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ORIGINAL

piRNAs and PIWI-like proteins in cancer and their future as biomarkers and therapy targets in pancreatic cancer: a systematic review

piRNAs y proteínas similares a PIWI en el cáncer y su futuro como biomarcadores y dianas terapéuticas en el cáncer de páncreas: revisión sistemática

»Jheremy Sebastián Reyes Barreto [1]
»Laura Tatiana Picón Moncada [1]
»Iris Lorena Sánchez Moreno [1]
»Libia Adriana Gaona Fernández [1]

[1] Cancer and Molecular Medicine Research Group (CAMMO), Bogotá, Colombia.

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Abstract

Introduction: This systematic review explores the roles of PIWI-interacting RNAs (piRNAs) and PIWI-like proteins in pancreatic cancer, assessing their potential as diagnostic and therapeutic biomarkers. Recent studies suggest that piRNAs and PIWI proteins play roles in gene regulation associated with cancer progression, positioning them as promising targets in oncology. **Methods:** The review adhered to PRISMA guidelines, focusing on the potential of piRNAs and PIWI-like proteins as biomarkers for diagnosis, prognosis, or therapeutic prediction in pancreatic cancer. Studies in PubMed, EMBASE, and ScienceDirect were included, focusing on expression data, diagnosis, prognosis, or treatment of pancreatic tumors. Only studies published in English or Spanish from the last five years were considered. Risk of bias was assessed using SYRCLE's tool, a modified CONSORT checklist, and AMSTAR2. **Results:** Five key studies were selected. Findings indicate that piR-162725 enhances diagnostic accuracy for early-stage pancreatic cancer in combination with CA19-9, while piR-017061 inhibits pancreatic cancer cell growth through EFNA5 mRNA degradation.

*** Autor para correspondencia:** Jheremy Reyes. Cancer and Molecular Medicine Research Group.
Correo electrónico: js.reyesb@uniandes.edu.co
Doi: https//doi.org/10.51643/22562915.718

PIWIL1 promotes metastasis via a piRNA-independent pathway, and piR-hsa-30937 in small extracellular vesicles creates an immunosuppressive environment in pancreatic neuroendocrine tumors. **Conclusions:** piRNAs and PIWI-like proteins demonstrate potential as biomarkers and therapeutic targets in pancreatic cancer. Future studies are required to validate these findings in larger cohorts and explore piRNA-based therapies. An in-depth understanding of piRNAs' mechanistic roles could improve early detection and therapeutic outcomes in pancreatic cancer.

Keywords: piRNAs; PIWI-like proteins; pancreatic cancer; biomarkers; therapy targets.

Resumen

Introducción: Esta revisión sistemática examina los roles de los ARN interactuantes con PIWI (piRNAs) y las proteínas similares a PIWI en el cáncer de páncreas, evaluando su potencial como biomarcadores diagnósticos y terapéuticos. Estudios recientes sugieren que estos piRNAs y proteínas PIWI están involucrados en la regulación génica asociada con la progresión del cáncer, lo que los posiciona como objetivos prometedores en oncología. **Métodos:** La revisión se adhirió a las directrices PRISMA, enfocándose en el uso de piRNAs y proteínas PIWI como biomarcadores de diagnóstico, pronóstico o predicción terapéutica en el cáncer de páncreas. Se incluyeron estudios de PubMed, EMBASE y ScienceDirect considerando únicamente publicaciones en inglés o español de los últimos cinco años. Se evaluó el riesgo de sesgo mediante la herramienta SYRCLE, una lista de verificación CONSORT modificada y AMSTAR2. **Resultados:** Se seleccionaron cinco estudios clave. Los hallazgos incluyen que el piR-162725 mejora la precisión diagnóstica para el cáncer de páncreas en etapa temprana en combinación con CA19-9, mientras que el piR-017061 inhibe el crecimiento de células de cáncer pancreático mediante la degradación de ARNm de EFNA5. PIWIL1 promueve la metástasis a través de un mecanismo independiente de piRNA, y piR-hsa-30937 en vesículas extracelulares pequeñas genera un ambiente inmunosupresor en neoplasias neuroendocrinas pancreáticas. **Conclusiones:** Los piRNAs y las proteínas PIWI muestran potencial como biomarcadores y objetivos terapéuticos en el cáncer de páncreas. Futuros estudios deben validar estos hallazgos en cohortes más grandes y explorar terapias basadas en piRNAs. Comprender los roles mecanicistas de los piRNAs podría mejorar la detección temprana y los resultados terapéuticos en el cáncer de páncreas.

