front. Ecol. Evol. 9. https://doi.org/10.3389/fevo.2021.681100.
Neoptolemos, J.P., Kleeff, J., Michl, P., Costello, E., Greenhalf, W., Palmer, D.H., 2018. Therapeutic developments in pancreatic cancer: current and future perspectives. Nat. Rev. Gastroenterol. Hepatol. 15, 333–348. https://doi.org/10.1038/s41575-018-0005-x.
Nesta, A.V., Tafur, D., Beck, C.R., 2021. Hotspots of human mutation. Trends Genet 37, 717–729. https://doi.org/10.1016/j.tig.2020.10.003.
Noorbakhsh, J., Zhao, Z.-M., Russell, J.C., Chuang, J.H., 2020. Treating cancer as an invasive species. Mol. Cancer Res. 18, 20–26. https://doi.org/10.1158/1541-7786.MCR-19-0262.
Odling-Smee, F.J., Laland, K.N., Feldman, M.W., 1996. Niche construction. Am. Nat. 147, 641–648. https://doi.org/10.1086/285870.
Omori, Y., Furukawa, T., Scarpa, A., Luchini, C., 2023. Co-occurring IPMN and pancreatic cancer: the same or different? An overview from histology to molecular pathology. J. Clin. Pathol. 76, 734–739. https://doi.org/10.1136/jcp-2023-209012.
Oronsky, B., Cabrales, P., Alizadeh, B., Caroen, S., Stirn, M., Williams, J., Reid, T.R., 2023. TGF-β: the apex predator of immune checkpoints. Future Oncol. 19, 2013–2015. https://doi.org/10.2217/fon-2023-0491.
Paget, S., 1889. The distribution of secondary growths in cancer of the breast. Lancet 133, 571–573. https://doi.org/10.1016/S0140-6736(00)49915-0.
Pedro, B.A., Wood, L.D., 2025. Early neoplastic lesions of the pancreas: initiation, progression, and opportunities for precancer interception. J. Clin. Investig. 135, e191937. https://doi.org/10.1172/JCI191937.
Pienta, K.J., Hammarlund, E.U., Axelrod, R., Amend, S.R., Brown, J.S., 2020. Convergent evolution, evolving evolvability, and the origins of lethal cancer. Mol. Cancer Res. 18, 801–810. https://doi.org/10.1158/1541-7786.MCR-19-1158.
Pourshams, A., Sepanlou, S.G., Ikuta, K.S., Bisignano, C., Safiri, S., Roshandel, G., Sharif, M., Khatibian, M., Fitzmaurice, C., Nixon, M.R., Abbasi, N., Afarideh, M., Ahmadian, E., Akinyemiju, T., Alahdab, F., Alam, T., Alipour, V., Allen, C.A., Anber, N.H., Ansari-Moghaddam, A., Arabloo, J., Badawi, A., Bagherzadeh, M., Belayneh, Y.M., Biadgo, B., Bijani, A., Biondi, A., Bjørge, T., Borzì, A.M., Bosetti, C., Briko, A.N., Briko, N.I., Carreras, G., Carvalho, F., Choi, J.-Y.J., Chu, D.-T., Dang, A.K., Daryani, A., Davitoiu, D.V., Demoz, G.T., Desai, R., Dey, S., Do, H.T., Do, H.P., Eftekhari, A., Esteghamati, A., Farzadfar, F., Fernandes, E., Filip, I., Fischer, F., Foroutan, M., Gad, M.M., Gallus, S., Geta, B., Gorini, G., Hafezi-Nejad, N., Harvey, J.D., Hasankhani, M., Hasanzadeh, A., Hassanipour, S., Hay, S.I., Hidru, H.D., Hoang, C.L., Hostiuc, S., Househ, M., Ilesanmi, O.S., Ilic, M.D., Irvani, S.S.N., Jafari Balalami, N., James, S.L., Joukar, F., Kasaeian, A., Kassa, T.D., Kengne, A.P., Khalilov, R., Khan, E.A., Khater, A., Khosravi Shadmani, F., Kocarnik, J.M., Komaki, H., Koyanagi, A., Kumar, V., La Vecchia, C., Lopukhov, P.D., Manafi, F., Manafi, N., Manda, A.