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Review paper

Role of mi-RNAs in Pancreatic Cancers

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ABSTRACT

Pancreatic malignancy is one of the most lethal cancers that accounts for approximately 1000 annual reported deaths in Pakistan. Diagnosis and treatment of pancreatic cancers remain challenging due to complex anatomical location of pancreas, appearance of common symptoms and aggressive nature of the tumor. Currently, only conventional treatment options are available in Pakistan that is surgery, chemotherapy and/or radiotherapy. Recent studies around the globe have demonstrated mi-RNA as an important biomarker for cancer diagnosis, prognosis prediction and treatment selection. In addition, aberrant expression of mi-RNAs are also found to be associated with initiation, progression and metastasis of various cancers including pancreatic cancers. This review aims to discuss role of aberrantly expressed mi-RNAs in pancreatic cancers.

KEYWORDS: mi-RNA, Pancreatic Cancers, Oncogenic, Tumor Suppressor, Carcinogenesis

INTRODUCTION

Pancreatic malignancy is one of the most lethal of all cancers and stands 7th in the global as well as Pakistani ranking for cancer related deaths. Figure 1 shows comparison of Age Standardized Rates for incidence and mortality in global and Pakistani context. With Age-Standardized Mortality Rate (ASMR) of 0.63, it account for approximately 1000 reported annual deaths in Pakistan [1]. Number of annual incidence are seemingly smaller in comparison to other cancers but owing to the aggressive nature of pancreatic cancers, survival rate is extremely low and the tumor is frequently metastasized.

Due to complex location of pancreas in the body, limited sensitivity of the diagnostic tools and appearance of common symptoms, pancreatic tumors usually remain undiagnosed at early stages. More than 50% of the tumors are diagnosed with metastatic disease [2]. Standard treatment include surgical removal of tumor followed by chemotherapy. However, tumors with extensive invasion and/or metastasis fall under boarder-line resectable or unresectable category. These patients do not undergo surgery and are only treated with chemotherapy and/or radiotherapy [3, 4]. Owing to delayed diagnosis and limited treatment options, five-year survival rate in pancreatic cancers is extremely low and progress in its improvement has been slow. From 2006 to 2012, five year survival rate in USA was reported to be 9% while current reports shows it to be 9.3% [5, 6]. These data demonstrate immense need of tools for early diagnosis, prognosis prediction and appropriate treatment selection. Recent reports from various parts of the world have shown the key role played by mi-RNAs in initiation, invasion and metastasis of tumors [2].

BIOGENESIS AND FUNCTION OF mi-RNAs:

mi-RNAs were first described by Lee, Feinbaum and Ambros in 1993 as non-coding RNAs which interact with coding RNAs (mRNAs). To date, more than 2500 mi-RNAs have been discovered in humans. mi-RNAs are known to regulate expression of approximately 60% of all genes. Via gene expression regulation, they play essential role in processes such as cell growth, differentiation, apoptosis and immune responses. mi-RNAs are formed by RNA polymerase II dependent transcription. Initially, a stem loop structure, known as pri-miRNA, is produced. RNAse III (Drosha enzyme) and double-strand binding proteins (DGCR8) act on pri-miRNA in order to remove its stem loop and convert it into pre-miRNA. This newly formed structure is exported to cytoplasm via nuclear receptor, Exportin 5. In cytoplasm, action of dicer and Transactivation Response element RNA Binding Protein (TRBP) complex on pre-miRNA generates 18-24 nucleotide double stranded mature mi-RNA where one strand is guide and other passenger strand. In close vicinity to target mRNA, passenger strand is cleaved. Subsequently, guide strand interacts with argonuate proteins that forms RNA-induced Silencing Complex (RISC). Guide strand of mi-RNA in this complex binds to mRNA's complementary sequence. Depending on the extent of complementarity, it leads to translational repression in case of incomplete binding with target mRNA or degradation of mRNA in case of complete binding (Figure 2) [7-9].