Palabras clave: piRNAs; proteínas PIWI; cáncer de páncreas; biomarcadores; objetivos terapéuticos.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive and lethal malignancies worldwide, with a five-year survival rate below 10% for advanced stages.[1,2] This low survival rate is primarily due to the cancer's asymptomatic progression in early stages, which often results in diagnosis only after metastasis has occurred. Although early-stage detection could improve survival outcomes, it remains challenging due to the lack of specific and sensitive biomarkers.[1] Currently, the most commonly used biomarker, carbohydrate antigen 19-9 (CA19-9), has limited sensitivity and specificity, often leading to false positives and delayed detection. This underscores the critical need for novel biomarkers that can enable early diagnosis and provide insights into therapeutic targets for PDAC.[2, 3]

Emerging research highlights small non-coding

RNAs, particularly PIWI-interacting RNAs (piRNAs), as promising biomolecules in cancer biology. piRNAs are a class of small RNAs (24-32 nucleotides) that interact with PIWI proteins to form complexes capable of regulating gene expression, maintaining genomic stability, and influencing cellular processes.[2-4] Unlike other small non-coding RNAs such as microRNAs, piRNAs have shown tissue-specific expression patterns, which positions them as potential biomarkers for various cancers, including PDAC. PIWI-like proteins (PIWIL1, PIWIL2, PIWIL3, and PIWIL4) are members of the Argonaute family and are essential for piRNA function.[4] These proteins, when complexed with piRNAs, play roles in epigenetic regulation, mRNA silencing, and genome stability. Aberrant expression of piRNAs and PIWI proteins has been linked to various cancer types, where they are thought to contribute to oncogenic processes like cell proliferation, invasion, metastasis, and immune evasion.[3-5]

In the context of pancreatic cancer, studies suggest that piRNAs and PIWI-like proteins may have a dual role, acting as tumor suppressors or promoters depending on the molecular context. Specific piRNAs, such as piR-162725, have been identified as potential diagnostic biomarkers, showing elevated sensitivity when combined with CA19-9 in detecting early-stage PDAC.[4,5] Other piRNAs, like piR-017061, appear to have tumor-suppressive functions by promoting the degradation of pro-oncogenic transcripts, highlighting their therapeutic potential.[5] Additionally, certain PIWI proteins, such as PIWIL1, have been implicated in metastasis, acting independently of piRNAs by influencing protein complexes involved in cell cycle regulation. These findings underscore the multifaceted roles of piRNAs and PIWI proteins in pancreatic cancer, suggesting their utility as both diagnostic tools and therapeutic targets.

Given the increasing evidence of piRNAs and PIWI proteins in oncogenesis, this systematic review aims to provide a comprehensive analysis of their roles in PDAC.

Methods

This systematic review was conducted to evaluate the roles of piRNAs and PIWI-like proteins in pancreatic cancer, specifically examining their potential as diagnostic and therapeutic biomarkers. Following the PRISMA[6,7] guidelines, we aimed to assess available evidence on the expression and function of piRNAs and PIWI-like proteins in pancreatic cancer. The detailed methodology is described below.

Eligibility Criteria

To ensure a focused analysis, we established clear eligibility criteria based on study characteristics, language, and relevance to the clinical questions surrounding piRNAs and PIWI proteins in pancreatic cancer. Specifically, the review included:

Inclusion Criteria:

- Observational and experimental studies investigating the relationship between piRNAs and PIWI-like proteins with pancreatic cancer, particularly their role in diagnosis, prognosis, therapeutic prediction, or pathophysiological mechanisms.
- Studies that provided quantitative or qualitative data on piRNA or PIWI protein expression in pancreatic tumor tissues, blood, or other biological fluids.
- Articles published in English or Spanish within the last five years.

