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COMPREHENSIVE REVIEW OF PANCREATIC DUCTAL ADENOCARCINOMA: BIOLOGY, DIAGNOSIS, TREATMENT, AND FUTURE DIRECTIONS

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Abstract: Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal malignancies, with an overall 5-year survival rate of less than 10%. It represents the seventh leading cause of cancer-related mortality worldwide. The major reasons for poor prognosis include late-stage diagnosis, aggressive tumor biology, and resistance to both systemic and local therapies. This review provides an updated and comprehensive overview of PDAC, including epidemiology, molecular pathogenesis, clinical features, diagnostic modalities, therapeutic approaches, challenges, and future perspectives. The aim is to consolidate current knowledge and highlight areas that may improve early detection and treatment outcomes.

1. Introduction

Pancreatic ductal adenocarcinoma accounts for more than 90% of pancreatic malignancies. It is characterized by late detection, rapid progression, and resistance to therapy. Globally, approximately 500,000 new cases are reported annually, with mortality rates closely mirroring incidence. The disease is projected to become the second leading cause of cancer-related death in the next decade. Risk factors include smoking, chronic pancreatitis, obesity, diabetes mellitus, and family history of pancreatic cancer.

2. Epidemiology and Risk Factors

PDAC incidence varies geographically, with the highest rates observed in high-income countries. Lifestyle factors such as tobacco use, alcohol abuse, and dietary patterns play a crucial role. Genetic predispositions, such as germline BRCA1/2 mutations, Lynch syndrome, and Peutz–Jeghers syndrome, also increase susceptibility. Understanding the interplay between environmental and genetic risk factors is essential for risk stratification and targeted screening efforts.

3. Molecular Pathogenesis

The molecular biology of PDAC is dominated by four key driver mutations: KRAS, TP53, CDKN2A, and SMAD4. KRAS mutations occur in over 90% of PDAC cases and drive uncontrolled proliferation through MAPK and PI3K pathways. TP53 mutations lead to impaired DNA repair and apoptosis resistance. SMAD4 loss results in TGF-β pathway disruption, promoting tumor invasion and metastasis. In addition, alterations in DNA damage repair genes (BRCA1, BRCA2, PALB2) define a subgroup sensitive to platinum agents and PARP inhibitors. The tumor microenvironment, particularly dense desmoplastic stroma, impedes drug delivery and supports immune evasion.

4. Clinical Presentation

Most patients present with non-specific symptoms such as abdominal pain, weight loss, fatigue, or new-onset diabetes. Jaundice is common in tumors located at the pancreatic head due to bile duct obstruction. Unfortunately, the vague nature of early symptoms contributes to delayed diagnosis, with most cases detected at advanced or metastatic stages.

5. Diagnostic Modalities

Diagnosis relies on a combination of imaging, biomarkers, and histology. Contrast-enhanced CT remains the gold standard for staging, while MRI and endoscopic ultrasound (EUS) provide complementary detail. Positron emission tomography (PET) may be used in selected cases. Serum CA19-9 is the most widely used biomarker but lacks sensitivity and specificity. Ongoing research focuses on liquid biopsies (ctDNA, exosomes, CTCs) to enable earlier detection and real-time monitoring.

6. Current Therapeutic Strategies

Surgery offers the only curative option but is feasible in only 20–25% of patients at diagnosis. For resectable disease, pancreaticoduodenectomy (Whipple procedure) or distal pancreatectomy is performed, usually followed by adjuvant chemotherapy with FOLFIRINOX or gemcitabine-based regimens. Borderline resectable and locally advanced tumors may benefit from neoadjuvant therapy to improve resectability rates. In metastatic disease, systemic chemotherapy with FOLFIRINOX or gemcitabine/nab-paclitaxel remains the mainstay. Radiation therapy may provide local control but has limited survival impact when used alone.

7. Targeted Therapy and Immunotherapy

Targeted approaches are under development. Patients with DNA repair deficiencies (BRCA1/2, PALB2) show responses to PARP inhibitors. KRAS inhibitors, though promising, are currently limited to rare KRAS G12C mutations. Stromal-modifying agents aim to improve drug delivery but have shown mixed results in clinical trials. Immunotherapy has had limited success due to the immunosuppressive tumor microenvironment. Strategies under investigation include vaccines, immune checkpoint inhibitors in combination with chemotherapy, and adoptive T-cell therapies.

8. Challenges and Limitations

The major challenges in PDAC management are late detection, drug resistance, and poor therapeutic penetration. Tumor heterogeneity complicates personalized treatment. Furthermore, lack of effective screening tools limits early detection in asymptomatic patients.

The unique biology of PDAC requires novel therapeutic paradigms that integrate molecular, immunological, and microenvironmental insights.

9. Future Perspectives

Advances in genomics, proteomics, and liquid biopsy technologies may revolutionize early detection. Precision medicine approaches will increasingly guide therapy selection based on molecular profiling. Nanotechnology-based drug delivery and synthetic lethality approaches hold promise. Multimodal strategies combining surgery, systemic therapy, immunotherapy, and stromal targeting may finally translate into improved survival outcomes for patients with PDAC.

10. Conclusion

Pancreatic ductal adenocarcinoma remains a formidable clinical challenge. Despite incremental advances, survival rates remain poor. However, ongoing research into early detection, personalized therapy, and novel drug development provides cautious optimism. Collaborative translational efforts will be essential to transform scientific progress into clinical benefit.

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