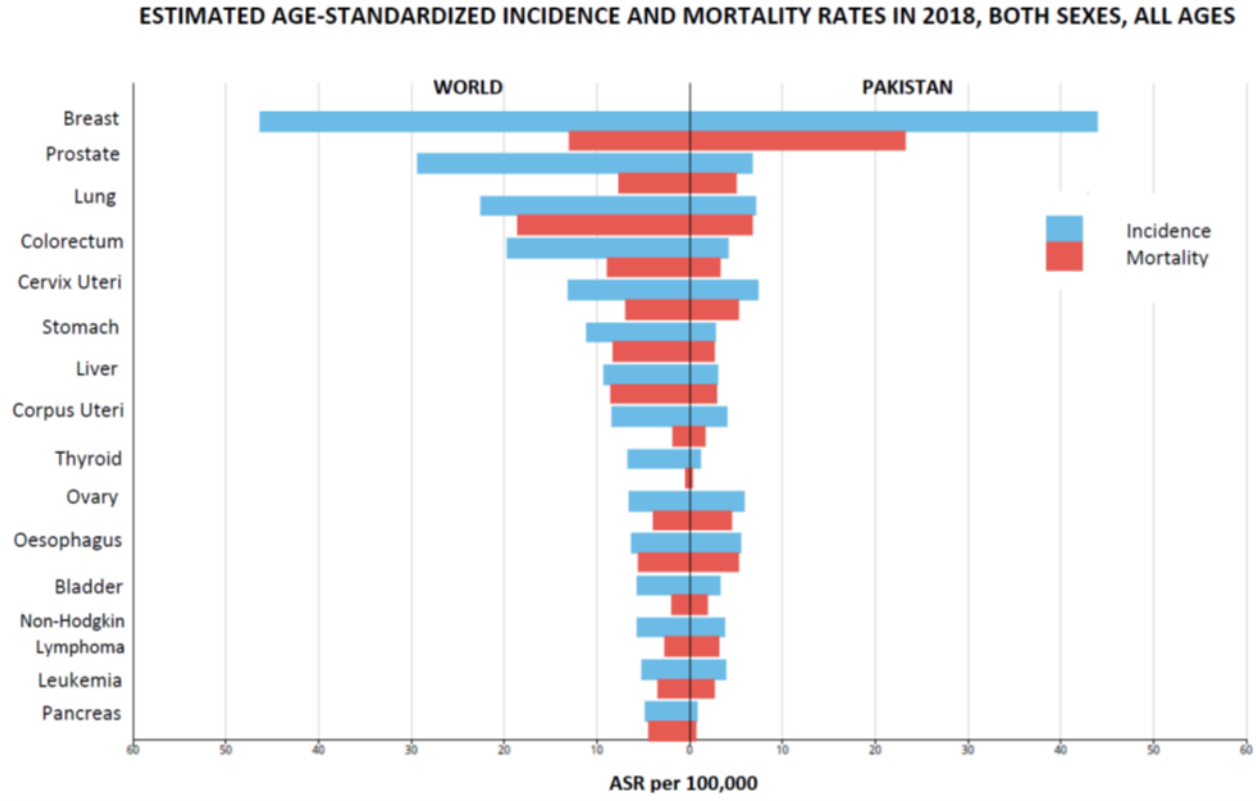


Figure 1: Comparison of Age Standardized Rates for incidence and mortality in global and Pakistani context [1].

mi-RNAs IN CANCERS:

Role of mi-RNAs in cancers was first reported in 2002 by Dr. Croce's group while studying tumor suppressor genes on chromosome 13q14 in B-cell chronic lymphocytic leukemia. Results from the study revealed that this region encoded two mi-RNAs (mi-R 15a and mi-R 16-1). Both mi-RNAs were found to be frequently downregulated in B-cell chronic lymphocytic leukemia due to deletion in the respective genes. Further studies showed that both mi-RNA 15a and mi-RNA 16-1 are tumor suppressors and part of pathways that were involved in inducing cellular apoptosis by BCL-2 repression [10, 11]. Since then, several mi-RNAs have been discovered that perform tumor suppressive or oncogenic functions in various cancers including colorectal, lung, liver, breast and pancreatic cancers [12]. Mechanisms underlying mi-RNAs dysregulation include deletion or amplification of mi-RNA genes, altered regulation at transcriptional level, changes at epigenetic control and alteration in mi-RNA biogenesis. Various studies have experimentally demonstrated that dysregulation of mi-RNAs play significant role in tumor initiation and progression. It also assist mutated cells in achieving cancer hallmarks like evading growth suppressors, apoptosis resistance, sustained proliferation, angiogenesis induction and invasion and metastasis [11].

