Diagnosis and therapies with miRNAS in Pancreatic Ductal Adenocarcinoma

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Introduction

Pancreatic Ductal Adenocarcinoma (PDAC) it's one of the most lethal carcinomas. The overall median survival is 2–8 months, and only 1%–4% of all the patients with PDAC survive for more than 5 years. The epithelial-mesenchymal transition (EMT) it's a process in which the epithelial cells change their properties into motile mesenchymal cells playing an important role in conferring metastatic properties in many solid tumors like the PDAC. Both processes, PDAC and EMT, have aberrant expressions of transcription factors and miRNAs, molecules that control the cell cycle, apoptosis, differentiation, proliferation and response to cellular stressors. The aim of this final degree project it's make a revision of the different transcription factors and miRNAs involved in this two processes and propose a few therapies and diagnostics, based in measuring and controlling the expression of miRNAs, that can help to make an early diagnostic of the PDAC and control or stop the development of the disease.

Pancreatic ductal adenocarcinoma

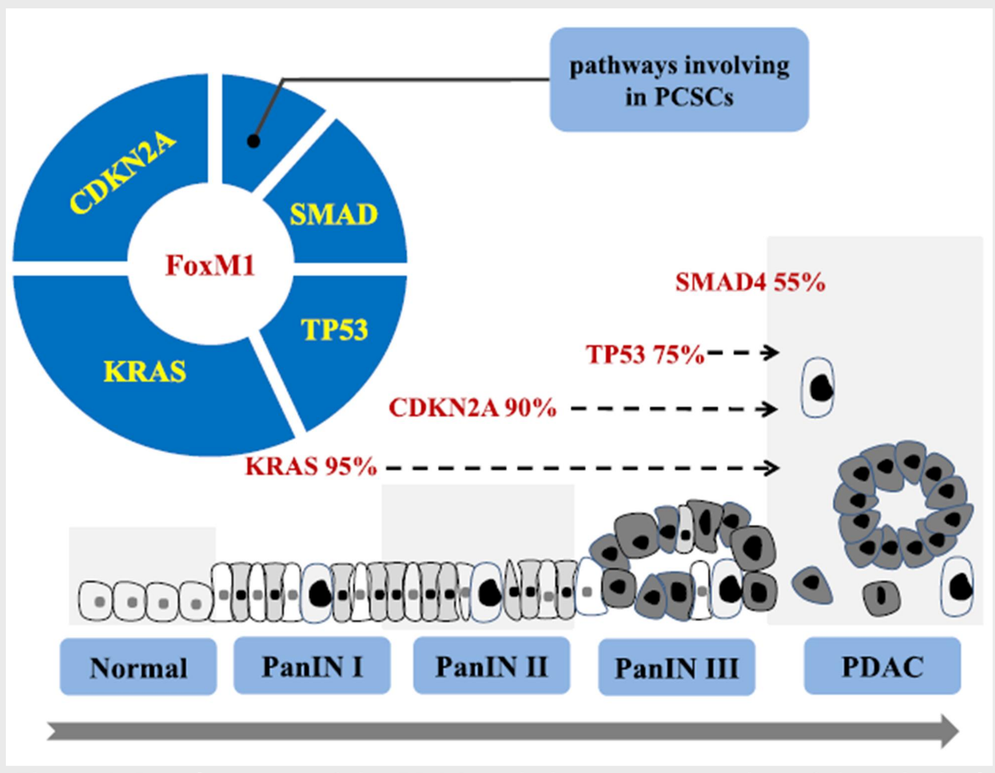

Figure 1. Development of the PDAC and aberrant expression of the principal genes involved.

Due to the action of different signaling pathways controlled by the transcription factor FOXM1 the PanIN could develop to PDAC. There is an aberrant expression of the gens controlled by FOXM1 (KRAS,TP53, CDKN2A, and SMAD4) during the different states of the lesion, which at the end could become PDAC. Also there are some miRNAs that have an altered expression, such as miR-21, miR-34a,miR-155 and the family of miR-200.

