Role of MicroRNA in IPMN Lesions

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ABSTRACT

Pancreatic ductal adenocarcinoma is one of the leading causes of cancer related death which could be explained by typically late diagnosis and chemo- radioresistance. The majority of pancreatic ductal adenocarcinoma develops from three precursor lesions, including intraductal papillary mucinous neoplasm. Therefore, an effective screening tool to detect early stages of pancreatic ductal adenocarcinoma or its precursor lesions is needed. MicroRNAs belong to a class of short non-coding RNAs and act as tumor oncogenes or tumor suppressors. They play an important role in life-cycle of normal cells, as well as cancer cells, supporting their cancerogenous and metastatic potential. Different panels of upregulated and downregulated miRNAs have been associated with pancreatic ductal adenocarcinoma and its precursor lesions. In the present review, we discuss the recent studies focusing on miRNAs in intraductal papillary mucinous neoplasm. A summary of the most important miRNAs involved in intraductal papillary mucinous neoplasm pathogenesis is provided. Identification of key miRNA networks in pancreatic ductal adenocarcinoma precursors might provide diagnostic tools for early detection and subsequently extended life expectancy for this disease.

INTRADUCTUAL PAPILLARY MUCINOUS NEOPLASM (IPMN)

Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive neoplasm with poor prognosis, mainly due to its late diagnosis and resistance to current anticancer treatments. Only less than 6% of PDAC patients survive 5-years after initial diagnosis [1, 2]. Surgical asportation of PDAC is the only way which could lead to complete cancer cure, though, only 15-20% of patients are resecable at the moment of diagnosis [3, 4]. Early detection and surgical resection can increase PDAC 5-year survival rate up to 50% for stage I [5, 6, 7]. The majority of PDAC develop from three precursor lesions: pancreatic intraepithelial lesions (PanIN), intraductual papillary mucinous neoplasm (IPMN), and mucinous cystic neoplasm (MCN), that may progress to cancer following different pathways [8]. The malignant transformation of IPMN is characterized by an orderly adenoma-carcinoma sequence from low-grade to high-grade dysplasia and further to invasive carcinoma and the risk of cancer development and consequently the management of precursor lesions derive from stratification of patients on the basis of specific physical and imaging findings according to worldwide accepted guidelines [9, 10]. In general, they can be divided into main duct type (MD-IPMN) or branch duct type (BD-IPMN). The malignant potential is higher for MD-IPMN (around 44%-48%) compared to BD-IPMNs, which only carry a 11%-17% risk of malignant transformation [11, 12, 13].

Given the aggressive nature of PDAC, detection of precursor lesions with malignant potentional would be critical to increasing the survival of these patients. Nowadays, no reliable biomarkers for early detection of PDAC or its precursors exist. Specific miRNAs have been found to be deregulated in PDAC and IPMN, suggesting their role as potential early biomarkers of this disease.

MICRORNAs

MicroRNAs (miRNAs) are short non-coding RNAs that contain circa 19-24 nucleotides. Most miRNA loci are found in non-coding intronic transcription regions and therefore do not encode any proteins. Remarkably, each miRNA can regulate the expression of numerous target genes and also

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the same target gene can be regulated by several types of miRNAs which create a complex network of interactions [14, 15, 16, 17, 18, 19, 20, 21, 22]. miRNAs are initially processed in the nucleus from longer transcripts called pri-miRNAs [23, 24, 25, 26] with subsequent splicing step and active trasportation from the nucleus to the cytoplasm [27, 28, 29, 30]. In the cytoplasm they achieve the final size and functional form by further cleavage step and by combination with proteins of the Argonaute (AGO) family [31], creating the miRNA-induced silencing complexes (miRISCs). In general, these complexes bind to the target mRNA with complementarity which can be described as perfect (leading to complete mRNA degradation) or near perfect (leading to induction of translational repression) [32], as described in Figure 1. Besides the aforementioned canonical miRNA biogenesis, certain miRNAs are also processed in a Drosha-or Dicerindependent manner [33, 34]. MiRNAs can be detected in the nucleus as well as in membrane-bound compartments, such as secreted vesicles and mitochondria [35].

miRNAs affect important cell processes such as differentiation and apoptosis in non malignant cells, but also contribute to carcinogenesis and metastatic potentional of cancer cells [2, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45]. Several studies have shown that miRNAs' deregulation is tissue and cancer specific which enhance their possibilities as diagnostic, predictive, prognostic biomarkers as well as therapeutic targets in clinical cancer practice, favoured also by its accessibility [2, 19, 20, 21, 22, 23, 24, 25, 26, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39]. miRNA expression levels can easily be detected both in human tissues (fresh or formalin fixed fixed paraffin-embedded) and body fluids, including blood and are more stable than protein and mRNA [44, 45].