Exclusion Criteria:

- Studies that did not directly address the relationship between piRNAs or PIWI proteins

and pancreatic cancer (e.g., studies focusing on other cancers or on piRNAs without specific relevance to pancreatic cancer).

- Review articles, commentaries, letters to the editor, and animal studies without direct clinical relevance.

- Studies published more than five years ago to ensure the inclusion of the most recent evidence.

Information Sources and Search Strategy

The literature search was conducted in June 2024 across several databases, including PubMed, ScienceDirect, EMBASE, and Web of Science, to ensure comprehensive coverage. We used a structured search strategy with Boolean operators to combine terms like "Pancreatic Cancer," "piRNA," and "Therapeutic Targets." Additionally, the search included variations such as "Pancreatic Neoplasms," "Pancreatic ductal carcinoma," "piwi-interacting RNAs," "Therapy," and "Treatment" to capture relevant studies. Google Scholar was also consulted to identify grey literature or additional articles not indexed in the primary databases.

Selection Process

The selection process involved three distinct phases: identification, screening, and inclusion.

- Identification: Using the specified search strategy, all results from the databases were included for initial screening due to the limited number of studies available on this specific topic.

- Screening: We used Rayyan[8], a web-based software for systematic reviews, to screen the articles. The initial screening involved reading the titles and abstracts of all identified studies, with three reviewers classifying each study as "Included," "Maybe," or "Excluded" based on the inclusion and exclusion criteria. Studies marked as "Maybe" were discussed further until a consensus was reached.

- Inclusion: For the final inclusion phase, a full-text review of the selected articles was conducted by the three reviewers to confirm eligibility. Conflicts were resolved through discussion to ensure an unbiased selection process. Ultimately, five articles met the inclusion criteria and were selected for the systematic review.

Data Collection Process and Data Items

Data extraction was performed independently by all review authors to minimize bias and ensure accuracy. Each study's data were entered into a structured Excel 2024 sheet for organization and analysis. The specific data items extracted included:

- General Information: Names of authors, year of publication, and study title.

- Study Design: Type of research design (e.g., observational, experimental), and study objective.

- Methodology: Details on the methods used, including sample source (e.g., tissue, blood, cell lines) and detection techniques.

- Population: Characteristics of the study population, such as cancer type, tumor stage, and any relevant controls.

- Outcomes: Primary findings related to piRNA or PIWI protein expression, their roles in pancreatic cancer diagnosis, prognosis, or therapeutic potential, and any mechanistic insights provided by the study.

Risk of Bias and Quality Assessment

To assess the quality and risk of bias, we employed different tools based on the type of study:

- SYRCLE's[9] Risk of Bias Tool was applied for in vivo studies to assess animal research quality. This tool evaluates biases such as selection, performance, detection, and reporting bias.

- CONSORT[10] Modified Checklist was used for in vitro studies to ensure rigorous reporting, focusing on aspects like experimental design, reproducibility, and statistical analysis.