-L., Mansour-Ghanaei, F., Mehta, D., Mehta, V., Meier, T., Meles, H.G., Mengistu, G., Miazgowski, T., Mohamadnejad, M., Mohammadian-Hafshejani, A., Mohammadoo-Khorasani, M., Mohammed, S., Mohebi, F., Mokdad, A.H., Monasta, L., Moossavi, M., Moradzadeh, R., Naik, G., Negoi, I., Nguyen, C.T., Nguyen, L.H., Nguyen, T.H., Olagunju, A.T., Olagunju, T.O., Pennini, A., Rabiee, M., Rabiee, N., Radfar, A., Rahimi, M., Rath, G.K., Rawaf, D.L., Rawaf, S., Reiner, R.C., Rezaei, N., Rezapour, A., Saad, A.M., Saadatagah, S., Sahebkar, A., Salimzadeh, H., Samy, A.M., Sanabria, J., Sarveazad, A., Sawhney, M., Sekerija, M., Shabalkin, P., Shaikh, M.A., Sharma, R., Sheikhbahaei, S., Shirkoohi, R., Siddappa Malleshappa, S.K., Sisay, M., Soreide, K., Soshnikov, S., Sotoudehmanesh, R., Starodubov, V.I., Subart, M.L., Tabarés-Seisdedos, R., Tadesse, D.B.B., Traini, E., Tran, B.X., Tran, K.B., Ullah, I., Vacante, M., Vahedian-Azimi, A., Varavikova, E., Westerman, R., Wondafrash, D.D.Z., Xu, R., Yonemoto, N., Zadnik, V., Zhang, Z.-J., Malekzadeh, R., Naghavi, M., 2019. The global, regional, and national burden of pancreatic cancer and its attributable risk factors in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Gastroenterol. Hepatol. 4, 934–947. https://doi.org/10.1016/S2468-1253(19)30347-4.
Qi, H., Lv, G., Zhang, S., Xue, R., Liu, M., 2026. Unraveling pancreatic ductal adenocarcinoma at single-cell resolution with spatial insights: from mechanisms to clinical translation. Cancer Lett. 645, 218391. https://doi.org/10.1016/j.canlet.2026.218391.
Qian, J.J., Akçay, E., 2018. Competition and niche construction in a model of cancer metastasis. PLoS One 13, e0198163. https://doi.org/10.1371/journal.pone.0198163.
Qian, Y., Gong, Y., Fan, Z., Luo, G., Huang, Q., Deng, S., Cheng, H., Jin, K., Ni, Q., Yu, X., Liu, C., 2020. Molecular alterations and targeted therapy in pancreatic ductal adenocarcinoma. J. Hematol. Oncol. 13, 130. https://doi.org/10.1186/s13045-020-00958-3.
Raghavan, S., Winter, P.S., Navia, A.W., Williams, H.L., DenAdel, A., Lowder, K.E., Galvez-Reyes, J., Kalekar, R.L., Mulugeta, N., Kapner, K.S., Raghavan, M.S., Borah, A.A., Liu, N., Väyrynen, S.A., Costa, A.D., Ng, R.W.S., Wang, J., Hill, E.K., Ragon, D.Y., Brais, L.K., Jaeger, A.M., Spurr, L.F., Li, Y.Y., Cherniack, A.D., Booker, M.A., Cohen, E.F., Tolstorukov, M.Y., Wakiro, I., Rotem, A., Johnson, B.E.,