MICRORNAS AND IMPLICATION IN CANCER AND PRECANCEROGENOUS LESIONS

miRNA expression profiles differ between normal and malignant tissues but differ also between different tumor types. Most cancer types are characterized by a specific miRNAs' expression pattern or "miRNome" that might be correlated to some of the clinical and pathological features as for example tumor stage, proliferation index or grading [46]. MiRNAs are involved in multiple cellular functions, affecting cancer growth, progression and resistance to therapy [2, 19], Upregulated miRNAs often act as oncogenes and downregulated miRNAs act as tumor suppressors [2, 19, 47] and it is not excluded that the same

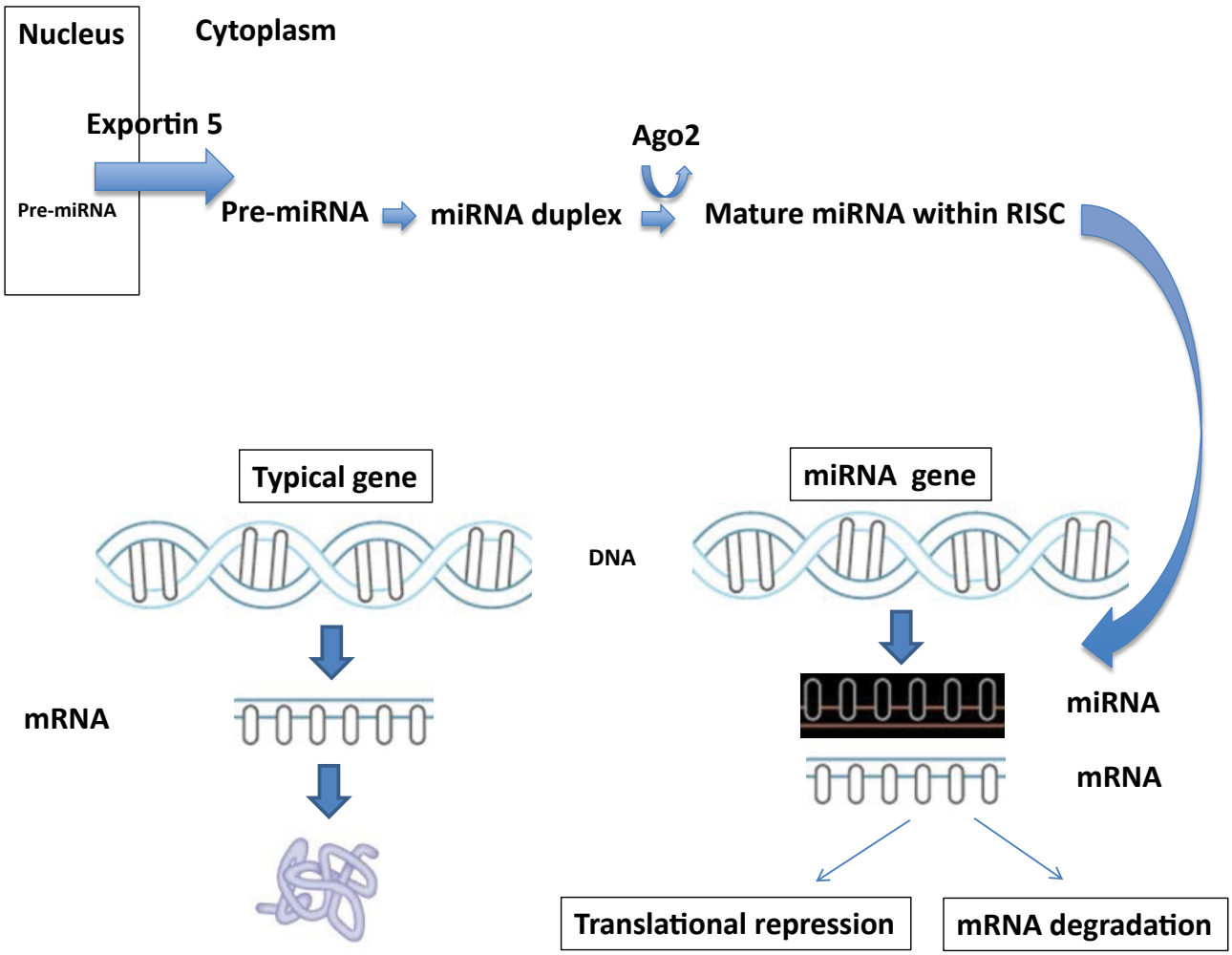

Figure 1. MiRNAs and regulation of gene expression.

