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COMMON GENETIC MUTATIONS BETWEEN TYPE 2 DIABETES AND PANCREATIC CANCER: A SYSTEMATIC REVIEW OF THE LITERATURE

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ABSTRACT

INTRODUCTION: Pancreatic cancer (PC) is one of the most aggressive and lethal neoplasms. Among the main risk factors is diabetes mellitus (DM), which significantly increases its probability and development. Studies indicate that patients with DM have a higher risk due to genetic mutations common to both conditions, which affect both the cell cycle and metabolism, promoting oncogenesis and insulin resistance. METHODS: This is a literature review on the genetic mutations shared between PC and DM and current therapeutic approaches, with a focus on gene therapy. The search was performed in the PubMed Advanced database, using the descriptors (DECS/MeSH): "pancreatic cancer", "diabetes mellitus" and "genetic therapy". A total of 15 articles were selected for detailed analysis. RESULTS: The review identified significant genetic mutations associated with both PC and DM. Among the most relevant genes are KRAS, CDKN2A, TP53, CFTR and SPINK1. In terms of therapeutic approaches, gene editing with CRISPR/Cas9, the use of viral vectors for the delivery of therapeutic genes, and the modulation of microRNAs stand out. DISCUSSION: The interrelationship between PC and DM is profound and goes beyond a simple coexistence of conditions. Mutations in genes such as KRAS, TP53, and CDKN2A not only drive oncogenesis but also affect glucose metabolism, contributing to insulin resistance. Gene therapy, especially CRISPR/Cas9 editing, appears as a promising solution, offering a more specific and less invasive alternative compared to conventional treatments, such as chemotherapy and radiotherapy. CONCLUSION: The study highlights the importance of understanding the common genetic mutations between PC and DM, with emphasis on the KRAS, CDKN2A, TP53, CFTR, and SPINK1 genes. Gene therapy, especially through gene editing with CRISPR/Cas9, shows promise for correcting these mutations. However, more studies are needed to ensure the safety and efficacy of these techniques in humans, especially about possible off-target effects and immune response.

Keywords: Pancreatic Cancer. Diabetes Mellitus. Gene Therapy.

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INTRODUCTION

Pancreatic cancer (PC) is widely recognized as one of the most aggressive and lethal neoplasms. It is the seventh most lethal type globally and the fourth leading cause of cancer death in the United States, with about 57,600 new cases diagnosed and approximately 47,050 deaths annually. In Brazil, it is estimated that there are 10,980 new cases per year for the 2023-2025 triennium, with 11,893 deaths recorded in 2020. Between 80% and 90% of patients already have metastases at the time of diagnosis, significantly limiting therapeutic options and resulting in a median survival of only 17 months. (1) (2,3) (4) (1,5,6)

Among the most significant risk factors for pancreatic cancer (PC), type 2 diabetes mellitus (DM2) stands out. Data indicate that 47% of patients with PC have the condition, compared to only 7% of control individuals. Patients with T2DM, particularly those with a history of long-term diabetes, have a 1.5- to 2-fold increased risk of developing PC. The obesity common in T2DM may increase this risk due to hyperinsulinemia and adipokines, and pancreatic cancer itself may induce diabetes by unknown mechanisms. Distinguishing new-onset diabetes caused by PC from other forms of DM may allow for early diagnosis and curative intervention. This relationship suggests a complex interconnection between the genetic and metabolic mechanisms that influence the development of both conditions. (7) (8) (9) (8) (10)

Recent studies point to several genetic mutations that are common to both T2DM and PC. Genes such as *KRAS, TP53, CDKN2A, PALB2,* and *CFTR* play essential roles in cell cycle regulation and metabolism. These mutations promote tumor progression and interfere with metabolic processes, such as insulin resistance, evidencing a genetic connection between the two pathologies. (7,8,11) (7)

Patients carrying mutations in the *PRSS1* or *SPINK1* genes have a considerably high risk of developing PC, with an increase of up to 87 times compared to the general population. In addition, obesity and long-standing T2DM (more than 5 years) are strongly associated with PC, with studies demonstrating an increased risk of up to 2-fold for individuals living with chronic diabetes. (12) (9)

Therefore, the present article seeks to investigate the mutations that are common to DM and PC, with emphasis on how these genetic alterations can contribute to the development of these simultaneous conditions. In addition, this research explores the role of gene therapy as a potential approach to correct these mutations, offering new

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therapeutic perspectives that address both cancer progression and metabolic regulation issues in the context of diabetes. (8,11)

METHODOLOGY

The methodology of this article consisted of a systematic review of the literature to explore the relationship between PC, DM, and gene therapy. To structure the search and analysis of the articles, the PECO (Population, Exposure, Comparison and Outcome) strategy was adopted.