McFarland, J.M., Sicinska, E.T., Jacks, T.E., Sullivan, R.J., Shapiro, G.I., Clancy, T.E., Perez, K., Rubinson, D.A., Ng, K., Cleary, J.M., Crawford, L., Manalis, S.R., Nowak, J. A., Wolpin, B.M., Hahn, W.C., Aguirre, A.J., Shalek, A.K., 2021. Microenvironment drives cell state, plasticity, and drug response in pancreatic cancer. Cell 184, 6119–6137.e26. https://doi.org/10.1016/j.cell.2021.11.017.

Rahib, L., Smith, B.D., Aizenberg, R., Rosenzweig, A.B., Fleshman, J.M., Matrisian, L.M., 2014. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res. 74, 2913–2921. https://doi.org/10.1158/0008-5472.CAN-14-0155.

Raja Arul, G.L., Toruner, M.D., Gatenby, R.A., Carr, R.M., 2022. Ecoevolutionary biology of pancreatic ductal adenocarcinoma. Pancreatology 22, 730–740. https://doi.org/10.1016/j.pan.2022.06.005.

Rampias, T., 2020. Exploring the eco-evolutionary dynamics of tumor subclones. Cancers 12, 3436. https://doi.org/10.3390/cancers12113436.

Rana, S., Malinowska, K., Zöller, M., 2013. Exosomal tumor microRNA modulates premetastatic organ cells. Neoplasia 15, 281–295. https://doi.org/10.1593/neo.122010.

Roe, J.-S., Hwang, C.-I., Somerville, T.D.D., Milazzo, J.P., Lee, E.J., Da Silva, B., Maiorino, L., Tiriac, H., Young, C.M., Miyabayashi, K., Filippini, D., Creighton, B., Burkhart, R.A., Buscaglia, J.M., Kim, E.J., Grem, J.L., Lazenby, A.J., Grunkemeyer, J. A., Hollingsworth, M.A., Grandgenett, P.M., Egeblad, M., Park, Y., Tuveson, D.A., Vakoc, C.R., 2017. Enhancer reprogramming promotes pancreatic cancer metastasis. Cell 170, 875–888.e20. https://doi.org/10.1016/j.cell.2017.07.007.

Rosenzweig, M.L., 1971. Paradox of enrichment: destabilization of exploitation ecosystems in ecological time. Science 171, 385–387. https://doi.org/10.1126/science.171.3969.385.

Rossi, L., 1985. Interactions between invertebrates and microfungi in freshwater ecosystems. Oikos 44, 175. https://doi.org/10.2307/3544059.

Roughgarden, J., 1972. Evolution of niche width. Am. Nat. 106, 683–718. https://doi.org/10.1086/282807.

Rumie Vittar, N.B., Lamberti, M.J., Pansa, M.F., Vera, R.E., Rodriguez, M.E., Cogno, I.S., Milla Sanabria, L.N., Rivarola, V.A., 2013. Ecological photodynamic therapy: new trend to disrupt the intricate networks within tumor ecosystem. Biochim. Biophys. Acta 1835, 86–99. https://doi.org/10.1016/j.bbcan.2012.10.004.

Sebestyén, A., Dankó, T., Sztankovics, D., Moldvai, D., Raffay, R., Cervi, C., Krencz, I., Zsiros, V., Jeney, A., Petővári, G., 2021. The role of metabolic ecosystem in cancer progression - metabolic plasticity and mTOR hyperactivity in tumor tissues. Cancer Metastas Rev. 40, 989–1033. https://doi.org/10.1007/s10555-021-10006-2.

Shapiro, A.M., 1985. Biogeography then and now geographical ecology: patterns in the distribution of species r. h. macarthur the fragmented forest: island biogeography theory and the preservation of biotic diversity larry D. Harris. BioScience 35, 188–189. https://doi.org/10.2307/1309875.

Sherman, M.H., Beatty, G.L., 2023. Tumor microenvironment in pancreatic cancer pathogenesis and therapeutic resistance. Annu Rev. Pathol. 18, 123–148. https://doi.org/10.1146/annurev-pathmechdis-031621-024600.

Siegel, R.L., Kratzer, T.B., Giaquinto, A.N., Sung, H., Jemal, A., 2025. Cancer statistics, 2025. CA Cancer J. Clin. 75, 10–45. https://doi.org/10.3322/caac.21871.

Singhi, A.D., Wood, L.D., 2021. Early detection of pancreatic cancer using DNA-based molecular approaches. Nat. Rev. Gastroenterol. Hepatol. 18, 457–468. https://doi.org/10.1038/s41575-021-00470-0.

Sivapalan, L., Kocher, H.M., Ross-Adams, H., Chelala, C., 2022. The molecular landscape of pancreatic ductal adenocarcinoma. Pancreatology 22, 925–936. https://doi.org/10.1016/j.pan.2022.07.010.

Somarelli, J.A., 2021. The hallmarks of cancer as ecologically driven phenotypes. Front. Ecol. Evol. 9.

