

Elevated expression of microRNAs 155, 203, 210 and 222 in pancreatic tumors is associated with poorer survival

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Pancreatic cancer is the eighth most common cancer and has an overall 5-year survival rate lower than 10%. Because of their ability to regulate gene expression, microRNAs can act as oncogenes or tumor-suppressor genes and so have garnered interest as possible prognostic and therapeutic markers during the last decade. However, the prognostic value of microRNA expression in pancreatic cancer has not been thoroughly investigated. We measured the levels of miR-155, miR-203, miR-210, miR-216, miR-217 and miR-222 by quantitative RT-PCR in a cohort of 56 microdissected pancreatic ductal adenocarcinomas (PDAC). These microRNAs were chosen as they had previously been shown to be differentially expressed in pancreatic tumors compared to normal tissues. The possible association of microRNA expression and patients' survival was examined using multivariate Cox's regression hazard analyses. Interestingly, significant correlations between elevated microRNA expression and overall survival were observed for miR-155 (RR = 2.50; $p = 0.005$), miR-203 (RR = 2.21; $p = 0.017$), miR-210 (RR = 2.48; $p = 0.005$) and miR-222 (RR = 2.05; $p = 0.035$). Furthermore, tumors from patients demonstrating elevated expression levels of all 4 microRNAs possessed a 6.2-fold increased risk of tumor-related death compared to patients whose tumors showed a lower expression of these microRNAs. This study provides the first evidence for an oncogenic activity of miR-155, miR-203, miR-210 and miR-222 in the development of pancreatic cancer as has been reported for other tumor types. Furthermore, the putative target genes for these microRNAs suggest a complex signaling network that can affect PDAC tumorigenesis and tumor progression.

Because of its poor prognosis, pancreatic cancer is one of the leading causes of cancer-related death, despite its relative low incidence with 9 cases per 100,000 people.¹ The poor prognosis of patients is a result of the late clinical presentation and the high metastatic potential. Three-fourths of pancreatic carcinomas are ductal adenocarcinomas (PDAC).²

There are molecular prognostic markers known for pancreatic cancers. For example, higher levels of protein expression of VEGF or EGFR have been shown to associate with

poorer survival rates.³ Besides non-physiological KRAS activation, which is mutated in about 95% of all pancreatic carcinomas,⁴ inactivation of known tumor-suppressor genes such as p53 or SMAD4 (deleted in 75% or 55% of all PDACs, respectively) have been demonstrated.^{5,6}

MicroRNAs are small, non-coding RNAs of endogenous origin, which mainly function as negative regulators of gene expression. The association of altered microRNA expression with cancerogenesis as well as tumor progression is well established.⁷⁻⁹ There is a growing number of microRNAs, which are classified as oncogenes or tumor-suppressor genes.¹⁰ For instance, miR-17-92-cluster has gained interest by being regulated via c-myc and its ability to accelerate tumor formation.^{11,12} Also, let-7 expression was described to correlate with a poor prognosis when being underexpressed in adenocarcinomas of the lung.¹³ Furthermore, the miR-15-16 cluster targeting BCL-2 was shown to be down-regulated in chronic lymphocytic leukemia (CLL) and to contribute to tumor progression.¹⁴ Altogether, misregulated expression of microRNAs seems to have a major impact on tumor progression and prognosis in many malignancies.

Interestingly, recent studies have demonstrated that the expression of a subset of microRNAs varies in tumors compared to normal tissues and tumors derived from other

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