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MICRORNAS AND PANCREATIC DUCTAL ADENOCARCINOMA: A SYSTEMATIC REVIEW OF THE LITERATURE

Leandro Alves Martins
``Universidade de Marília``(UNIMAR)
Marília – SP
http://lattes.cnpq.br/3535325004952448

Paulo Cezar Novais
``Universidade de Marília``(UNIMAR)
Marília – SP
http://lattes.cnpq.br/4616229099221681

Isabela Bazzo da Costa
``Universidade de Marília``(UNIMAR)
Marília – SP
http://lattes.cnpq.br/0592696919456258

Cintia Gisele de Andrade Pozenato
``Universidade de Marília``(UNIMAR)
Marília – SP
https://lattes.cnpq.br/5079525303079300

Lara Cristina Casadei Ubeda
`` Universidade de Marília ``(UNIMAR)
Marília – SP
http://lattes.cnpq.br/5156416274719853

Matheus Bento Medeiros Moscatel
`` Universidade de Marília ``(UNIMAR)
Marília – SP
http://lattes.cnpq.br/1712836798933085

Camila Maria de Arruda
`` Universidade de Marília ``(UNIMAR)
Marília – SP
http://lattes.cnpq.br/2704022904566027

Bruno Alves Martins
Centro Universitário de Santa Fé do Sul
Santa Fé do Sul – SP
http://lattes.cnpq.br/2055194442459466

Anderson Luís Alves da Silva
`` Universidade de Marília ``(UNIMAR)
Marília – SP
http://lattes.cnpq.br/1974548395923427

Mariza Pereira
`` Universidade de Marília ``(UNIMAR)
Marília – SP
http://lattes.cnpq.br/2075419451959863

Mara Silvia Foratto Marconato
`` Universidade de Marília ``(UNIMAR)
Marília – SP
http://lattes.cnpq.br/8351091573145936

Rodrigo Buzinaro Suzuki
`` Universidade de Marília ``(UNIMAR)
Marília – SP
http://lattes.cnpq.br/3179595652644776

Abstract: Pancreatic cancer (PC) is considered one of the malignant tumors of the annexed organs of the gastrointestinal system that presents the highest mortality rates, presents non-specific clinical symptoms and the diagnosis is normally made only in advanced stages. In 2020, around 495,773 new cases and 466,003 deaths from PC were recorded worldwide, with a worrying mortality rate of 93.9%. PC involvement and mortality are prominent in Asia and Europe Asia, in Brazil, PC ranks 6th in mortality and 10th in incidence, in addition, there is a predominance of this event, mostly in men globally. MiRNAs are non-coding molecules that play a role in regulating gene expression, regulating the expression of more than 60% of protein-coding genes in humans, providing the ability to modulate biological processes, involving the cell cycle, apoptosis, tumor invasion, differentiation cellular and stress response. More than 700 miRNAs have been reported so far, covering approximately 3% of the human genome. In the case of pancreatic ductal adenocarcinoma (PDAC), several microRNAs are associated with the development, involvement and progression of PC, therefore, this research seeks to analyze the main miRNAs (such as miR-21 which is frequently overexpressed, miR-196a which may be related to a worse prognosis, and miR-210 which has been identified as a miRNA with positive prognostic potential) to determine and identify the relationship between the development of PDAC and miRNAs, in a systematic review of the literature since the scientific literature is vast and fragmented, making it difficult to obtain a comprehensive and updated overview of the role of miRNAs in this disease. Therefore, a systematic review of the literature is necessary to synthesize and critically analyze the available evidence on miRNAs and PDAC, providing a solid basis for future studies and clinical applications.

Keywords: Pancreatic Ductal Adenocarcinoma, Tumor Development, MicroRNAs, Tumor Biomarkers.

INTRODUCTION

Pancreatic cancer (PC) is considered one of the malignant tumors with the highest mortality rate, even though it has a low incidence in individuals acquiring it. Among the malignant neoplasms of the annexed organs of the gastrointestinal system, it is considered one of the most lethal that exists (Ilic, 2016). In 2020, 495,773 new cases of CP were observed, across all ages and in both sexes, of which 466,003 were deaths, remaining in position 12th in the highest number of cases in the world and 7th in deaths. Therefore, a death rate of 93.9% is concluded. According to this global perception, Asia (incidence: 233,701) and subsequently Europe Asia (incidence: 140,116) have the highest incidences and mortality in relation to other continents. In Latin America and the Caribbean, there is an incidence of 37,352, and in Brazil, the incidence and mortality are 13,307 new cases, with a cumulative risk for developing cancer of 0.52 and a cumulative risk of death of 0.50. In Brazil, PC ranks 10th (incidence) and 6th (deaths), behind lung, breast, prostate and thyroid cancer, among others. (IARC, Globocan 2020).