Biosynthesis of miRNAs starts in the nucleus from pri-miRNAs which are actively transported from the nucleus to the cytoplasm by Exportin-5 with subsequent cleavage step to achieve the final size. Each molecule is combined with the proteins of Argonaute (AGO) family to obtain its functional form, thus forming the mi-RNA-induced silencing complexes (RISCs).

Table 1. miRNA in IPMN lesions.

miRNA	Expression in IPMN
miR-10b	↑ [ref 64]
miR21	↑ [ref 56, 63, 64, 65, 71]
miR-33a-5p	↓ [ref 76]
miR-92a	↑ [ref 74]
miR-99a	↓ [ref 73, 74]
miR-99b	↓ [ref 73]
miR-100	↓ [ref 73, 74]
miR-101	↓ [ref 71]
miR-125b	↑ [ref 74]
miR-126	↓ [ref 73]
miR-130a	↓ [ref 73]
miR-145	↑ [ref 74]
miR-155	↑ [ref 64]
miR-200a-3p	↓ [ref 76]
miR-210	↑ [ref 64]
miR-212	↓ [ref 74]
miR-221	↑ [ref 76]
miR-342-3p	↓ [ref 73]
miR-483-3p	↑ [ref 56]
miR-574-4p	↓ [ref 76]
miR-664b	↓ [ref 76]
miR- 1185-5p	↓ [ref 76]

miRNA might act as oncogene in one tumor type and as tumor suppressor in another primary due to different targets and mechanisms of action [45]. The aberrant miRNA expression can be caused by genomic deletion, errors in transcription regulation/miRNA processing or can be directly control the epigenetic variations. All these steps can affect the cell phenotype and cancer susceptibility [48, 49, 50, 51]. It has been well established that miRNAs play an important role in intracellular processes, though, new evidences have shown that miRNAs can move from one type of cell to another where they produce functional effects. Moreover, the malignant component of the tumor can also influence the microenvironment by miRNA release [45]. Some recent studies have demostrated that miRNAs are essential for immune cell functioning and in consequence the abberations in expression of immune-related miRNAs can modify immune responses [52, 53].

PDAC is characterized by multiple gene mutations, responsible for activating the signal transduction downstream pathways which are influenced by miRNAs [54]. Nowadays, miRNAs have been isolated from tissue and blood of PDAC patients as well as from bile, stool or pancreatic juices [55]. Specific miRNA deregulation were identified to distinguish PDAC from non-malignant pancreatic tissue. Moreover, specific circulating serum, plasma or bile miRNAs are able to discriminate PDAC patients from healthy controls [56, 57, 58, 59, 60]. Recently, diagnostic miRNA kits have been developed to distinguish benign and malignant pancreatic lesions [62, 63]. Specific miRNAs' expressions differ between PDAC in metastatic and nonmetastatic setting, as reported by Singh *et al.* [61].

MIRNA IN IPMN LESIONS

Recent studies have identified specific miRNAs whose alterations are associated with IPMN in various phases of its process of malignant transformation, providing basis for a future identification of early markers and a useful clinical guide for correct management of precursor lesions. The first evidence of the aberrant miRNA expression in IPMN came from the study published by Habbe *et al.* who assessed the relative expression of twelve miRNAs. Two miRNAs (miR-155 and miR-21), were significantly overexpressed within the neoplastic epithelium of IPMNs, as shown by locked nucleic acid in situ hybridization (LNA-ISH), and their levels were significantly higher in IPMNs with carcinoma-in-situ compared to IPMNs with adenomas, suggesting a potential correlation between both miRNAs and histological features of malignant progression [63]. The potential role of miR-21 in an early step of pancreatic carcinogenesis is provided by the evidence that the expression of miR-21 is significantly higher in PDAC cells compared to IPMN and, moreover, the expression of miR-21 is significantly higher in IPMN compared to noncancerogenous pancreatic tissue. Furthermore, plasma levels of miR-21, evaluated by quantitative RT-PCR, are significantly increased in IPMNs compared to healthy controls [56]. Finally, a recent study showed that miR-21 and miR-155, extracted by endoscopic-ultrasound fine-needle aspiration (EUS-FNA), can discriminate between benign and malignant pancreatic lesions with a sensitivity and a specificity of 81.5% and 85.7%, respectively [56, 64].