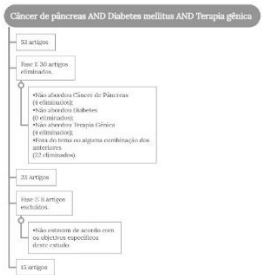
The search was performed in the PubMed Advanced database, using the descriptors (DECS/MeSH): "pancreatic cancer", "diabetes mellitus" and "genetic therapy", with the Boolean operator AND, which initially resulted in 53 relevant articles.

In the first phase of the process, the titles and abstracts of the 53 articles identified were read. Exclusion criteria were established to eliminate articles that did not mention diabetes mellitus, pancreatic cancer, or gene therapy, as well as articles that were completely outside the scope of the proposed topic.

After this initial screening, 23 articles were selected for the next phase. In the second phase, the remaining 23 articles were analyzed in full to assess their adequacy to the objectives of the review. Those who did not make significant contributions or did not adequately address the interrelationship between the themes were excluded. As a result, 15 articles were considered relevant and included in the final analysis.

The methodology applied ensured a careful selection of articles, allowing the review to focus on relevant studies that contributed to the understanding of the relationship between PC, DM, and gene therapy. The use of the PRISMA protocol (Preferred Reporting Items for Systematic Reviews and MetaAnalyses) strengthened the organization and selection of studies and the clarity of the presentation of the review results, as illustrated in Figure 1.

Figure 1: Flowchart of the selection of articles.



Source: Authorship.

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RESULTS

The search in the database resulted in the identification of 53 studies that, after evaluation, were selected 15 studies for the final analysis, which made it possible to identify the main genetic mutations associated with PC and DM, as well as the therapeutic approaches investigated to correct these mutations. The following are the genes most frequently identified in the studies, as well as the main therapeutic methods explored.

GENETIC MUTATIONS

Kras

The *KRAS* gene is one of the most prevalent mutations and is present in more than 90% of cases of pancreatic ductal adenocarcinoma, standing out as one of the initial events in PC oncogenesis. Mutations in (8) *KRAS,* especially at codon 12, promotes the continuous activation of signaling pathways that result in dysregulated cell proliferation and resistance to the apoptosis mechanism. These mutations have a direct impact on metabolic homeostasis, contributing to the insulin resistance seen in patients with DM. (7)

Cdkn2a and Tp53

The *CDKN2A* and *TP53* genes are widely recognized for their functions as tumor suppressors. *CDKN2A* plays an essential role in cell cycle regulation and because of this, mutations in this gene have been associated with pancreatic cancer in about 40-80% of the cases analyzed, contributing to uncontrolled cell proliferation. Mutations in TP53 have been identified in approximately 50-75% of cases, and their inactivation allows the survival of cells with DNA damage, facilitating the accumulation of mutations and tumor progression. In addition, its dysfunction is associated with metabolic changes in pancreatic cancer, influencing cellular processes that favor tumor proliferation and adaptation to the tumor microenvironment. (2) (10) (7)

Cftr and Spink1

CFTR and *SPINK1* have been identified in studies with genes whose mutation increases susceptibility to chronic pancreatitis, a condition that often precedes type 3c diabetes (pancreatogenic diabetes), a form of diabetes associated with pancreatic dysfunction. Mutations in (12) *CFTR* causes ion transport dysfunctions, leading to

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obstruction of the pancreatic ducts and contributing to recurrent inflammatory processes that affect both the exocrine and endocrine pancreas. The mutation in (11) *SPINK1* is related to the risk of hereditary pancreatitis, a condition that increases the predisposition to pancreatic cancer and the development of diabetes, due to chronic inflammation of the pancreatic tissue. (11)

APPROACHES IN GENE THERAPY

The reviewed studies suggest that gene therapy has the potential to correct or attenuate the effects of PC- and DM-related mutations. The main therapeutic approaches identified include gene editing by CRISPR/Cas9, the use of viral vectors, and the modulation of microRNAs.