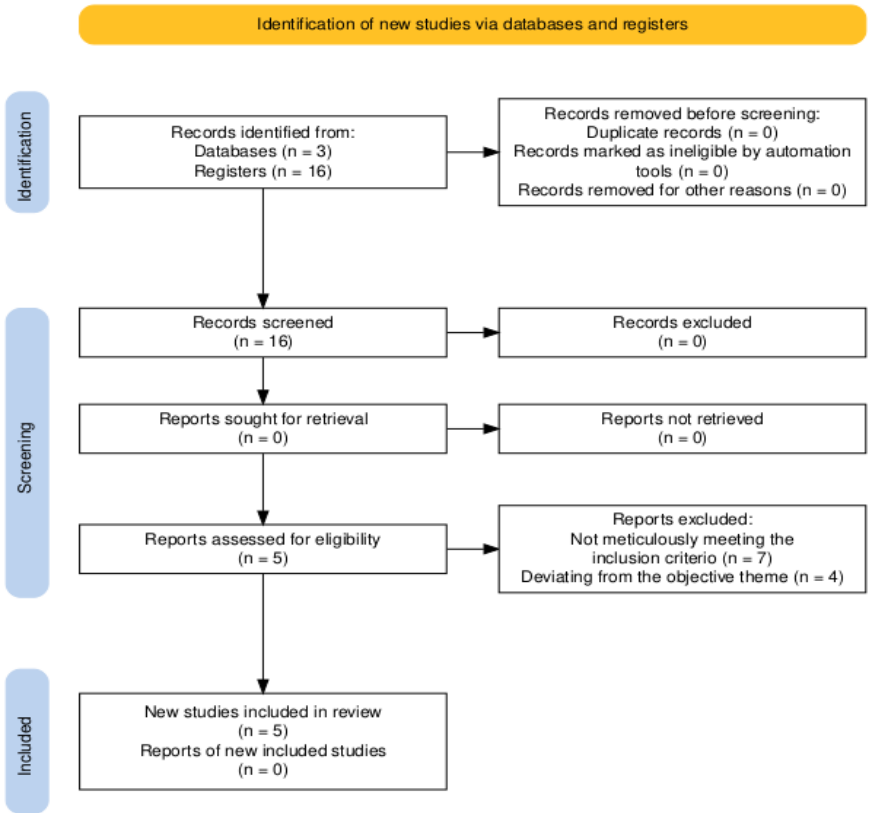
- AMSTAR2[11] was applied to assess the overall quality of this systematic review, evaluating factors like comprehensiveness, transparency in study selection, and consistency in methodology.

Each study received a score based on these tools, and a minimum threshold of 50% was set for inclusion. Studies scoring below this threshold were excluded due to concerns about quality and reliability. Discrepancies in quality assessment were discussed among the authors to reach a consensus.

Results

We conducted a search in 3 databases (PubMed, Embase, and ScienceDirect) for relevant literature, identifying 16 papers. After eliminating duplicates (n = 0), we screened the titles and abstracts (n = 16) and excluded review articles and unrelated papers (n = 11). Ultimately, 5 studies were included in this systematic review (Figure 1).

Figure 1.
PRISMA flow chart[6,7].



This research analyzed 5 articles that highlighted the roles of piRNAs and PIWI-like proteins in cancer and their potential as biomarkers and therapeutic targets in pancreatic cancer (Table 1).

Table 1.

Characteristics of the reviewed studies

Author	Molecule	Year	Summary
Li F et al.	piRNA/PIWIL1	2020	PDAC, PIWIL1 acts as an oncoprotein independently of piRNAs by activating the APC/C complex and promoting metastasis through the protein Pinin.
Xie J et al.	piR-017061	2021	piR-017061 is significantly downregulated in PC. It inhibits tumor growth by degrading EFNA5 mRNA in cooperation with PIWIL1. Loss of piR-017061 promotes PC, suggesting it as a potential therapeutic target.
Li W et al.	piR-16725 piR-168112 piR.162725 piR-366845	2022	Differentially expressed piRNAs associated with PIWIL3/PIWIL4 were identified in PC. piR-162725, combined with CA19-9, shows potential as a non-invasive biomarker for early pancreatic cancer detection.
Wan D et al.	piRNA	2023	piRNAs regulate the tumor microenvironment and are crucial for immunotherapy. The ImmPI tool links piRNAs to immune infiltration and prognosis, providing a resource for future piRNA-based therapies.
Zhong Y et al.	piR-hsa-30937	2024	PNEN, piR-hsa-30937 in sEV activates the AKT pathway by targeting PTEN, promoting CD276+ macrophage expression, which inhibits T-cell immunity. Inhibiting piR-hsa-30937 and CD276 suppresses PNEN progression.

Note: PDAC = Pancreatic ductal adenocarcinoma; PC = Pancreatic Cancer; sEV = Small Extracellular vesicles; PNEN = Pancreatic neurodendocrine neoplasms.