Being one of the types of cancer that progresses silently and presents specific clinical symptoms, therefore, upon diagnosis, most individuals who suffer from this disease are in advanced stages, even with therapeutic development in the area of oncology, as there is limited receptivity to most therapies involving chemotherapy agents currently available. (Aguiar et al., 2019; Liu et al., 2020). Therefore, it is crucial to advance research and discover new markers that can facilitate early detection of this highly aggressive cancer. Currently, few markers are used in the differential diagnosis of pancreatic ductal adenocarcinoma (PDAC), but they have limited diagnostic value due to their low sensitivity or specificity, such as MUC1, p53, smad4 and Ki-67 (Ibrahim, 2016).

However, recent research has focused on identifying new tumor markers for PDAC. An example of these studies is the work carried out by Ibrahim, 2016, in which they verified the expression of the IMP3 protein by immunohistochemical staining, revealing its overexpression in 85% of cases of PDACs.

In addition to the latter, Manne, 2023 found that the glycosylated protein mucin 5AC (MUC5AC) in its mature form is present in most cases of PDACs and not observed in histologically normal pancreatic tissues (Ibrahim, 2016; Manne, 2023). With regard to MicroRNAs, their dysfunction has emerged as a factor recently linked to the development and advancement in PDAC (Prinz, 2022).

MicroRNAs (miRNA) are small non-coding RNA molecules of approximately 20-24 nucleotides in length, which control gene expression in both transcription and post-transcription. MiRNAs have the ability to modulate a wide variety of biological processes, including, but not limited to, the cell cycle, feedback to stress stimuli, cell differentiation, apoptosis and invasion. In addition, aberrations in the expression and functionalities of MiRNAs have been reported. associated with tumor generation and development (Su, 2018). Representing approximately 3% of the human genome, being capable of controlling the expression of more than 60% of protein-coding genes in humans. Several genetic alterations involved in the development of PDAC are influenced by miRNAs. An estimate made shows 17,401 interactions between miRNA and mRNA relevant in PC, which highlights the complexity of these interactions in PDAC and the challenge of identifying the most relevant

target for the development of therapies (Tesfaye, 2019).

In numerous publications, several types of miRNAs have been reported, associating them with potential predictive factors for disease progression, response to chemotherapy and individual survival. Among these biomarkers, miR-21, showing notable levels of expression, is often suggested as an indicator of poor patient prognosis. According to Kong et al., high serum levels of miR-196a may be a predictor of poor survival, in addition to the ability to distinguish between patients eligible for resection and those who cannot undergo resection. MiR-155, miR-203, miR-210 and miR-222, have been shown in research whose high expression is indicative of a poor prognosis.

From another perspective, increased miR-210 in plasma was associated with better individual survival (Szabo et al., 2020).

METHODOLOGY

The methodology adopted in the study adopted a theoretical framework, using an exploratory and descriptive approach to examine the theme and related issues. Initially, a clear hypothesis was formulated to direct the research, with the central question being defined as: "What scientific evidence is available on the relationship between MicroRNAs and Pancreatic Ductal Adenocarcinoma?". Subsequently, a research plan was developed to guide the collection and analysis of data in a systematic way. Stage in which the definition of inclusion criteria and segregation of articles to be selected was included. In this case, the selected descriptors were "Pancreatic cancer", "MicroRNAs", "Pancreatic ductal adenocarcinoma" and Tumor biomarkers". The bibliographic search was carried out in relevant scientific databases, such as PubMed, Google Scholar, Nature, The Lancet, using the defined descriptors, in addition to using informative cancer data from the International Agency for Research on Cancer (IARC), The Global Cancer Observatory (GCO). It is worth noting that, to guarantee the timeliness of the selected studies, a publication period of a maximum of 10 years was established.

MICRORNAS

MicroRNAs (miRNAs) constitute a class of non-coding RNA molecules that have central functionality in cell differentiation, proliferation and survival. They act by binding to complementary sequences in mRNAs (messenger RNAs), causing inhibition or degradation of mRNA translation. The discovery of miRNAs originated in 1993, being a small RNA transcribed from the lin-4 locus of the organism Caenorhabditis elegans. Seven years later, the first miRNA in mammals, called let-7, was identified.

Such eventualities have made it possible to deepen and develop cell biology, such as diseases at molecular levels, since they are often affected due to genomic events such as mutations, deletions, amplifications or changes in transcription regulation, or even due to defects in biogenesis. resulting from mutations or negative regulation of enzymes that control the biogenesis of miRNAs (Rupaimoole, 2017).

The biogenesis of these molecules begins with the transcription of their gene by RNA polymerase II, generating pri-miRNA, a more extensive primary transcription of the miRNA. Still in the nucleus, the pri-miRNA is processed by the Drosha-DGCR8 ribonuclease complex, originating pre-miRNA. Subsequently, the latter is transported through transport proteins Exportin-5 and Ran-GTP6, to the cytoplasm.