Gene Editing with CRISPR/Cas9

CRISPR/Cas9 technology has been widely investigated for its ability to correct point mutations in specific genes. In preclinical models, *editing KRAS* at codon 12 using CRISPR/Cas9 showed promise in reducing uncontrolled cell proliferation and partial cell cycle restoration in pancreatic cells. While initial results are promising, the specificity and risks of (3) *Off-target* effects remain critical challenges that need further investigation for safe application in humans. (13)

Viral Vectors for Gene Therapy

Among the studies reviewed, viral vectors such as adenovirus and lentivirus were used for the delivery of functional *CDKN2A* and *TP53* genes into cells with these mutations. These vectors have been modified to restore the function of tumor suppressor genes and thus promote cell cycle control and apoptosis in mutated cell lines. The studies reported a limited immune response in experimental models, although long-term safety has yet to be evaluated in large-scale clinical trials. (7) (14)

Modulation of microRNAs

Modulation of microRNAs, such as miR-21, has been investigated to suppress the expression of oncogenic genes and restore the function of tumor suppressor genes. Inhibition of miR-21 in *TP53-mutated* cells resulted in the activation of apoptotic pathways,

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indicating a potential application for the use of gene therapy as an adjunct to conventional treatments for pancreatic cancer. (3)

DISCUSSION

The relationship between PC and DM goes beyond mere coexistence. Insulin resistance and pancreatic β cell dysfunction, associated with diabetes, create an environment that facilitates oncogenesis. High levels of glucose and insulin, common features in diabetes, stimulate cell signaling pathways that favor tumor growth. This understanding reinforces the need for an integrated approach, such as gene therapy, that addresses the genetic dysfunctions underlying both conditions. (15)

Therefore, the results of this study highlight the genetic mutations common to PC and DM, with emphasis on the KRAS*, CDKN2A, TP53, CFTR,* and *SPINK1* genes, and their clinical implications. The identification of these mutations not only elucidates the pathogenic mechanisms shared between these conditions but also opens the way for specific therapeutic approaches. Gene therapy, especially through gene editing with CRISPR/Cas9, presents innovative potential to correct these genetic dysfunctions and attenuate the metabolic and oncological impact of these mutations.

The KRAS mutation is one of the initial events in pancreatic oncogenesis, favoring uncontrolled cell proliferation and resistance to apoptosis. These processes are often exacerbated in patients with diabetes mellitus due to the impact of mutations on glucose metabolism and pancreatic β cell function. The persistence of (8,12) *The KRAS* mutation in pancreatic tissues poses a significant challenge to conventional PC treatment, such as chemotherapy and radiation therapy, which often fail to selectively target mutated cells. In this sense, genetic correction presents itself as an innovative solution, with greater specificity about the affected cells. (7)

Mutations in *the CDKN2A* and *TP53* genes also significantly compromise the capacity for tumor suppression and cell cycle regulation, contributing to the development of neoplasms and metabolic disorders. Dysfunction in *TP53* has been related to the development of insulin resistance and exacerbation of metabolic complications in diabetes mellitus. (10,11)

Gene therapy, particularly gene editing with CRISPR/Cas9, has shown promise in correcting mutations in *KRAS, TP53,* and *CDKN2A*. Preclinical studies indicate that restoring the normal function of these genes can limit uncontrolled cell proliferation and

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promote apoptosis in mutated pancreatic cells, suggesting a more targeted and potentially effective approach than conventional treatments. (3)

CONCLUSION

This study concludes that it is essential to understand and deepen the relationship between specific genetic mutations that connect to PC and DM, following a complex line between the main genes identified, *KRAS, CDKN2A, TP53, CFTR,* and *SPINK1.* Possible mutations in these genes triggered by a series of factors, such as high levels of glucose and insulin in the body, combined with pathogenic conditions, are responsible for linking the progression of cancer to insulin resistance and other metabolic alterations. Furthermore, given as an example, the mutation of the *KRAS* gene, present in more than 90% of the cases of PC analyzed, is correlated with excessive and uncontrolled cell growth, which makes conventional treatment difficult, thus, it is a chain of factors that makes PC with DM something so deadly to life.

Regarding gene therapy, this study highlights it as something promising for humanity, connecting PC and DM as a mitigating factor to these diseases. As analyzed, the CRISPR/CAS9 gene editing technique acts at the heart of our study as a tool that enables action on the *KRAS gene*, correcting the mutation at codon 12 of the same. It is seen that the increase in increasingly revolutionary technologies such as CRISPR/CAS9 favors results, which attenuated the uncontrolled cell proliferation of pancreatic cells, the use of gene therapy still provides a more human side because it is a less aggressive procedure to the human body, in addition to providing a specific approach to PC and DM due to the focus on the affected tissue.

It is also worth mentioning the use of viral vectors in the treatment of PC and DM. In preclinical studies, the use of these adenovirus or lentivirus vectors induces apoptosis in the cells affected by the tumor, which ends up interrupting the malignant cycle. This "wing" of gene therapy relies on the transport of healthy material to tumor cells, to alter the cell cycle and block the tumor cycle. Like CRISPR/CAS9, the administration of viral vectors requires care and studies, due to the immune system of different patients acting differently with each vector or genetic mutations.