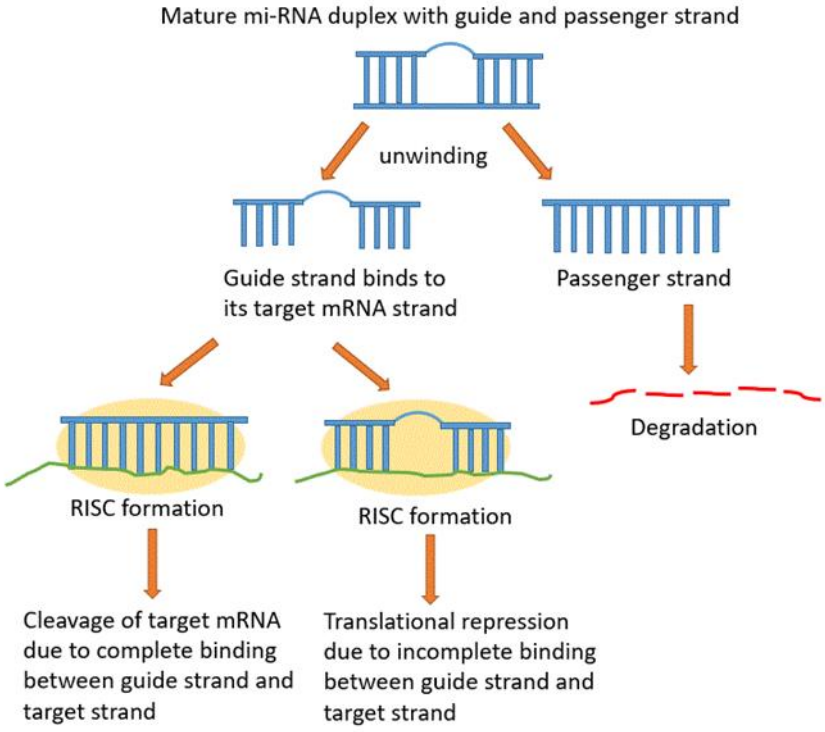


Figure 2: Function of mi-RNAs.

mi-RNAs IN PANCREATIC CANCERS (Table 1):

1. **<u>mi-RNA 200c:</u>**

Studies have shown role of mi-RNA 200c in several neoplasms including melanoma, breast, lung, bladder, pancreatic and colon cancers. mi-RNA 200c may act as oncogenic or tumor suppressor based on organ. Its expression is co related with progression of bladder tumors, metastatic phenotype in colon cancers and

advanced clinical stage in non-small cell lung cancers. It regulates the action of transcription factor ZEB1 (known for promoting EMT) via integrin signaling pathway. On the contrary, its downregulation has been associated with the increasing thickness of melanoma. Decreased expression of mi-RNA 200c is also observed to confer cisplatin resistance in breast adenocarcinoma cells [13, 14].

Therapeutic high expression of mi-R 200c in pancreatic cancer stem cells results in reduction of their colony formation, invasion and chemotherapy resistance. Studies have associated higher expression of mi-R 200c with better survival in pancreatic cancers [12, 15].

2. mi-RNA 124:

mi-RNA 124 is a tumor suppressor RNA and is found to be downregulated in numerous human cancers including hepatocellular carcinoma, breast cancers, pancreatic cancers, prostate cancers, cervical cancers, colorectal cancers, gastric cancers and brain tumors. It is experimentally evident that downregulation of mi-RNA 124 occurs mostly by epigenetic silencing of its gene. In hepatocellular carcinoma, mi-RNA 124 is found to be negatively co-related with aquaporin 3 (AQP3) which is a regulator of NOTCH and AKT signaling. In addition, AQP3 plays role in tumor progression by transport of molecules required for tumor growth. In breast tissues, ZEB2 was found to be direct target of mi-RNA 124. ZEB2, particularly in triple negative breast cancers, confers stem cells like characteristics and aggressiveness to the tumor cells. mi-RNA 124 replacement therapy in these tumor cells reverted the phenotype and limited the proliferation of cells. In prostate cancers, lower expression of mi-RNA 124 was found to be associated with downregulation of p53 and initiation and progression of prostate cancer. Therapeutic overexpression of mi-RNA 124 have shown to increase p53 levels in these tumor cells [16-18].

mi-RNA 124 gene is frequently found methylated in pancreatic cancers. Two important targets of mi-RNA 124 are Ras-related C3 botulinum toxin substrate 1 (Rac1) and MCT1. It has been shown that the downregulation of Rac1 and MCT1 via induced overexpression of mi-RNA 124 inhibits proliferation, invasion and metastasis of pancreatic cancer cells. Another target of mi-RNA 124 is Erythropoietin producing hepatocellular receptor 2 (EphA2). Overexpression of EphA2 in pancreatic cancers promote erlotinib resistance. Therapeutic upregulation of mi-RNA 124 enhances drug sensitivity in these cells and improves clinical outcome in patients [17].

3. mi-RNA 34a:

mi-RNA 34a is one of the strongest candidate for mi-RNA based therapies as it strongly retards Epithelial to Mesenchymal Transition (EMT) and tumor progression. It is regulated by p53 protein and produces its anti-tumor effect in synergy with p53 pathway. mi-RNA 34a is widely downregulated in various cancers such as colorectal cancers, prostate cancers, breast cancers, liver cancers, lung cancers osteosarcoma, hematological malignancies and ovarian cancers. In colorectal and lung cancers, mi-RNA 34a is known to be under expressed because of its promotor hyper methylation. It is associated with inhibition of tumor cell migration and invasion and increased overall survival in colorectal, lungs and breast cancers. According to investigation results, mi-RNA 34a plays significant role in transformation of benign prostate tumors into malignant. Its overexpression in prostate cancers negatively regulate Wnt pathway and subsequently inhibits EMT, invasion and migration [19, 20].