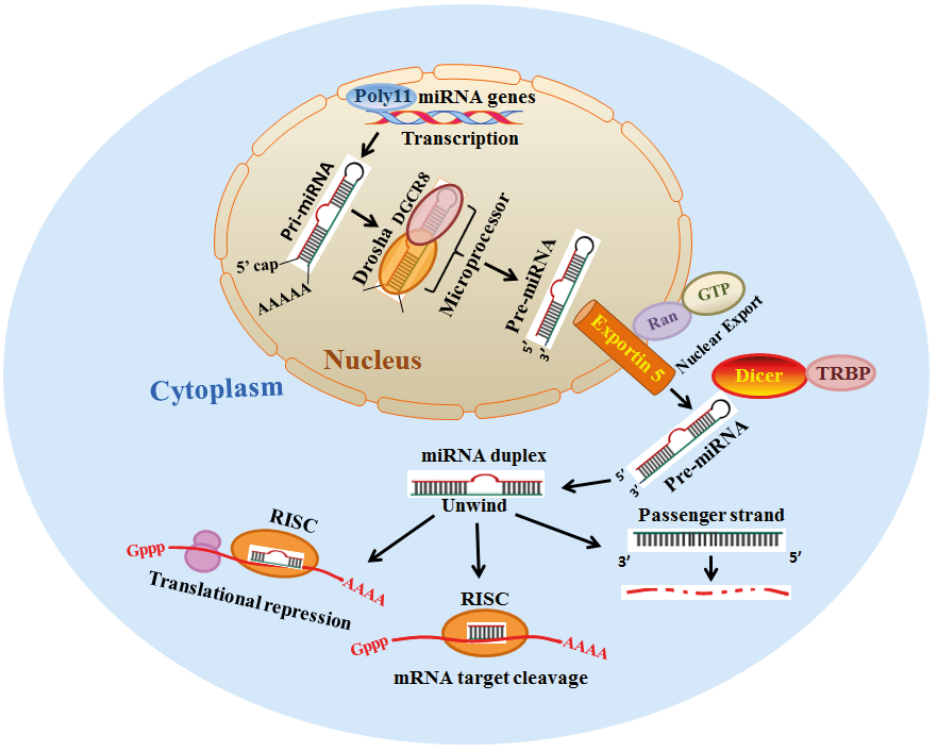

Figure 1: microRNA biogenesis

Synthesis is initiated in the nucleus in which the pri-miRNA transcript is made by RNA Polymerase II. From DNA sequences, pri-miRNA are cleaved by Drosha-DGCR8 forming pre-miRNA that is exported to the cytoplasm by Exportin-5 and Ran-GTP6, which is then processed by the activity of the Dicer enzyme into mature stranded miRNA pair. Subsequently, the miRNA will be coupled to the RISC, which separates the double strand, resulting in the mature miRNA with the ability to bind to messenger RNAs, inhibiting their translation. Source: Ranganna, 2013.

In the cytoplasm, the RNase III endoribonuclease enzyme, Dicer, cleaves the terminal loop of the pre-miRNA, creating a mature double-stranded RNA miRNA.

Then, the mature miRNA is unwound in the cytoplasm, one of the strands is degraded, in return the other strand is incorporated into the RNA-induced silencing complex (RISC) (Rawat et al., 2019). A panoramic representation of the miRNA biogenesis process can be seen in Figure 1 (Ranganna, 2013). MiRNAs recognize the target mRNA sequence, and after that, it can follow two paths for inhibition. If the complementarity between the miRNA and the target sequence is imperfect, the miRNA only prevents this sequence from being translated into protein. From another perspective, if complementarity is considered perfect, the miRNA causes degradation of the target sequence, making expression by the cell impossible. Consequently, the degree of complementarity or base correspondence plays a substantial role in determining the regulatory mechanism mediated by miRNAs. In other words, the extent to which the miRNA and mRNA sequences align and complement each other influences whether the miRNA will impede the translation of the mRNA or induce its degradation. This level of complementarity is a conclusive and fundamental factor in directing how miRNAs will regulate gene expression within cells (Silva, 2017).

In addition to its role as a class of functional molecules in gene regulation, for the evaluation of the physiological functions

of miRNAs, expression studies in animals and cell cultures, or through the use of antisense molecules to interfere with the pairing with their targets and that the Based on these experimental methodological mechanisms, it was possible to attribute critical roles to miRNAs in fundamental processes, such as cell proliferation, differentiation and survival. They emerge as crucial actors during normal development, maintenance of homeostasis and also in disease contexts (Vidigal, 2014).

Lately, evidence has emerged to show that miRNAs are not limited to the intracellular environment; on the contrary, these molecules are released into the extracellular environment and can be found circulating in various body fluids. These circulating forms are called circulating MicroRNAs (c-miRNAs). These, in turn, play a fundamental role in intercellular communication, being responsible for functions in both physiological and pathological processes. It was also found that c-miRNAs are involved in transport and release mechanisms that include association with proteins and/or encapsulation in vesicles formed by lipoproteins, such as exosomes (30-150 nm) secreted by exocytosis and which can play a role in eliminating excess and non-essential cellular elements, they also have the ability to reuse cell surface proteins and influence signaling pathways. These small vesicles include tissue-specific proteins that can encapsulate RNAs (mRNAs and miRNAs), transporting them to different cells through the circulating fluid. This perspective represents the most accepted hypothesis currently about the functional role of exosomes. It is believed that c-miRNAs play a role in preparing the metastatic microenvironment, which favors contact with new environments by cancer cells. However, we still do not have full knowledge about the precise mechanisms that control this release, but it is observed that c-miRNAs can also be used as biomarkers, of course, by collecting samples of body fluids (Jorge et al., 2021; Gao, 2019).