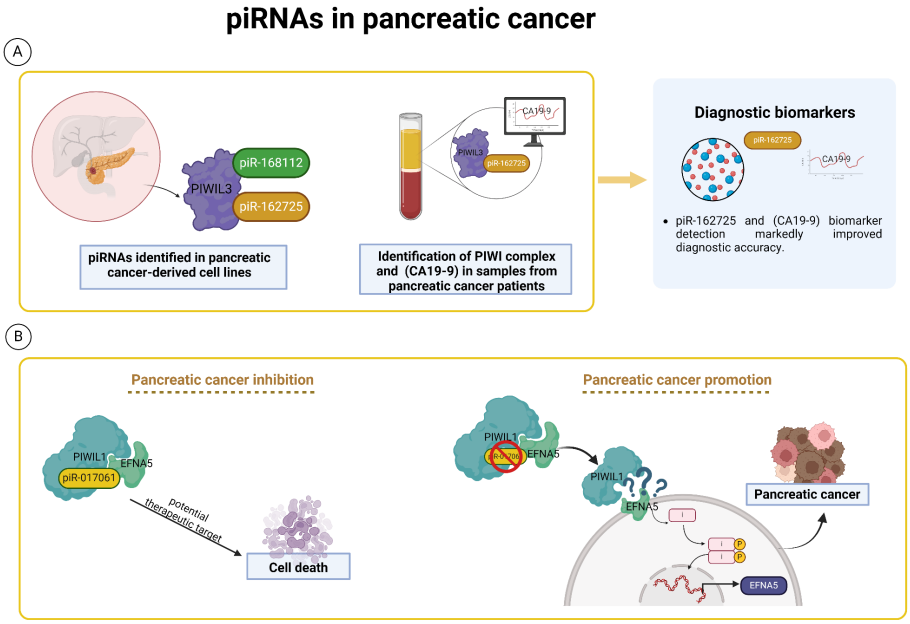
Diagnostic Potential of piRNAs and PIWI Proteins in Pancreatic Cancer

piR-162725 as a Diagnostic Biomarker

Li et al. (2022) identified piR-162725 as a promising diagnostic biomarker for early-stage PDAC. The study demonstrated that piR-162725 levels in plasma samples from pancreatic cancer patients were significantly elevated compared to healthy controls. When combined with the conventional serum biomarker CA19-9, piR-162725 improved the diagnostic accuracy for early detection of PDAC. This suggests that piR-162725 could enhance the specificity and sensitivity of current diagnostic methods, addressing a major challenge in PDAC management (Figure 2A).[3]

Figure 2.

piRNAs in pancreatic cancer. **A.** piRNAs identified in pancreatic cancer-derived cell lines and plasma samples demonstrating that piR-162725 and (CA19-9) biomarker detection markedly improved diagnostic accuracy[3]. **B.** Increased expression or inhibition of piR-017061 influences the regulation or overexpression of EFNA5[12].



Prognostic and Mechanistic Insights of piRNAs

Tumor-Suppressive Role of piR-017061: Xie et al. (2021) explored the functional role of piR-017061 in pancreatic cancer cells and found it significantly downregulated in PDAC tissues and cell lines. Through in vitro and in vivo experiments, the study demonstrated that piR-017061 inhibits pancreatic cancer cell proliferation by targeting and degrading EFNA5 mRNA, a gene associated with tumor growth and migration. This effect is mediated by piR-017061 in cooperation with the PIWIL1 protein, highlighting its potential as a therapeutic target (Figure 2B).[12]

Metastasis-Promoting Role of PIWIL1 Independent of piRNAs: Li et al. (2020) investigated the role of PIWIL1 in PDAC and discovered a novel piRNA-independent mechanism through which PIWIL1 promotes metastasis. The study found that PIWIL1 activates the anaphase-promoting complex/cyclosome (APC/C), a protein complex involved in cell cycle regulation, which in turn influences the protein Pinin, associated with cell adhesion. Unlike its typical function with piRNAs, PIWIL1 independently drives PDAC metastasis through this mechanism. This finding opens new avenues for targeting PIWIL1 to control PDAC spread (Figure 3B).[12-15]