Somarelli, J.A., Johnson, N.A., 2024. Cancer Through the Lens of Evolution and Ecology, First ed. CRC Press, Boca Raton. https://doi.org/10.1201/9781003307921.

Søreide, K., Ismail, W., Roalsø, M., Ghotbi, J., Zaharia, C., 2023. Early diagnosis of pancreatic cancer: clinical premonitions, timely precursor detection and increased curative-intent surgery. Cancer Control 30. https://doi.org/10.1177/10732748231154711.

Swiatczak, B., 2021. Struggle within: evolution and ecology of somatic cell populations. Cell Mol. Life Sci. 78, 6797–6806. https://doi.org/10.1007/s00018-021-03931-6.

Tabassum, D.P., Polyak, K., 2015. Tumorigenesis: it takes a village. Nat. Rev. Cancer 15, 473–483. https://doi.org/10.1038/nrc3971.

Thakur, R., Mullen, N.J., Mehla, K., Singh, P.K., 2025. Tumor-stromal metabolic crosstalk in pancreatic cancer. Trends Cell Biol. 35, 1068–1083. https://doi.org/10.1016/j.tcb.2025.04.007.

Tjomsland, V., Niklasson, L., Sandström, P., Borch, K., Druid, H., Bratthäll, C., Messmer, D., Larsson, M., Spångeus, A., 2011. The desmoplastic stroma plays an essential role in the accumulation and modulation of infiltrated immune cells in pancreatic adenocarcinoma. Clin. Dev. Immunol. 2011, 1–12. https://doi.org/10.1155/2011/212810.

Truong, L.-H., Pauklin, S., 2021. Pancreatic cancer microenvironment and cellular composition: current understandings and therapeutic approaches. Cancers 13, 5028. https://doi.org/10.3390/cancers13195028.

Ullman, N.A., Burchard, P.R., Dunne, R.F., Linehan, D.C., 2022. Immunologic strategies in pancreatic cancer: making cold tumors hot. J. Clin. Oncol. 40, 2789–2805. https://doi.org/10.1200/JCO.21.02616.

Vandermeer, J.H., 1972. Niche theory. Annu. Rev. Ecol. Syst. 3, 107–132. https://doi.org/10.1146/annurev.es.03.110172.000543.

Venkatas, J., Singh, M., 2020. Cervical cancer: a meta-analysis, therapy and future of nanomedicine. Ecancermedicalscience 14, 1111. https://doi.org/10.3332/ecancer.2020.1111.

Vishwakarma, M., Piddini, E., 2020. Outcompeting cancer. Nat. Rev. Cancer 20, 187–198. https://doi.org/10.1038/s41568-019-0231-8.

Wang, K., Wang, X., Pan, Q., Zhao, B., 2023. Liquid biopsy techniques and pancreatic cancer: diagnosis, monitoring, and evaluation. Mol. Cancer 22, 167. https://doi.org/10.1186/s12943-023-01870-3.

West, J., Adler, F., Gallaher, J., Strobl, M., Brady-Nicholls, R., Brown, J., Roberson-Tessi, M., Kim, E., Noble, R., Viossat, Y., Basanta, D., Anderson, A.R., 2023. A survey of open questions in adaptive therapy: bridging mathematics and clinical translation. eLife 12, e84263. https://doi.org/10.7554/eLife.84263.

West, J.B., Dinh, M.N., Brown, J.S., Zhang, J., Anderson, A.R., Gatenby, R.A., 2019. Multidrug cancer therapy in metastatic castrate-resistant prostate cancer: an evolution-based strategy. Clin. Cancer Res. 25, 4413–4421. https://doi.org/10.1158/1078-0432.CCR-19-0006.

Whatcott, C.J., Diep, C.H., Jiang, P., Watanabe, A., LoBello, J., Sima, C., Hostetter, G., Shepard, H.M., Von Hoff, D.D., Han, H., 2015. Desmoplasia in primary tumors and metastatic lesions of pancreatic cancer. Clin. Cancer Res. 21, 3561–3568. https://doi.org/10.1158/1078-0432.CCR-14-1051.

Whiting, F.J.H., Househam, J., Baker, A.-M., Sottoriva, A., Graham, T.A., 2024. Phenotypic noise and plasticity in cancer evolution. Trends Cell Biol. 34, 451–464. https://doi.org/10.1016/j.tcb.2023.10.002.