Downregulation of mi-R 34a contributes to pancreatic tumor progression and is significantly co related with its poor prognosis and decreased survival. Therapeutic inventions that over express mi-R 34a in pancreatic cancers have shown significantly suppress NOTCH and BCL2 signaling that subsequently inhibits CD44+ stem cell population, suppress

tumor invasion, induce apoptosis and sensitizes tumor to chemotherapy [21, 22].

4. mi-RNA 222:

mi-RNA 222 is an oncogenic mi-RNA and its high expression is associated with poor Overall Survival (OS) and Disease Free Survival (DFS). Upregulation of mi-RNA 222 is reported in various cancers including gastric cancers, breast cancers, glioma, glioblastoma, hepatocellular carcinoma, bladder cancers and pancreatic cancers. Studies on breast cancers have reported co-relation of high grade and aggressive breast tumor phenotype with enhanced expression of mi-RNA 222. It promotes tumor aggressiveness by promoting G1 to S phase transition in cell cycle. It also accelerates EMT by downregulation of adiponectin receptor 1 (Adipo R1). mi-RNA 222 inhibits RECK in gastric cancers. RECK functions for maintenance of extracellular matrix and regulation of angiogenesis. Breakage of this regulatory circuit leads to enhanced cellular proliferation and colony formation in gastric cancers. In glioblastoma, mi-RNA 222 targets p53 upregulated modulator of apoptosis (PUMA) and Protein Tyrosine Phosphatase μ (PTPμ). As a result, apoptosis is inhibited and tumor invasion is increased [23-25].

In pancreatic cancers, mi-R 222 play significant role in the regulation of p27 protein which is a cell cycle inhibitor. mi-R 222 activates AKT by inhibition of PPP2R2A. This activation of AKT phosphorylates p27 and increases the localization of p27 from nucleus to cytoplasm. Overexpression of mi-R 222 and cytoplasmic p27 have been co-related with malignant phenotype in pancreatic cancers. Significantly high expression of mi-R 222 have been detected in actively invading pancreatic adenocarcinoma cells and have been associated with shorter overall survival of these patients [26, 27]. Studies have shown mi-R 222 to be independent prognosis prediction marker in pancreatic cancers [28].

5. mi-RNA 155:

mi-RNA 155 is highly upregulated in various cancers including liver cancers, pancreatic cancers, leukemia, B cell lymphoma, glioma and lung cancers [29]. Studies have co-related high expression of mi-RNA 155 with poor survival in non-small cell lung cancer and lung adenocarcinoma. It has also been associated with appearance of malignant phenotype in pancreatic cancers [30]. Targets of mi-RNA 155 includes PTEN, PDCD4, SOX6, SMAD5, K-Ras and BCL2. Studies have investigated the role of mi-RNA 155 in therapy resistance. Results show that it is involved in geftinib, cisplatin and doxorubicin resistance in lung cancers while tamoxifen, paclitaxel and doxorubicin resistance in breast cancers. It is also associated with induction of radio-resistance in lung and colorectal cancers [31].

Among several mi-RNAs that are up regulated in pancreatic cancers, one of the most important is mi-RNA 155. Its role is being observed in transformation of pancreatic pre-cancerous lesion into malignant phenotype. It has been experimentally shown that in pancreatic cancers, mi-RNA 155 facilitates the induction of oxidative stress in the cell. Activation of K-Ras pathway leads to transcription of mi-RNA 155 via MAPK and NF- κB signaling. Subsequently, mi-RNA 155 targets FOXO3a and hence decreasing concentration of two important antioxidants; SOD2 and catalase. This causes elevation of ROS (Reactive Oxygen Species) like O_2^- and H_2O_2 hence greater probability of DNA damage and mutations [32]. mi-RNA 155 has also been identified as potential prognostic marker in pancreatic cancers as it's overexpression is significantly associated with decreased overall survival and disease free survival. mi-RNA 155 has also been shown to confer gemcitabine chemo-resistance by inhibition of DCK gene which metabolizes gemcitabine in cells [31, 33].

6. mi-RNA 142-5p:

mi-RNA 142-5p is involved in immune response by regulating expression of various

proteins in tumor cells such as PD-L1, PTEN, Wnt and CYR61. It may play oncogenic or tumor suppressor role based on the type of organ. High expression of mi-RNA 142-5p has been demonstrated in cutaneous squamous cell carcinoma and breast cancers where it targets PTEN and lowers its expression. In breast cancers, its overexpression has been positively co-related with tumor size and metastasis [34, 35]

Its low expression has been co related with tumor recurrence and poor survival in gastric cancers and with tumor progression in colon cancers. Upregulation of mi-RNA 142-5p in pancreatic cancers has been demonstrated to decrease PD-L1 expression on tumor cells and accelerated appearance of T lymphocytes and TNF on tumor site [36]. Its overexpression has also been co-related with longer survival of the pancreatic cancer patients hence mi-RNA 142-5p is a potential prognostic marker [37]. Studies have shown mi-RNA 142-5p as potential biomarker for gemcitabine responsiveness in pancreatic adenocarcinoma patients. Downregulation of mi-RNA 142-5p is associated with gemcitabine resistance in these patients while its overexpression is found to improve patient's survival [2].