Furthermore miR-21 is overexpressed in pancreatic cyst fluid of mucinous cystic neoplasm compared to non-mucinous cystic lesions. Upregulation of miR-155 was observed in the pancreatic juice of IPMN patients [65]. MiR-21 influences proliferation, invasion, and also chemoresistance of neoplastic cells by increasing mRNA expression of matrix metalloproteinase-2 and -9, and vascular endothelial growth factor [66, 67, 68, 69], while miR-155 contributes to tumor development by reducing activity of tumour protein 53-induced nuclear protein 1 (TP53INP1), a proapoptotic stress-induced p53 target gene [70]. A multicenter study analyzed the different expression of three miRNAs, in particular miR-21, miR-101, and miR-155 in invasive/non-invasive IPMN and normal control tissue. The authors found that miR-155 and miR-21 expression were significantly increased in invasive IPMN lesions as compared to non-invasive lesions. Conversely, low levels of miR-101 were associated with invasive IPMNs, suggesting that progression from benign to invasive precursor lesions was correlated with increasing and decreasing levels of these markers, respectively. Moreover, Caponi *et al.* showed a strong relationship between miR-21 expression and clinical outcome of PDAC patients since higher miR-21 expression was associated with worse outcome of patients undergoing surgical resection. The independent prognostic value of miR-21 was also confirmed by a multivariate analyses [71]. The relationship between low expression levels of miR-101 and malignant transformation of IPMN lesions may be explained by the evidence that reduced levels of miR-101 in malignant IPMN could increase expression of its target protein Enhancer of Zeste Homolog-2 (EZH2), a histone

methyltransferase involved in epigenetically mediated transcriptional silencing, and so promote neoplastic progression [72]. Recent results from a genomewide miRNA expression analysis showed that six miRNAs (miR-100, miR-99b, miR- 99a, miR-342-3p, miR-126, miR-130a) were downregulated in high-risk as compared to low-risk IPMNs, probably promoting neoplastic progression by increasing aktivity of target oncogenes involved in pancreatic carcinogenesis. Downregulation of one of the above mentioned miRNAs, miR-99a, is also associated with main duct involvement that represents a reliably predictor of malignant potential in IPMN [73].

Further, Henry *et al.* correlated miRNA levels in pancreatic duct aspirate to histopathological samples of resected lesions. The authors found that nine specific miRNAs (let-7b, miR-27b, miR-92a, miR-99a, miR-100, miR-125b, miR-145, miR-212, and miR-483) were differentially expressed between benign and premalignant/malignant specimens. Furthermore, the likelihood of presenting a malignant lesion appears to be linked to high amount of RNA in the cystic fluid [74].

A remarkable difference in miRNA expression profiles between PDAC and non-malignant pancreatic cystic neoplasm was highlighted by Lee *et al.* who identified panels of specific miRNAs that could distinguish malignant and benign lesions. Four specific miRNAs (miR-21-5p, miR-485-3p, miR-708-5p, and miR-375) was able to differentiate pancreatic cancer from IPMN with a specificity and a sensitivity of 85% and 95%, respectively [75]. Permuth *et al.* conducted a genome-wide miRNA analysis from plasma of patients with surgically-resected IPMNs, revealed a 5-microRNA signature (miR-200a-3p, miR-1185-5p, miR-33a-5p, miR-574-4p, and miR-664b) that discriminate between high grade/invasive and low/moderate grade IPMNs, and proposed a novel combined non–invasive approach to improve early detection of IPMN malignancy [76]. Finally, Hernandez *et al.* suggested that there is a evidence of different expression levels of miRNAs like miR-21, miR-155 and miR-196 in different tissue, serum, cyst fluid, and stool of patients with PDAC and IPMN which might make them reliable candidate for future clinical applications [1].

CONCLUSIONS

In conclusion, miRNAs might be used as prognostic and predictive biomarkers, using their potentional to influence tumour malignat behaviour and response to chemotherapy. The potential clinical relevance of using miRNA as early biomarker of malignant transformation is supported by the correlation between different expression levels of specific miRNAs in high-risk and low risk IPMN, defined by histopathological features. Identification of key miRNA networks in PDAC might provide diagnostic tools for early detection, early treatment and subsequently extended life expectancy of these patients. Finally, miRNA-based therapeutic strategies, both based to either restoring or inhibiting miRNA function though exogenous delivery of miRNAs mimics or inhibitors, open new horizonts in cancer treatment and prevention.

Conflicts of interests

The authors indicated no potential conflict of interests.

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