Epithelial to Mesenchymal transition

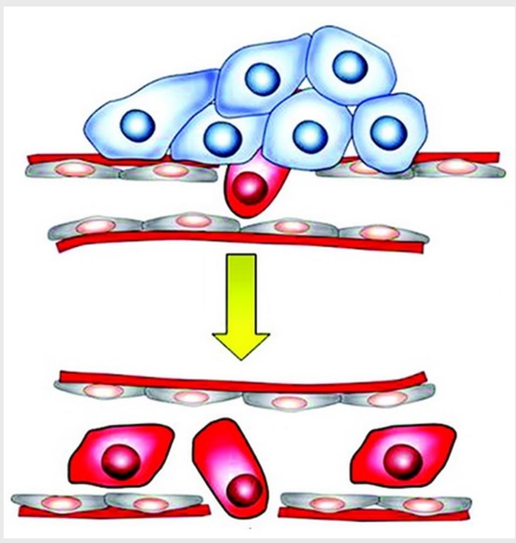

Figure 2. Schema of the complex metastatic process. Epithelial–mesenchymal transition (EMT) alters the cell phenotype to allow intravasation into the systemic circulation.

The process of EMT alters the integrity of cell–cell junctions, promoting loss of polarity and epithelial markers, resulting in loss of contact between neighboring cells. Due to this process, tumor cells become more mesenchymal-like, exhibiting higher migratory and invasive properties that allow them to interact with the extracellular matrix and invade surrounding tissues promoting metastasis. The principal families of transcription factors involved in this process are Snail, BhLH, ZEB and the transcription factor VEGF-β. Also there is an alteration in some miRNAs like miR-1, miR-29b, miR-34a, and the family of miR-200

Materials and methods

The samples for study the possible diagnosis of PDAC were obtained of PDAC tissues. Firstly was made an RNA extraction, and after it were used the methods of quantitative real-time PCR and microarray technology for detect the miRNAs overexpressed.

For study possible therapies against PDAC were used the cell lines L3.6pl and Hs776T and the antagomirs miR-10b, miR-21, miR-221 and miR-222. The methods used include, encapsulation of antagomirs in lipoplexes, RNA extraction and quantitative real-time PCR.

Diagnostic and therapies

- The change in the expression of the miRNAs can be used in the diagnostic of the pancreatic cancer. A recent study showed that miR-21 and miR-34a are the most useful miRNAs as biomarkers. The results demonstrated that high expression of miR-21 and down expression of miR34a is related with poor prognosis of the pancreatic cancer. Also the upregulation of miR-221/222 miRNAs promotes the proliferation of tumors in PDAC cell lines.
- In another study was evaluated the utility of miR-21, miR-34a, miR-198 and miR-217 as diagnostic and prognostic biomarkers of PDAC. The results showed an increase in the levels of miR-21 and miR-198 and a decreased level of miR-217 in the PDAC tissue.The high levels of miR-21 and miR-198 were significantly correlated with poor prognosis. Furthermore, the high expression of miR-21 was related with a poor response to the chemotherapeutic agent gemcitabine.
- Recent studies showed that is possible to inhibit the expression of miRNAs using antagomirs. A combined therapy using antagomirs against miR-21 and miR-221 lead to a change of the expression in more than 1300 genes in a highly metastatic human pancreatic cancer cell line (L3.6pl), and reduced the proliferation and invasion of this tumor cells and also helps to the reconstitution of sensitivity to different chemotherapeutic agents like 5-fluoracil or gemcitabine.
- Another therapeutic option using antagomirs was founded, using lipoplexes containing antagomirs against miR-21, miR-221 and miR-221. The results of the work showed that the administration of a nanosystem called, HSA-EPOPC:Chol/AMOs (+/-) has the ability of efficiently deliver the antagomirs into the tumor cells of PDAC. These administrated antagomirs achieved and almost total inhibition of the principal miRNAs involved in pancreatic cancer, such as miR-21, miR-221, and miR-222; aberrantly expressed in this cancer model.

Conclusions

- The EMT it's a crucial process in the developing of PDAC, and controlling the principal pathways involved on it could be the key for cure the disease.
- The results of these recent studies showed that the most useful miRNAs for the diagnosis and prognosis of the PDAC are the miR-21, miR-34a, miR-198 and the miR-200 family.
- Antagomirs against the miRNA-21 and the family of miRNA-200 are showing promising reduction of the cell viability and could be a suitable therapy in the future.

References

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