Immune-Related Implications of piRNAs in the Tumor Microenvironment

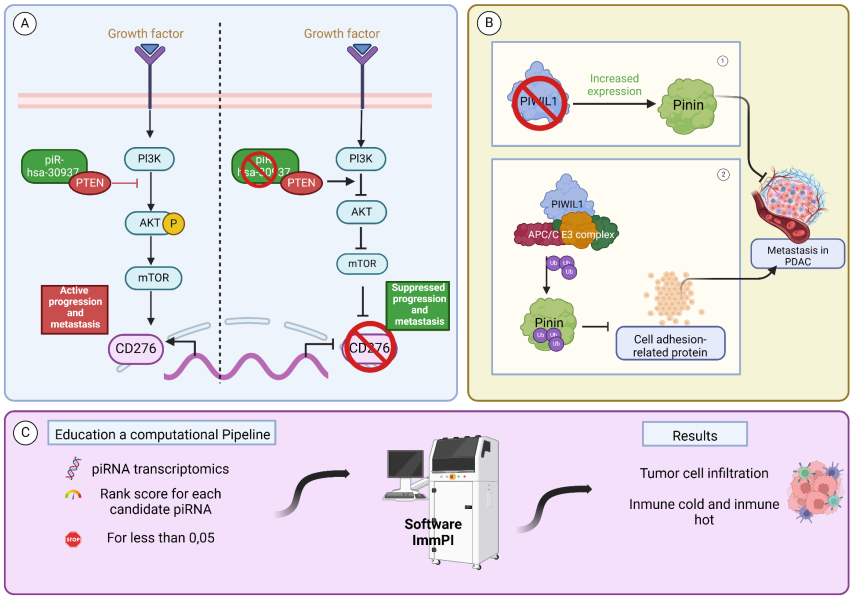
Immunomodulatory Role of piR-has-30937 in Pancreatic Neuroendocrine Neoplasms (PNEN): Zhong et al. (2024) studied the role of piR-hsa-30937 in the tumor microenvironment of pancreatic neuroendocrine neoplasms (PNEN). They found that piR-hsa-30937, present in small extracellular vesicles (sEVs) derived from PNEN,

contributes to an immunosuppressive environment by promoting the expression of CD276, a marker associated with immune evasion. Mechanistically, piR-hsa-30937 targets PTEN, activating the AKT pathway and driving immune suppression. In preclinical models, inhibiting piR-hsa-30937 or CD276 enhanced T-cell activity, reducing tumor progression (Figure 3A).[13]

ImmPI Pipeline and Immune Profiling in Pancreatic Cancer: Wan et al. (2023) developed the ImmPI pipeline, a computational tool to analyze piRNAs in the context of immune cell infiltration and tumor prognosis. This study provided a comprehensive overview of piRNA expression in immune cells within PDAC, showing that certain piRNAs were significantly overexpressed in tumors with high immune cell infiltration. Additionally, the ImmPI score effectively distinguished immune "hot" and "cold" tumor phenotypes, which correlate with different prognoses and immunotherapy responses. The ImmPI pipeline thus serves as a resource for identifying piRNAs with immunomodulatory roles in cancer (Figure 3C).[15]

Figure 3.

PIWI mechanisms of action and diagnostic methods in pancreatic cancer **A.** Inhibition of piR-hsa-30937 and CD276 potential therapeutics to increase T cell production[13] **B.** piRNA-independent pathway[14] **C.** New methods for piRNA detection[15].



Discussion

This systematic review highlights the emerging role of piRNAs and PIWI-like proteins in pancreatic cancer, underscoring their potential as biomarkers and therapeutic targets. The studies reviewed collectively provide evidence that piRNAs, such as piR-162725 and piR-017061, as well as PIWI proteins like PIWIL1, hold promise for applications in early detection, prognosis, and therapeutic intervention in pancreatic cancer. [3, 16-21]

The identification of piR-162725 as a biomarker that enhances the diagnostic accuracy of

CA19-9 for early-stage PDAC is significant. Early detection remains a substantial challenge in PDAC due to its asymptomatic progression, and existing markers like CA19-9 lack the specificity and sensitivity needed to detect PDAC at treatable stages. Combining piR-162725 with CA19-9 could provide a more robust diagnostic tool, particularly for identifying PDAC at an earlier, more manageable stage. This approach of combining traditional markers with novel biomarkers is gaining traction in oncology. In breast and lung cancers, similar strategies have shown improved diagnostic capabilities when combining circulating tumor DNA with protein markers. However, the current findings on piR-162725 are limited to small patient cohorts, indicating a need for larger studies to validate these results across diverse populations and stages of PDAC.[12, 22-26, 28-30].