Many malignant neoplasms can exhibit differences in gene expression through the differential expression of miRNAs - since miRNAs regulate gene expression homeostasis, in addition to ensuring the robustness of cellular responses, executing an assignment on cell fate, maintaining cellular characteristic and influencing their state of cellular differentiation. Therefore, mutations do not occur only in key genes, in the same way that they can modify their terminal differentiation, culminating in a proliferative state.

Logically, the question about tumor formation, miRNAs regulate tumor suppressors – miRNAs that exert a negative regulation on tumor suppressor genes are amplified in tumor cells, that is, in greater quantities than in normal cells. Therefore, such an increase in gene expression of miRNAs, generated by amplification, results in the silencing of tumor suppressor genes and oncogenes, where oncogenic miRNAs (on-comiRs) can, under regular conditions, inhibit oncogenes repeatedly found in fragile loci, and then, the decrease in the levels of on-comiRs can result in an increase in the expression of the specific oncogene, which makes it impossible for genes capable of suppressing tumor growth to perform, causing the division of cancer cells. This segmentation according to the function of miRNAs, being tumor suppressors and on-comiRs, considers the competence of these molecules to influence processes related to carcinogenesis, covering mechanisms linked to cell migration and invasion, apoptosis and proliferation (Silva, 2017; Jorge et al., 2021). Furthermore, some miRNAs respond to cellular damage and can be used as targets to improve the effectiveness of conventional cancer treatments. They influence DNA repair and damage tolerance, favoring apoptosis in tumor cells (Silva, 2017).

PANCREATIC CANCER AND THE SPECIFIC CASE OF PANCREATIC DUCTAL ADENOCARCINOMA

Cancer can be defined as a condition of cellular disarray, in which it has the ability to infiltrate neighboring tissues or spread to distant organs in the human body. The pancreas is qualified as a glandular organ belonging to the digestive and endocrine system, responsible for the production of digestive enzymes such as amylase, lipase and trypsin, in addition to its functionality in the synthesis of some hormones such as somatostatin and insulin (Pádua, 2022). PDAC originates in pancreatic exocrine cells and represents the most common form of pancreatic cancer, which accounts for 95% of cases.

Furthermore, it has a high lethality rate, bringing an expected survival rate of 5% over five years. The elements that increase the risk for CP involve chronic pancreatitis, cirrhosis, obesity, smoking, physical inactivity, diabetes mellitus, high consumption of foods rich in fat and cholesterol in the diet, workplace exposure to carcinogens, unfavorable socioeconomic conditions and Jewish ancestry. It is interesting to note that clinical diagnoses normally occur after the affected individual is 50 years old, often between the ages of 70 and 75, occurring mostly in men. Along with this, familial syndromes have been associated with the disease. Hereditary pancreatitis, hereditary non-polypoid colorectal cancer, Peutz-Jeghers syndrome, hereditary breast and ovarian cancer are some of the familial conditions that have been shown to have a connection to PC (Soldan, 2017). Histologically, common PDAC is defined as a dense desmoplastic stroma integrated with angulated glands, small nests of malignant epithelial cells, and/or single tumor cells. It is typical for them to present a range of cellular differentiation of high or low differentiation, within a single neoplasm and show a relevant variety in histomorphological patterns both between different tumors and within the same tumor (Figure 2); (Taherian, 2022).

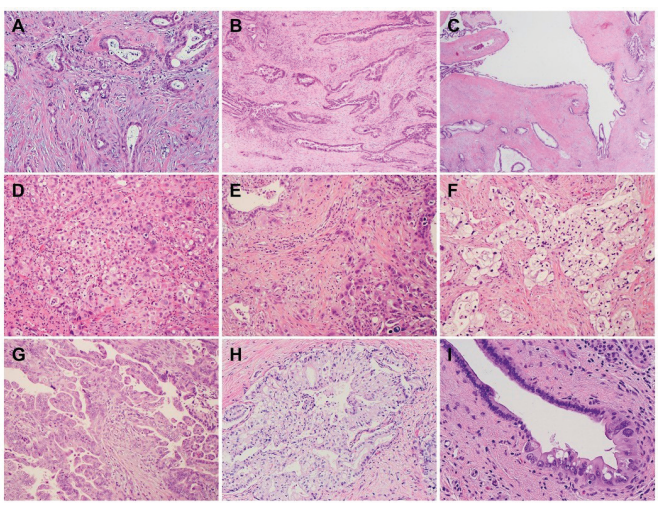

Figure 2: PDACs displaying distinct histomorphological patterns after hematoxylin and eosin staining.