7. mi-RNA 137:

It is a tumor suppressor mi-RNA and is downregulated in several cancers such as lung, colorectal, gastric, pancreatic and cervical cancers. mi-RNA 137 inhibits cell proliferation, cell cycle progression and migration via regulation of Wnt/ β-catenin and SRC pathways. It directly targets SRC and paxillin proteins in the cells which are required for invasion and tumor progression [38].

Overexpression of mi-RNA 137 have shown to suppress CD133+ stem cells and decrease tumor invasion in pancreatic cancers [39]. It also induces doxorubicin sensitivity in pancreatic tumor cells which subsequently leads to apoptosis and inhibition of cell survival [40]. Under expression of mi-RNA 137 has also been associated with worse prognosis in pancreatic cancer patients [41].

8. mi-RNA 30b:

mi-RNA 30b functions in the regulation of snail and EGFR pathway. In non-small cell lung cancers overexpression of mi-RNA 30b suppressed proliferation, migration and invasion, enhanced apoptotic signaling and sensitized tumor for tyrosine kinase inhibitor therapy [42]. Decreased expression of mi-RNA 30b has been experimentally shown to predict dismal prognosis in pancreatic carcinoma patients. Via snail pathway, mi-RNA 30b represses cell adhesion and promotes Epithelial to Mesenchymal Transition (EMT). Therapeutic interventions that up regulate the expression of mi-RNA 30b suppress EMT, migration and invasion in pancreatic cancers [43].

9. mi-RNA 301a:

mi-RNA 301a plays role in the regulation of BIM and SOCS5 pathways. BIM is a pro-apoptotic factor while SOCS5 is an inhibitor of JAK/STAT pathway. Overexpression of mi-RNA 301a in cancers has been experimentally demonstrated by various studies. Its enhanced expression, downregulates both BIM and SOCS5 factors. As a result, apoptosis of tumor cells is decreased while JAK/STAT pathway is triggered. The activation of JAK/STAT pathway signals the transcription of various genes responsible for cellular proliferation. This phenotype has been co-related with invasion, migration, angiogenesis and metastasis in various cancers such as melanoma, pancreatic cancers, lung cancers, breast cancers and leukemia [12, 44, 45]. In pancreatic cancers, cells with upregulated mi-RNA 301a are shown to induce EMT via downregulation of cadherin 1 expression. It also confers gemcitabine resistance in these cells [46].

10. mi-R 21:

Overexpression of mi-R 21 has been found to downregulate the tumor suppressing function of BCL-2, PTEN, SMAD7 and PDCD4 in cancers while it acts to upregulate PI3K-AKT signaling. This results in enhanced proliferation and

inhibition of apoptosis in tumor cells [47, 48]. Various studies have shown approximately 3 to 9 fold higher expression of mi-RNA 21 in breast cancers and is also co related with its advanced stage and high ki-67 index [49]. mi-RNA 21 is significantly associated with increased cell growth and invasion in colorectal cancers, gastric cancers and neuroblastoma. Therapeutic inhibition of mi-RNA 21 in gastric cancers has shown to suppress cell proliferation and metastasis [50].

Increased expression of mi-RNA 21 has been associated with tumor size, tumor stage, invasion, poor prognosis and resistance to chemotherapies (5-Flourouracil and gemcitabine) in pancreatic adenocarcinoma. In vitro trials for combination of gemcitabine and anti-sense mi-RNA 21 have been successfully carried out in pancreatic cancers cell lines. These experiments have shown decrease in invasion, migration and metastasis of pancreatic tumor cells [47, 48].

CONCLUSION:

mi-RNAs are critical regulators of important cellular functions like proliferation, survival, differentiation and immune response. Their important role has emerged in various cancers. Some mi-RNAs act specifically as tumor suppressors or oncogenes while role of others depend on the organ of tumor origination. Elucidating the regulatory pathways and targets of these mi-RNAs have potential to provide new directions for cancer diagnosis, prognosis prediction and targeted treatment options. However, despite such vast area for benefits that mi-RNAs possess, lesser number of studies have been published till date. One of the key reasons for this is there are several challenges for studying mi-RNAs in cancers. For cancers with smaller incidence number like pancreatic cancers, it is difficult to get fresh samples. Although, methods have now been developed for RNA extraction from Formalin-Fixed Paraffin Embedded (FFPE) samples but yield is lower as compared to fresh samples. As RNAs are single stranded and extremely prone to disintegration, therefore extraction of RNAs after harsh treatment like FFPE may not always provide accurate results. Another challenge in mi-RNA based studies is the identification of relevant target. Owing to the heterogeneity of mi-RNA expression in tumors, it is difficult to identify significantly important targets. Moreover, tumor heterogeneity should also be taken into account. Biopsy sample from one part of the tumor may provide result for mi-RNA expression with limited scope only. In order to address these challenges, clinicians and molecular biologist will have to work together in order to make possible the availability of fresh tumor samples. In addition, databases and repositories with mi-RNA data needs to be pooled in order to obtain clear picture of altered mi-RNAs and their targets in various cancers. Studies based on panel of mi-RNAs, rather than individual mi-RNAs, may assist in elucidating the consolidated role of various mi-RNAs in cancer and their interaction with each other. Extensive mechanistic studies are also required before moving forward to utilize the maximum potential of mi-RNAs in diagnosis, prognosis prediction and therapeutics of cancers.