Wu, C.J., 2012. CLL clonal heterogeneity: an ecology of competing subpopulations. Blood 120, 4117–4118. https://doi.org/10.1182/blood-2012-09-452805.

Yachida, S., Jones, S., Bozic, I., Antal, T., Leary, R., Fu, B., Kamiyama, M., Hruban, R.H., Eshleman, J.R., Nowak, M.A., Velculescu, V.E., Kinzler, K.W., Vogelstein, B., Iacobuzio-Donahue, C.A., 2010. Distant metastasis occurs late during the genetic evolution of pancreatic cancer. Nature 467, 1114–1117. https://doi.org/10.1038/nature09515.

Yang, J., Lin, P., Yang, M., Liu, W., Fu, X., Liu, D., Tao, L., Huo, Y., Zhang, J., Hua, R., Zhang, Z., Li, Y., Wang, L., Xue, J., Li, H., Sun, Y., 2021. Integrated genomic and transcriptomic analysis reveals unique characteristics of hepatic metastases and pro-metastatic role of complement C1q in pancreatic ductal adenocarcinoma. Genome Biol. 22, 4. https://doi.org/10.1186/s13059-020-02222-w.

Yang, J., Yu, Xiaoning, Xiao, M., Xu, H., Tan, Z., Lei, Y., Guo, Y., Wang, W., Xu, J., Shi, S., Yu, Xianjun, 2025. Histone lactylation-driven feedback loop modulates cholesterol-linked immunosuppression in pancreatic cancer. Gut 74, 1859–1872. https://doi.org/10.1136/gutjnl-2024-334361.

Yang, X., Qin, C., Zhao, B., Li, Tianhao, Wang, Y., Li, Z., Li, Tianyu, Wang, W., 2022. Long noncoding RNA and circular RNA: two rising stars in regulating epithelial-mesenchymal transition of pancreatic cancer. Front Oncol. 12, 910678. https://doi.org/10.3389/fonc.2022.910678.

Yao, W., Maitra, A., Ying, H., 2020. Recent insights into the biology of pancreatic cancer. EBioMedicine 53, 102655. https://doi.org/10.1016/j.ebiom.2020.102655.

Yousuf, S., Qiu, M., Voith von Voithenberg, L., Hulkkonen, J., Macinkovic, I., Schulz, A. R., Hartmann, D., Mueller, F., Mijatovic, M., Ibberson, D., AlHalabi, K.T., Hetzer, J., Anders, S., Brüne, B., Mei, H.E., Imbusch, C.D., Brors, B., Heikenwälder, M., Gaida, M.M., Büchler, M.W., Weigert, A., Hackert, T., Roth, S., 2023. Spatially resolved multi-omics single-cell analyses inform mechanisms of immune dysfunction in pancreatic cancer. Gastroenterology 165, 891–908.e14. https://doi.org/10.1053/j.gastro.2023.05.036.

Zamboni, G., Hirabayashi, K., Castelli, P., Lennon, A.M., 2013. Precancerous lesions of the pancreas. Best. Pr. Res Clin. Gastroenterol. 27, 299–322. https://doi.org/10.1016/j.bpg.2013.04.001.

Zhang, J., Cunningham, J., Brown, J., Gatenby, R., 2022. Evolution-based mathematical models significantly prolong response to abiraterone in metastatic castrate-resistant prostate cancer and identify strategies to further improve outcomes. Elife 11, e76284. https://doi.org/10.7554/eLife.76284.

Zhang, J., Cunningham, J.J., Brown, J.S., Gatenby, R.A., 2017. Integrating evolutionary dynamics into treatment of metastatic castrate-resistant prostate cancer. Nat. Commun. 8, 1816. https://doi.org/10.1038/s41467-017-01968-5.

Zhang, Y., Wang, W., 2025. Advances in tumor subclone formation and mechanisms of growth and invasion. J. Transl. Med 23, 461. https://doi.org/10.1186/s12967-025-06486-3.

Zobel, M., 1997. The relative of species pools in determining plant species richness: an alternative explanation of species coexistence? Trends Ecol. Evol. 12, 266–269. https://doi.org/10.1016/s0169-5347(97)01096-3.

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