A: Moderately differentiated PDAC with extensive desmoplastic stroma; B: Moderately differentiated PDAC with complex interconnected glands embedded in desmoplastic stroma; C: Large duct variant of PDAC; D: poorly differentiated PDAC; E: poorly differentiated PDAC interspersed with moderately differentiated areas; F: Clear cell variant of PDAC; G: Moderately differentiated PDAC showing extensive and complex intra-luminal micropapillary formation; H: cribriform histology with foam cells; I: pagetoid involvement of the pancreatic duct by PDAC (intra-ductal carcinoma). Source: Taherian, 2022.

MIRNAS AND PANCREATIC DUCTAL ADENOCARCINOMA

An assessment carried out identified 17,401 notable interactions between miRNA and mRNA in the context of pancreatic cancer, highlighting the intricate nature of these connections in PDAC and the difficulty of determining which target is most significant for advancing therapies (Tesfaye, 2019). On the other hand, miRNAs exhibit superior sensitivity as tumor markers compared to CA 19-9 (carbohydrate antigen), in particular with regard to the diagnosis of PDAC (Mortoglou et al., 2022). In a study by Xue et al., through the extraction of RNA from tissues using Real-Time Reverse Transcription Polymerase Chain Reaction (RT-qPCR), it was demonstrated that the expression levels of miR-148a were decreased in all pancreatic lesions, regardless of whether they are benign or malignant, when compared with healthy pancreatic tissue.

The aforementioned decrease was particularly notable in tumor samples.

When we compared miR-148a levels between neoplastic lesions and chronic pancreatitis, it was evident that miR-148a levels were substantially lower in PDAC. Also, the expression of miR-217 showed a highly significant reduction in pancreatic neoplasms, mainly in PDAC. In addition to these, the expression of miR-21 is significantly elevated in PDAC and presents significant variations in isolated studies, miR-196a was found overexpressed in PDAC and pancreatic intraepithelial neoplasia (PanIN). (Xue et al., 2013). In research conducted on tumor tissue samples and frozen preserved normal pancreatic tissue and on formalin-fixed paraffin-embedded (FFPE) samples, using both microarrays and RT-qPCR, overexpression of miR-210, miR-21 and miR- 155 when comparing with normal tissues. Furthermore, a prognostic panorama composed of miR-155, miR-203, miR-210 and miR-222 was proposed by Greither et al., where the increase in their expression level indicates an unfavorable prognosis, unlike the increased expression of serum levels of miR-210 were correlated with a higher survival rate of patients, and according to Kong et al., increased serum levels of miR-196a may indicate an unfavorable prognosis, demonstrating not only the ability to differentiate between patients suitable for resection and those not amenable to such a procedure, but also predicting a possible reduction in survival. (Szabo et al., 2020).

MiRNAs within exosomes can be found in the serum of individuals who have PDAC. According to Madhavan et al., miRNA-1246, miRNA-4644, miRNA-3976 and miRNA-4306 in PDAC patients were found overexpressed in more than 80% of serum exosomes once compared with the control group, another research, proposed a differentiation between PDAC, regular control specimens and specimens from chronic pancreatitis through the overexpression of miRNA-10b, miRNA-21, miRNA-30c and miRNA-181a within exosomes and the reduction of miRNA-let7a. According to research, there are indications that miRNAs contained in exosomes from serum may represent possible biomarkers for early identification of patients with PDAC (Gao, 2019)

In another study, miRNAs were investigated from plasma and PDAC tissue, as well as from peritumoral tissue, associated or potentially related to PDAC. Using a study population consisting of three groups: a PDAC group, a tissue control group, and a plasma control group. Furthermore, data was crossed with the CA 19-9 marker to possibly improve diagnoses in clinical applications. Regarding the expression of miRNAs in the tissue, which present an AUC (Area Under the Curve) ROC (Receive Operating Characteristic) greater

than 0.80 (metric recommended for clinical use), miR-21 = 0.85; miR-210= 0.88. MiR-107, miR-100, miR-181c, exhibited below the AUC-ROC criterion. At the plasma level, miR-181c≅ 1 and miR-210= 0.80. Furthermore, CA 19-9 exhibited AUC=0.95 in the PDAC study group and the combination of this with miR-210 increased it to AUC=0.99. Furthermore, the combination of CA 19-9 with the expression of miR-210 and miR-21 in tumor tissue increased AUC-ROC= 1 with a confidence interval (CI) of 95%, sensitivity and specificity of 100%, therefore, there is an increase in the accuracy of diagnosing PDAC. Considering the parameters of this research, there was overexpression of miR-21 and miR-210 in tumor tissue, and miR-181c and miR-210, at plasma levels, were revealed to be overexpressed when compared with physiological normality.