Table 1: Important mi-RNAs altered in pancreatic cancers

No.	mi-RNAs	Role	Pathways Involved	Action
1	mi-RNA 200c	Oncogenic or Tumor suppressor based on organ of expression	Integrin signaling	Oncogenic: Increases thickness of melanoma Tumor suppressor:

				Regulates ZEB transcription factor to suppress EMT Sensitizes breast adenocarcinoma cells to cisplatin Decreases tumor cell colony formation, invasion and chemotherapy resistance in pancreatic cancers
2	mi-RNA 124	Tumor suppressor	NOTCH, AKT, p53	Decreases transport of molecules required by tumor cells by lowering the expression of transport protein AQP3 in hepatocellular carcinoma Suppresses stem-like characteristics in breast cancers by targeting ZEB2 Decreases invasion and proliferation in pancreatic

				cancers by targeting Rac1 and MCT1 Sensitizes pancreatic cancer cells to erlotinib by targeting EphA2
3	mi-RNA 34a	Tumor suppressor	p53, Wnt, NOTCH, BCL2	Inhibits proliferation and migration of prostate cancer cells by regulation of Wnt pathway Inhibits CD44+ stem cells, induces apoptosis and suppresses tumor invasion in pancreatic cancers
4	mi-RNA 222	Oncogenic	p53, AKT	In glioblastoma, it targets regulators of p53 hence inhibits apoptosis and increases tumor invasion. Activates AKT which phosphorylates p27 and localizes it to cytoplasm in pancreatic cancers which subsequently increases tumor invasion.

5	mi-RNA 155	Oncogenic	K-Ras, PTEN, PDCD4, SOX6, SMAD5, BCL2, gemcitabine metabolism pathway	In pancreatic cancers, it decreases concentration of antioxidants in cell by targeting FOXO3a which increases ROS species concentration and hence probability of DNA damage. Confers chemo-resistance in lung and breast cancers and radio-resistance in lung and colorectal cancers.
6	mi-RNA 142-5p	Oncogenic or Tumor suppressor based on organ of expression	PD-L1, PTEN, Wnt, CYR61, PD-L1	Oncogenic: In cutaneous squamous cell carcinoma, it targets PTEN and lowers its expression Tumor suppressor: In pancreatic cancers, it targets PD-L1 and lowers its expression which subsequently increases

				action of T-lymphocytes on tumor cells Increases gemcitabine sensitivity in pancreatic tumors
7	mi-RNA 137	Tumor suppressor	Wnt/ β-catenin, SRC	Targets SRC and paxillin proteins in various cancers and decreases tumor invasion and progression Suppresses CD133+ stem cells and induces doxorubicin sensitivity in pancreatic cancer cells
8	mi-RNA 30b	Tumor suppressor	Snail, EGFR	In non-small cell lung cancers, it suppresses invasion, enhances apoptosis and sensitizes cells for tyrosine kinase therapy Represses migration of cells and EMT in pancreatic cancers

9	mi-RNA 301a	Oncogenic	BIM, SOCS5, JAK/STAT, Cadherin 1	Targets BIM in melanoma, pancreatic cancers, lung cancers, breast cancers and leukemia and decreases apoptotic signaling Triggers JAK/STAT pathway in melanoma, pancreatic cancers, lung cancers, breast cancers and leukemia by targeting its inhibitor which subsequently increases cell proliferation Enhances EMT in pancreatic cancers by downregulating cadherin 1
10	mi-RNA 21	Oncogenic	BCL-2, PTEN, SMAD7, PDCD4, PI3K-AKT	Targets BCL-2 and amplifies anti-apoptotic signals in the cells

				Triggers PI3K-AKT pathway to increase cell proliferation Associated with tumor size, tumor stage, invasion, poor prognosis and resistance to chemotherapies (5-Flourouracil and gemcitabine) in pancreatic adenocarcinoma