Mechanistic studies, such as those on piR-017061, offer insights into the pathways through which piRNAs may exert tumor-suppressive effects in PDAC. By targeting EFNA5 mRNA, piR-017061 inhibits tumor growth, providing a novel approach to suppress PDAC progression. This mechanism aligns with findings in other cancer types where piRNAs regulate genes involved in cell proliferation and apoptosis, such as in colorectal and hepatocellular carcinomas. The piR-017061/PIWIL1 interaction represents a potential therapeutic pathway in pancreatic cancer, as restoring piRNA function could inhibit the expression of oncogenes. However, piRNA-based therapies, while promising, face challenges in terms of stability, delivery, and off-target effects. Developing piRNA mimics or small-molecule activators that can selectively enhance piRNA expression or restore its tumor-suppressive activity will be crucial for translating these findings into effective therapies.[14, 31-37].

Similarly, the role of PIWIL1 in metastasis through a piRNA-independent pathway offers a new perspective on the oncogenic roles of PIWI proteins. PIWIL1's activation of the anaphase-promoting complex/cyclosome (APC/C) and the subsequent promotion of metastasis via cell adhesion modulation is a novel finding that could have implications beyond pancreatic cancer. This piRNA-independent mechanism highlights the versatility of PIWI proteins, which have been found to play diverse roles in various cancers, such as gastric and ovarian cancers, where they regulate proliferation and metastasis through different pathways. Targeting PIWIL1 and its downstream signaling components could represent a therapeutic strategy to limit metastasis, although the development of specific inhibitors that can target this pathway without affecting normal cell functions remains a considerable challenge.[5,15, 38-43]

The role of piRNAs in modulating the immune microenvironment, as shown with piR-hsa-30937 in pancreatic neuroendocrine neoplasms (PNEN), introduces a novel dimension for piRNAs as immunomodulators. The study demonstrates that piR-hsa-30937, via small extracellular vesicles (sEVs), promotes an immunosuppressive environment by upregulating CD276 in tumor-associated macrophages, leading to T-cell inhibition. This immunosuppressive mechanism is particularly relevant in the context of PDAC and other immune-resistant tumors, where immune evasion contributes to poor response to immunotherapy. While piRNAs have traditionally been associated with gene silencing and genomic stability, their emerging role in immune regulation could offer new opportunities to enhance the efficacy of immunotherapies. For example, blocking piR-hsa-30937 in combination with immune checkpoint inhibitors may provide a synergistic effect, potentially overcoming immune resistance in PDAC.[13, 44-51]

The ImmPI pipeline further supports the immune-regulatory potential of piRNAs, offering a computational framework to identify piRNAs associated with immune cell infil-

tration and tumor prognosis.[13, 44, 45, 46, 47, 48] This tool could facilitate the discovery of piRNAs that differentiate immune "hot" and "cold" tumor phenotypes, which is critical in tailoring immunotherapy strategies. In other cancers, such as melanoma, the immune profile of the tumor has been a key determinant in selecting patients for immunotherapy. Applying a similar approach to PDAC, using piRNAs as markers of immune activity, could guide patient selection for emerging immunotherapies, particularly in tumors with an otherwise poor immune response.[49-56]

Limitations and future directions

While these findings present promising avenues for piRNA and PIWI protein research in pancreatic cancer, the limitations of the current evidence must be acknowledged. Most studies included in this review were preclinical, with limited clinical validation in human cohorts. The small sample sizes and retrospective nature of some studies may introduce selection and detection biases, potentially limiting the generalizability of the findings. Furthermore, piRNA and PIWI protein functions are complex, with variations in expression and function across different tumor types and biological contexts. These challenges underscore the need for carefully designed clinical studies to validate piRNAs and PIWI proteins as reliable biomarkers and therapeutic targets in pancreatic cancer.