Besides, miR-181c (plasma) was superior to CA 19-9 for the possible differentiation between patients with PDAC and individuals in the control group, enabling possible ways of non-intrusive diagnosis in relation to the condition, but it is still necessary new studies to confirm the function of this miRNA as a biomarker for PDAC (Vieira et al., 2021). In evaluating the plasma expression of miRNAs in PDAC, intra-ductal papillary neoplasia (IPMN) and healthy control subjects, in which miR-483-3p and miR-21 were significantly increased in PDAC. miR-483-3p in PDAC higher than in IPMN and control group, the plasma expression level of miR-21 was higher in PDAC than in normal patients. Furthermore, no difference was demonstrated in the expression of miR-21 between PDAC and IPMN, however, as seen, the plasma expression of miR-483-3p in PDAC was significantly higher than in IPMN, which makes it possible to use it to distinguish PDAC of IPMN.

In tissue analysis, the expression of miR-21 was significantly higher in PDAC than in IPMN, and also higher when comparing IPMN and normal pancreatic tissue, which indicates that miR-21 collaborates with the initial process of tumorigenesis in the pancreas. miR-483-3p, on the other hand, showed a significantly higher elevation when compared to the level of non-tumor cells, in PDAC, the expression was also higher than in IPMN. Through ROC curve analysis, the combination of miR-483-3p+miR-21 (AUC= 0.839), similar to the AUC of the ROC curves of CA19-9 (AUC= 8.66), and this combination was superior compared to carcinoembryonic antigen (CEA), which presented AUC= 0.719. (Abue et al., 2014).

Using next generation sequencing (NGS) and RT-qPCR in order to establish the differentiation of the expression of miRNAs in FFPE tissue in samples of PDAC, chronic pancreatitis and pancreatic tissues in autopsy situations with normal patterns. In PDAC, 4 overexpressed (miR-215-p5, miR-122-5p, miR-192-5p, miR-181a-2-3p) and 4 under expressed (miR-30b-5p, miR-216b-5p) miRNAs were found., miR-320b, miR-214-5p). When analyzing the serum level of PDAC miRNAs by RT-qPCR, overexpression (miR-215-p5, miR-122-5p, miR-192-5p) and hypo expression (miR-30b-5p, miR-320b) were identified. The concordance between blood and tissue FFPE levels suggests that these miRNAs can be used as non-invasive biomarkers in the detection of PDAC. Furthermore, significant disparities were identified in the relative levels of miRNAs in the serum of patients with PDAC compared to those with chronic pancreatitis and healthy control subjects. Using ROC-AUC, sensitivity and specificity for each miRNA, to discriminate PDAC from chronic pancreatitis: miR-320b (AUC= 1) and between PDAC and the healthy control group, miR-122-5p (AUC= 0.988), miR-320b (AUC=

0.992) and miR-215-5p (AUC= 0.832), all miRNAs with CI=95%. The expression of miR-181a-2-3p, miR-216b-5p and miR-214-5p showed statistically significant differences in PDAC tissue in relation to chronic pancreatitis tissue, this finding is not exclusive to this study, other previous studies indicate limited or no concordance between levels of the same miRNA in tissues and circulation as seen in Zhou et al., and Flammang et al. (Khan et al., 2021).

In analyzing the plasma values of the miRNAs miR-181b, miR-196a and miR-210 using the ROC curve and AUC values, obtained by RT-qPCR and measuring CA 19-9 by electrochemiluminescence (ECL) assay, they obtained miR-181b (AUC= 0.789), miR-196a (AUC= 0.865), miR-210 (AUC= 0.834) and CA 19-9 (AUC= 0.947), combining them, achieved miR-181b+miR-196a (AUC= 0.944), miR-181b+miR-210 (AUC= 0.830), miR-196a+miR-210 (AUC=0.888) and miR-181b+miR-196a+miR-210 (AUC= 0.968). This confirms the efficacy and a promising diagnostic approach through combination with CA 19-9 and associations between plasma miRNAs. Furthermore, the expression of miR-181b, miR-196a and miR-210 were overexpressed in individuals with CP (Liu et al., 2020), a fact also previously seen according to Szabo et al. and Xue et al. on miR-210 and miR-196a respectively.

CONCLUSION

Dysregulation of microRNAs in pancreatic ductal adenocarcinoma (PDAC) is a prominent feature, with several microRNAs showing overexpression (such as miR-21, miR-155 and miR-210) and others under expression (such as miR-30b, miR-216b and miR- 320b). This alteration has a significant impact on tumorigenesis, influencing crucial processes such as cell proliferation, apoptosis, invasion and metastasis, and understanding it provides valuable insights into the processes that drive the development and progression of PDAC.

MicroRNAs emerge as promising biomarkers in PDAC, offering potential for early diagnosis, prognosis and prediction of treatment response. These molecular markers are capable of overcoming the limitations of traditional biomarkers, such as CA 19-9, and provide important information for personalizing therapy. Notable examples include the prognostic role of miR-21 and miR-196a, as well as the early diagnostic potential of miR-210 and miR-320b, highlighting their clinical relevance.

Despite advances, significant challenges remain, including the need to validate these findings in larger studies and improve the development of microRNA-based diagnostic and therapeutic tools. However, it is clear that the investigation of microRNAs represents a promising area for advancing the diagnosis, prognosis and treatment of PDAC, offering the potential to improve clinical outcomes and quality of life for patients affected by this devastating disease.