REFERENCES

1. Globocan. (2018). Accessed: Aug 22, 2019: https://gco.iarc.fr/today/.
2. Rawat M, Kadian K, Gupta Y, et al. MicroRNA in pancreatic cancer: from biology to therapeutic potential. Genes. 2019, 10: 752.
3. Kamarajah SK, Burns WR, Frankel TL, Cho CS and Nathan H. Validation of the American Joint Commission on Cancer (AJCC) staging system for patients with pancreatic adenocarcinoma: a Surveillance, Epidemiology and End Results (SEER) analysis. Ann. Surg. Oncol. 2017, 24: 2023-2030.
4. Neoptolemos JP, Kleeff J, Michl P, et al. Therapeutic developments in pancreatic cancer: current and future perspectives. Nat. Rev. Grastroenterol. Hepatol. 2018, 15: 333.
5. SEER Database. Accessed on: October 4, 2020. https://seer.cancer.gov/statfacts/html/pancreas.html .
6. American Cancer Society. Accessed on: October 20,2020. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2017/cancer-facts-and-figures-2017.pdf.
7. Michlewski G and Cáceres JF. Post-transcriptional control of miRNA biogenesis. RNA. 2019, 25: 1-16.
8. Qadir MI and Faheem A. miRNA: a diagnostic and therapeutic tool for pancreatic cancer. Crit. Rev. Eukaryot. Gene Expr. 2017, 27.
9. Vos PD, Leedman PJ, Filipovska A, et al. Modulation of miRNA function by natural and synthetic RNA-binding proteins in cancer. Cell. Mol. Life. Sci. 2019: 1-8.
10. Paul P, Chakraborty A, Sarkar D, et al. Interplay between miRNAs and human diseases. J. Cell. Physiol. 2018, 233: 2007-2018.
11. Peng Y and Croce CM. The role of microRNAs in human cancer. Signal Transduct. Target Ther. 2016, 1: 15004.
12. Tesfaye AA, Azmi AS and Philip PA. miRNA and gene expression in pancreatic ductal adenocarcinoma. Am. J. Pathol. 2019, 189: 58-70.

13. Chen Y and Zhang L. Members of the microRNA-200 family are promising therapeutic targets in cancer. Exp. Ther. Med. 2017, 14: 10-17.
14. Yin Y, Song WW, Wang Y, et al. MicroRNA-200 families and prognostic value in various carcinomas: a systematic review and meta-analysis. Aging Med. 2018, 1: 39-45.
15. Lv Y and Huang S: Role of non-coding RNA in pancreatic cancer. Oncol. Lett. 2019, 18: 3963-3973.
16. Di Gennaro A, Damiano V, Brisotto G, et al.: A p53/miR-30a/ZEB2 axis controls triple negative breast cancer aggressiveness. Cell Death Differ. 2018, 25: 2165.
17. Jia X, Wang X, Guo X, et al. MicroRNA-124: an emerging therapeutic target in cancer. Cancer Med. 2019, 8: 5638-5650.
18. Marlar S, Jensen HH, Login FH, et al. Aquaporin-3 in cancer. Int. J. Mol. Sci. 2017, 18: 2106.
19. Xu M, Li D, Yang C, et al. MicroRNA-34a inhibition of the TLR signaling pathway via CXCL10 suppresses breast cancer cell invasion and migration. Cellular Physiol. Biochem. 2018, 46: 1286-1304.
20. Zhang L, Liao Y and Tang L. MicroRNA-34 family: a potential tumor suppressor and therapeutic candidate in cancer. J. Exp. Clin. Cancer Res. 2019, 38: 53.
21. Tang Y, Tang Y and Cheng Y. miR-34a inhibits pancreatic cancer progression through snail1-mediated epithelial–mesenchymal transition and the notch signaling pathway. Sci. Rep. 2017, 7: 38232.
22. Li Y and Sarkar FH. MicroRNA targeted therapeutic approach for pancreatic cancer. Int. J. Biol. Sci. 2016, 12: 326.
23. Liu K, Wang L and Sun E. Prognostic value of miR-221 in human malignancy: evidence from 3041 subjects. BMC cancer. 2019, 19:867.
24. Ravegnini G, Cargnin S, Sammarini G, et al. Prognostic role of miR-221 and miR-222 expression in cancer patients: a systematic review and meta-analysis. Cancers. 2019, 11: 970.
25. Wei T, Ye P, Peng X et al. Prognostic value of miR-222 in various cancers: a systematic review and meta-analysis. Clin Lab. 2016, 62: 1387-1395.
26. Lee C, He H, Jiang Y, et al. Elevated expression of tumor miR-222 in pancreatic cancer is associated with Ki67 and poor prognosis. Med. Oncol. 2013, 30: 700.
27. Li Z, Tao Y, Wang X, et al. Tumor-secreted exosomal miR-222 promotes tumor progression via regulating P27 expression and re-localization in pancreatic cancer. Cell. Physiol. Biochem. 2018, 51: 610-629.
28. Song J, Ouyang Y, Che J, et al. Potential value of miR-221/222 as diagnostic, prognostic, and therapeutic biomarkers for diseases. Front. Immunol. 2017, 8: 56.
29. Rupaimoole R and Slack FJ. MicroRNA therapeutics: towards a new era for the management of cancer and other diseases. Nat. Rev. Drug Discov. 2017, 16: 203.
30. Trang P, Weidhaas JB and Slack FJ: MicroRNAs and cancer: the molecular basis of human cancer. Springer; 2017: 277-286.
31. Bayraktar R and Van Roosbroeck K. miR-155 in cancer drug resistance and as target for miRNA-based therapeutics. Cancer. Metastasis Rev. 2018, 37: 33-44.
32. Wang P, Zhu C-f, Ma M-z, et al. Micro-RNA-155 is induced by K-Ras oncogenic signal and promotes ROS stress in pancreatic cancer. Oncotarget. 2015, 6: 21148.
33. Hasan S, Jacob R, Manne U, et al. Advances in pancreatic cancer biomarkers. Oncol. Rev. 2019, 13.
34. Bai X, Zhou Y, Chen P, et al. MicroRNA-142-5p induces cancer stem cell-like properties of cutaneous squamous cell carcinoma via inhibiting PTEN. J. Cell. Biochem. 2018, 119: 2179-2188.
35. Xu W and Wang W. MicroRNA-142-5p modulates breast cancer cell proliferation and apoptosis by targeting phosphatase and tensin homolog. Mol. Med. Rep. 2018, 17: 7529-7536.
36. Jia L, Xi Q, Wang H, et al. miR-142-5p regulates tumor cell PD-L1 expression and enhances anti-tumor immunity. Biochem. Biophys. Res. Commun. 2017, 488: 425-431.
37. Yao R, Xu L, Wei B, et al. miR-142-5p regulates pancreatic cancer cell proliferation and apoptosis by regulation of RAP1A. Pathol. Res. Pract. 2019, 215: 152416.
38. Kokuda R, Watanabe R, Okuzaki D, et al. Micro RNA-137-mediated src oncogenic signaling promotes cancer progression. Genes Cells. 2018, 23: 688-701.
39. He Z, Guo X, Tian S, et al. MicroRNA-137 reduces stemness features of pancreatic cancer cells by targeting KLF12. J. Exp. Clin. Cancer Res. 2019, 38: 126.
40. Wang Z-C, Huang F-Z, Xu H-B, et al. MicroRNA-137 inhibits autophagy and chemosensitizes pancreatic cancer cells by targeting ATG5. Int. J. Biochem. Cell Biol. 2019, 111: 63-71.