Conclusions

This systematic review underscores the promising role of piRNAs and PIWI-like proteins in advancing the diagnosis, prognosis, and treatment of pancreatic cancer. The evidence suggests that piRNAs, such as piR-162725, could significantly enhance the diagnostic accuracy of traditional biomarkers like CA19-9, paving the way for earlier and more precise detection of PDAC. Similarly, piR-017061 has emerged as a potential tumor suppressor, with therapeutic implications due to its ability to inhibit oncogenic targets like EFNA5. Additionally, PIWIL1's role in promoting metastasis via a piRNA-independent pathway highlights the potential for PIWI proteins as multifaceted targets in cancer treatment, extending beyond their traditional roles in gene regulation.

The ability of piRNAs to influence the immune landscape of pancreatic cancer, as shown by piR-hsa-30937 in creating an immunosuppressive environment, introduces exciting possibilities for enhancing immunotherapy. By integrating piRNA-based biomarkers with immune profiling tools like the ImmPI pipeline, we may better characterize immune-active and immune-resistant tumors, guiding patient selection for immunotherapy and potentially improving response rates.

However, it is essential to acknowledge the preliminary nature of these findings. While piRNAs and PIWI-like proteins hold significant promise, the journey from preclinical discovery to clinical application requires extensive validation. Large-scale clinical trials, diverse patient cohorts, and robust mechanistic studies will be essential to confirm these biomarkers' utility and to refine piRNA-targeted therapies.

In conclusion, piRNAs and PIWI-like proteins represent a frontier in pancreatic cancer research with the potential to reshape diagnostic and therapeutic approaches. With focused research efforts, piRNA-based diagnostics and therapies could transform the landscape of pancreatic cancer care, offering new hope for earlier detection, tailored treatments, and improved survival outcomes in one of the most challenging malignancies.

Future directions

Future research should prioritize several key areas to further elucidate and leverage the potential of piRNAs in pancreatic cancer:

- Clinical Validation: Conducting large-scale, multicenter studies to validate the diagnostic and prognostic value of piR-162725, piR-017061, and PIWIL1 across diverse populations and tumor stages.
- Mechanistic Studies: Further investigation into piRNA-PIWI interactions and their influence on PDAC-specific pathways to identify potential druggable targets.
- Therapeutic Development: Developing piRNA-based therapies, such as piRNA mimics or small-molecule inhibitors, while addressing delivery and specificity challenges.
- Immunotherapy Combinations: Exploring the potential of piRNAs to enhance immunotherapy efficacy by modulating immune cell infiltration and activity within the tumor microenvironment.
- Advanced Biomarker Discovery Platforms: Using computational tools like the ImmPI pipeline to identify novel piRNA biomarkers for PDAC, enabling precision medicine approaches.

Abbreviation list

- piRNAs: PIWI-interacting RNAs
- PDAC: Pancreatic ductal adenocarcinoma
- PIWIL1: PIWI-like protein 1
- APC/C: Anaphase-promoting complex/cyclosome
- EFNA5: Ephrin A5 (a gene targeted by piR-017061)
- CA19-9: Carbohydrate antigen 19-9
- PNEN: Pancreatic neuroendocrine neoplasms
- sEVs: Small extracellular vesicles
- PTEN: Phosphatase and tensin homolog (a gene targeted by piR-hsa-30937)
- AKT pathway: A signaling pathway involved in cell survival and immune modulation
- TAMs: Tumor-associated macrophages
- ImmPI: Immunology piRNA pipeline (a computational tool for piRNA immune profiling)

Availability of data and Materials

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Conflicts of interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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Competing Interest

The authors declare that they have no competing interests.

Author's Contributions

Contributors played a substantial role in conception, design, acquisition, analysis, interpretation, writing, and critical review of the manuscript. All authors approved the final content and accepted responsibility for its accuracy and integrity.

Author's Bio

Jheremy Sebastian Reyes, Medicina, Universidad de Los Andes, Colombia.

Laura Tatiana Picón, Microbióloga.

Iris Lorena Sánchez, Bióloga.

Libia Adriana Gaona, Médica Familiar.

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