REFERENCES

ABUE, Makoto; YOKOYAMA, Misa; SHIBUYA, Rie; TAMAI, Keiichi; YAMAGUCHI, Kazunori; SATO, Ikuro; TANAKA, Nobuyuki; HAMADA, Shin; SHIMOSEGAWA, Tooru; SUGAMURA, Kazuo; SATOH, Kennichi. Circulating miR-483-3p and miR-21 is highly expressed in plasma of pancreatic cancer. **International journal of oncology**, v. 46, p. 539-547, 10 nov. 2014.

AGUIAR, Michelle de; NASCIMENTO, Ana; SOUSA, Beatriz; FERREIRA, Marina; CAVALCANTI, Paloma. A influência do IDH na incidência e mortalidade do câncer de pâncreas. **Revista Saúde & Ciência Online**, v. 8, n. 2, p. 15-23, 2019.

FLAMMANG, Isabelle; REESE, Moritz; YANG, Zixuan; EBLE, Johannes A.; DHAYAT, Sameer A. Tumor-Suppressive miR-192-5p Has Prognostic Value in Pancreatic Ductal Adenocarcinoma. **Cancers (Basel)**, v. 12, ed. 6, p. 1693, 25 jun. 2020.

GAO, Zhuqing; JIANG, Wei; ZHANG, Shutian; LI, Peng. The State of the Art on Blood MicroRNAs in Pancreatic Ductal Adenocarcinoma. **Analytical cellular pathology**, v. 2019, p. 1-7, 10 set. 2019.

IBRAHIM, Doaa Abdelaziz; ABOUHASHEM, Nehal S. Diagnostic value of IMP3 and mesothelin in differentiating pancreatic ductal adenocarcinoma from chronic pancreatitis**. Pathology - Research and Practice**, v. 212, p. 288-293, 22 jan. 2016.

ILIC, Milena; ILIC, Irena. Epidemiology of pancreatic cancer. **World Journal of Gastroenterology**, v. 22, n. 44, p. 9694-9705, 28 nov. 2016.

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER (IARC). Pancreas: Source: Globocan 2020. **Global Cancer Observatory (GCO)**: International Agency for Research on Cancer, 2020.

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER (IARC). Brazil: Source: Globocan 2020. **Global Cancer Observatory (GCO)**: International Agency for Research on Cancer, 2020.

JORGE, Ariany Lima; PEREIRA, Erik Ribeiro; OLIVEIRA, Christian Sousa de; FERREIRA, Eduardo dos Santos; MENON, Edmara Toledo Ninzoli; DINIZ, Susana Nogueira; PEZUK, Julia Alejandra. MicroRNAs: entendendo seu papel como reguladores da expressão gênica e seu envolvimento no câncer. **Einstein (São Paulo)**, v. 19, eRB5996, p. 1-7, 2021.

KHAN, Imteyaz Ahmad; RASHID, Safoora; SINGH, Nidhi; RASHID, Sumaira; SINGH, Vishwajeet; GUNJAN, Deepak; DAS, Prasenjit; DASH, Nihar Ranjan; PANDEY, Ravindra Mohan; CHAUHAN, Shyam Singh; GUPTA, Surabhi; SARAYA, Anoop. Panel of serum miRNAs as potential non-invasive biomarkers for pancreatic ductal adenocarcinoma. **Scientific Reports**, v. 11, 2 fev. 2021.

LIU, Gongpan; SHAO, Cunhua; LI, Anyun; ZHANG, Xiaobin; GUO, Xingjun; LI, Jiangong. Diagnostic Value of Plasma miR-181b, miR-196a, and miR-210 Combination in Pancreatic Cancer. **Gastroenterology Research and Practice**, v. 2020, p. 1-6, 6 ago. 2020.

MANNE, Ashish; KASI, Anup; ESNAKULA, Ashwini Kumar; PALURI, Ravi Kumar. Predictive Value of MUC5AC Signature in Pancreatic Ductal Adenocarcinoma: A Hypothesis Based on Preclinical Evidence. **International Journal of Molecular Sciences**, v. 24, n. 9, p. 8087, 30 abr. 2023.

MORTOGLOU, Maria; MIRALLES, Francesc; ARISAN, Elif Damla; DART, Alwyn; JURCEVIC, Stipo; LANGE, Sigrun; UYSAL-ONGANER, Pinar. MicroRNA-21 Regulates Stemness in Pancreatic Ductal Adenocarcinoma Cells. **International Journal of Molecular Sciences**, v. 23, p. 1275, 23 fev. 2022.

PÁDUA, Aline Fernandes de; CABRAL, Carlos Eduardo de Melo; MORAES, Isabel Cristina de; MIRANDA, Gabriele Castro. CÂNCER DE PÂNCREAS: DIAGNÓSTICO E TRATAMENTO. **Revista Científica Eletrônica Race Interdisciplinar**, v. 01/2022, p. 80-84, 3 jan. 2022.