41. Ding F, Zhang S, Gao S, et al. MiR-137 functions as a tumor suppressor in pancreatic cancer by targeting MRGBP. J. Cell. Biochem. 2018, 119: 4799-4807.
42. Qi Z, Zhang B, Zhang J, et al. MicroRNA-30b inhibits non-small cell lung cancer cell growth by targeting the epidermal growth factor receptor. Neoplasma. 2018, 65: 192-200.
43. Xiong Y, Wang Y, Wang L, et al. MicroRNA-30b targets snail to impede epithelial-mesenchymal transition in pancreatic cancer stem cells. J. Cancer. 2018, 9: 2147.
44. Hu H, Zhang Q, Chen W, et al. MicoRNA-301a promotes pancreatic cancer invasion and metastasis through the JAK/STAT3 signaling pathway by targeting SOCS5. Carcinogenesis. 2019.
45. Zheng J-Z, Huang Y-N, Yao L, et al. Elevated miR-301a expression indicates a poor prognosis for breast cancer patients. Sci. Rep. 2018, 8: 2225.
46. Funamizu N, Lacy CR, Kamada M, et al. MicroRNA-200b and-301 are associated with gemcitabine response as biomarkers in pancreatic carcinoma cells. Int. J. Oncol. 2019, 54: 991-1000.
47. Baradaran B, Shahbazi R and Khordadmehr M. Dysregulation of key microRNAs in pancreatic cancer development. Biomed. Pharmacother. 2019, 109: 1008-1015.
48. Słotwiński R, Lech G and Słotwińska SM. MicroRNAs in pancreatic cancer diagnosis and therapy. Cent. Eur. J. Immunol. 2018, 43: 314.
49. Elghoroury EA, ElDine HG, Kamel SA et al. Evaluation of miRNA-21 and miRNA Let-7 as prognostic markers in patients with breast cancer. Clin. Breast Cancer. 2018, 18: e721-e726.
50. Dan J, Wang J, Wang Y, et al. LncRNA-MEG3 inhibits proliferation and metastasis by regulating miRNA-21 in gastric cancer. Biomed. Pharmacother. 2018, 99: 931-938.