The maintenance of microRNAs is part of another strand of gene therapy, studies on this strand point out that miRNA-21 as an example is correlated with the expression of tumors. Thus, it is visible that the interference in miRNA-21 in cells with *TP53 mutation*

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(tumor suppressor) favors the resumption of the standard cycle of apoptosis, thus resuming the standard cell cycle for the affected cells.

In short, it is necessary to expand the studies on gene therapy and its aspects, to make it more efficient, that is, because it is an instrument of genetic correction, it is necessary to avoid unwanted results such as the accidental alteration of adjacent healthy cells or undesirable responses of the human organism. However, it is valuable to observe the interconnection of PC and DM opens the way for the evolution of increasingly effective treatment methods, paving the way for more humane and transformative medicine.

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REFERENCES

1. Vincent A, Herman J, Schulick R, Hruban RH, Goggins M. Pancreatic cancer. Lancet. 2011 Aug 13; 378(9791):607–20.

2. Kleeff J, Korc M, Apte M, La Vecchia C, Johnson CD, Biankin A V, et al. Pancreatic cancer. Nat Rev Dis Primers. 2016 Apr 21;2:16022.

3. Silva LG de O, Lemos FFB, Luz MS, Rocha Pinheiro SL, Calmon MDS, Correa Santos GL, et al. New avenues for the treatment of immunotherapy-resistant pancreatic cancer. World J Gastrointest Oncol. 2024 Apr 15; 16(4):1134–53.

4. National Cancer Institute - INCA. Available from: https://www.gov.br/inca/pt-br/assuntos/cancer/numeros/estimativa/sintese-de-resultados-e-comentarios. Synthesis of Results and Comments [Internet].

5. Kamimura K, Yokoo T, Terai S. Gene Therapy for Pancreatic Diseases: Current Status. Int J Mol Sci. 2018 Oct 31; 19(11).

6. Liu SH, Smyth-Templeton N, Davis AR, Davis EA, Ballian N, Li M, et al. Multiple treatment cycles of liposome-encapsulated adenoviral RIP-TK gene therapy effectively ablate human pancreatic cancer cells in SCID mice. Surgery. 2011 Apr; 149(4):484–95.

7. Liew SZH, Ng KW, Ishak NDB, Lee SY, Zhang Z, Chiang J, et al. Geographical, ethnic, and genetic differences in pancreatic cancer predisposition. Chin Clin Oncol. 2023 Jun; 12(3):27.

8. Andersen DK, Korc M, Petersen GM, Eibl G, Li D, Rickels MR, et al. Diabetes, Pancreatogenic Diabetes, and Pancreatic Cancer. Diabetes. 2017 May; 66(5):1103–10.

9. Li D, Abbruzzese JL. New strategies in pancreatic cancer: emerging epidemiologic and therapeutic concepts. Clin Cancer Res. 2010 Sep 1; 16(17):4313–8.

10. Wang Q, Zhao Z, Shang J, Xia W. Targets and candidate agents for type 2 diabetes treatment with computational bioinformatics approach. J Diabetes Res. 2014;2014:763936.

11. Shelton CA, Whitcomb DC. Precision medicine for pancreatic diseases. Curr Opin Gastroenterol. 2020 Sep; 36(5):428–36.

12. Suzuki M, Minowa K, Nakano S, Isayama H, Shimizu T. Genetic Abnormalities in Pancreatitis: An Update on Diagnosis, Clinical Features, and Treatment. Diagnostics (Basel). 2020 Dec 26; 11(1).

13. Alliouachene S, Tuttle RL, Boumard S, Lapointe T, Berissi S, Germain S, et al. Constitutively active Akt1 expression in mouse pancreas requires S6 kinase 1 for insulinoma formation. J Clin Invest. 2008 Nov; 118(11):3629–38.

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ISSN: 2358-2472

14. Morró M, Teichenne J, Jimenez V, Kratzer R, Marletta S, Maggioni L, et al. Pancreatic transduction by helper-dependent adenoviral vectors via intraductal delivery. Hum Gene Ther. 2014 Sep; 25(9):824–36.

15. Chepurny OG, Holz GG. Over-expression of the glucagon-like peptide-1 receptor on INS-1 cells confers autocrine stimulation of insulin gene promoter activity: a strategy for the production of pancreatic beta-cell lines for use in transplantation. Cell Tissue Res. 2002 Feb; 307(2):191–201.