PRINZ, Christian; FEHRING, Leonard; FRESE, Robin. MicroRNAs as Indicators of Malignancy in Pancreatic Ductal Adenocarcinoma (PDAC) and Cystic Pancreatic Lesions. **Cells**, v. 11, p. 2374, 2 ago. 2022.

RANGANNA, Kasturi; MATHEW, Omana P.; MILTON, Shirlette G.; HAYES, Barbara E. MicroRNAome of Vascular Smooth Muscle Cells: Potential for MicroRNA-Based Vascular Therapies. **Current Trends in Atherogenesis, InTech**, 2013.

RAWAT, Manmeet; KADIAN, Kavita; GUPTA, Yash; KUMAR, Anand; CHAIN, Patrick S.G; KOVBASNJUK, Olga; KUMAR, Suneel; PARASHER, Gulshan. MicroRNA in Pancreatic Cancer: From Biology to Therapeutic Potential**. Genes (Basel)**, v. 10, n. 10, p. 752, 25 set. 2019.

RUPAIMOOLE, Rajesha; SLACK, Frank J. MicroRNA therapeutics: towards a new era for the management of cancer and other diseases. **Nature Reviews Drug Discovery**, v. 16, n. 3, p. 203–222, 17 fev. 2017.

SILVA, Geilza Carla de Lima; SANTOS, Alanna Silva dos; SILVA, Sabrina Barbosa da. Micrornas no câncer: uma abordagem molecular, terapêutica e evolutiva. *In:* **CONGRESSO BRASILEIRO DE CIÊNCIAS DA SAÚDE (CONBRACIS) II**, 2017, Campina Grande. Anais II CONBRACIS. Campina Grande: Realize Editora, 2017.

SOLDAN, M. Rastreamento do câncer de pâncreas. **Revista do Colégio Brasileiro de Cirurgiões**, v. 44, n. 2, 109-111, 2017.

SU, Qiang; ZHU, Emily C; QU, Yao-long; WANG, Di-ya; QU, Wei-wei; ZHANG, Chen-guang; WU, Ting; GAO, Zu-hua. Serum level of co-expressed hub miRNAs as diagnostic and prognostic biomarkers for pancreatic ductal adenocarcinoma. **Journal of Cancer**, v. 9, n. 21, p. 3991-3999, 11 out. 2018.

SZABO, A; GURLICH, R; LIBERKO, M; SOUMAROVA, R; VERNEROVA, Z; MANDYS, V; POPOV, A. Expression of selected microRNAs in pancreatic ductal adenocarcinoma: is there a relation to tumor morphology, progression, and patient's outcome?. **Neoplasma**, v. 67, n. 5, p. 1170–1181, 2020.

TAHERIAN, Mehran; WANG, Hua; WANG, Huamin. Pancreatic Ductal Adenocarcinoma: Molecular Pathology and Predictive Biomarkers. **Cells**, v. 11, n. 19, p. 3068, 29 set. 2022.

TESFAYE, Anteneh A; AZMI, Asfar S; PHILIP, Philip A. MiRNA and Gene Expression in Pancreatic Ductal Adenocarcinoma. **The American Journal of Pathology**, v. 189, n. 1, p. 58-70, 2019.

VIDIGAL, Joana A; VENTURA, Andrea. The biological functions of miRNAs: lessons from in vivo studies. **Trends in Cell Biology**, v. 25, n. 3, p. 137-147, 4 dez. 2014.

VIEIRA, Nivaldo Faria; SERAFINI, Luciano Neder; NOVAIS, Paulo Cezar; NETO, Fermino Sanches Lizarte; CIRINO, Mucio Luiz de Assis; KEMP, Rafael; ARDENGH, José Celso; SAGGIORO, Fabiano Pinto; GASPAR, Alberto Facury; SANKARANKUTTY, Ajith Kumar; JÚNIOR, Jorge Resende Lopes; TIRAPELLI, Daniela Pretti da Cunha; SANTOS, José Sebastião dos. The role of circulating miRNAs and CA19-9 in pancreatic cancer diagnosis. **Oncotarget**, v. 12, ed. 17, p. 1638-1650, 17 ago. 2021.

XUE, Yue; TAYOUN, Ahmad N. Abou; ABO, Kristine M.; PIPAS, J. Marc; GORDON, Stuart R.; GARDNER, Timothy B.; BARTH JR, Richard J.; SURIAWINATA, Arief A.; TSONGALIS, Gregory J. MicroRNAs as diagnostic markers for pancreatic ductal adenocarcinoma and its precursor, pancreatic intraepithelial neoplasm. **Cancer genetics**, v. 206, ed. 6, p. 217-221, 2013.

ZHOU, Xin; LU, Zipeng; WANG, Tongshan; HUANG, Zebo; ZHU, Wei; MIAO, Yi. Plasma miRNAs in diagnosis and prognosis of pancreatic cancer: A miRNA expression analysis. **Gene**, p. 181-193, 5 out. 2018.