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Clinical implications of miRNAs in the pathogenesis, diagnosis and therapy of pancreatic cancer☆

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ABSTRACT

Despite considerable progress being made in understanding pancreatic cancer (PC) pathogenesis, it still remains the 10th most often diagnosed malignancy in the world and 4th leading cause of cancer related deaths in the United States with a five year survival rate of only 6%. The aggressive nature, lack of early diagnostic and prognostic markers, late clinical presentation, and limited efficacy of existing treatment regimens make PC a lethal cancer with high mortality and poor prognosis. Therefore, novel reliable biomarkers and molecular targets are urgently needed to combat this deadly disease. MicroRNAs (miRNAs) are short (19–24 nucleotides) non-coding RNA molecules implicated in the regulation of gene expression at post-transcriptional level and play significant roles in various physiological and pathological conditions. Aberrant expression of miRNAs has been reported in several cancers including PC and is implicated in PC pathogenesis and progression, suggesting their utility in diagnosis, prognosis and therapy. In this review, we summarize the role of several miRNAs that regulate various oncogenes (KRAS) and tumor suppressor genes (p53, p16, SMAD4, etc.) involved in PC development, their prospective roles as diagnostic and prognostic markers and as a therapeutic targets.

Contents

Abbreviations: AKT, protein kinase B; ALDOA, Aldolase A fructose-bisphosphate; Axl, AXL Receptor tyrosine kinase; BCL2, B-cell CLL/lymphoma 2; c-abl oncogene 1, non-receptor tyrosine kinase; CA19.9, Carbohydrate antigen 19.9; CCND1, Cyclin D1; CDC25B, Cell division cycle 25B; ABL-1, CDKN1C: Cyclin-dependent kinase inhibitor 1C; CDC7, Cell division cycle 7; CDK4, Cyclin-dependent Kinase 4; CDK6, Cyclin-dependent Kinase 6; CLL, Chronic Lymphocytic Leukemia; c-Met, Met proto-oncogene; c-MYC, v-Myc avian myelocytomatosis viral oncogene homolog; CUL5, Cullin 5; DNMT1, DNA methyltransferase; E2F1, E2F transcription factor 1; EMT, Epithelial–mesenchymal transition; EZH2, enhancer of zeste 2 polycomb repressive complex 2 subunit; FGF7, Fibroblast growth factor 7; GEM models, Genetically engineered mouse models; GLI1, GLI family zinc finger 1; GTP, Guanosine Triphosphate; HDM4, Mouse Double Minute 4 Human Homolog of P53-binding Protein; HIF-1α/β, Hypoxia inducible factor-1 α/β; HPDE, Human pancreatic ductal epithelial cells; INK4A (p16), Cyclin-dependent kinase inhibitor 2A; Jag1, Jagged 1; Jak2, Janus kinase 2; Kras, V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; LATS2, large tumor suppressor kinase 2; LDH, Lactate dehydrogenase; LOH, Loss of heterozygosity; MAD2L1, MAD2 mitotic arrest deficient-like 1 (yeast); Maml1/2, mastermind-like co-activators ½; MEK, Mitogen-activated protein kinase; miRNA, microRNA; MDM2, Mouse Double Minute 2; Nanog, Nanog homeobox; n-MYC, v-Myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog; NSCLC, Non-small cell lung cancer; PanIN, Pancreatic Intraepithelial Neoplasm; P15, Cyclin-dependent kinase inhibitor 2B; p21, Cyclin-dependent kinase inhibitor 1A; PC, Pancreatic cancer; PDAC, Pancreatic Ductal Adenocarcinoma; PDCD4, Programmed cell death 4; PI3K, Phosphatidylinositol-4,5-bisphosphate 3-kinase; PIP3, Phosphatidylinositol (3,4,5)-trisphosphate; PKC, Protein kinase C; PTEN, Phosphatase and tensin homolog; PP2A, Serine/threonine protein phosphatase 2A; PUMA, P53 Up-Regulated Modulator of Apoptosis; RAF, Raf/mil family of serine/threonine protein kinases; RREB1, RAS-responsive element-binding protein; Shh, Sonic Hedgehog; Spry2, Sprouty homolog 2; FNAs, fine needle aspirations; STAT3, Signal transducer and activator of transcription 3; SIRT1, Sirtuin 1; SMAD4, SMAD family member 4; SNAIL, Snail family zinc finger 1; TGF-β, Transforming growth factor beta; TGFβRI, Transforming growth factor beta Receptor I; TGFβRII, Transforming growth factor beta Receptor II; TPI1, Triosephosphate isomerase 1; TP53, Tumor suppressor p53; Wnt, Wnt oncogene analog; WNT3A, Wingless-type MMTV integration site family member 3A; ZEB1, Zinc finger E-box binding homeobox 1; ZNF652, Zinc finger protein 652; 3′UTR, 3′ Untranslated region.

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