Introduction: Pancreatic cancer is one of the leading causes of cancer-related mortality worldwide and is highly therapy-resistant to standard chemotherapy including gemcitabine. Glucocorticoids like dexamethasone (DEX) are often co-administered to reduce inflammation and side effects of tumor growth and therapy. Our group previously showed DEX to be a potent stimulator of epithelial to mesenchymal transition (EMT), cancer progression and metastasis, but the underlying mechanisms were not completely understood. MicroRNAs are a group of small non-coding RNAs that post transcriptionally regulate gene expression. They have been shown to affect several processes, including cancer. In this study, we evaluated the effect of DEX on the microRNA expression profile of pancreatic cancer cell lines with the aim of finding out if miRNAs play a role in modulating the DEX-induced phenotype.

Material and Methods: RNA was isolated at different time points after dexamethasone treatment. RNA was then labeled and hybridized to the Illumina Human miRNA Microarray (Release 21). miRNA data was analyzed using the LIMMA protocol. Differentially expressed miRNAs were validated by qRT-PCR. Potential targets of the selected miRNAs were identified in silico using TargetScan. Interaction of the miRNA with the 3′UTR of the predicted miRNAs was confirmed with 3′UTR reporter gene assays, and target site binding specificity by site-directed mutagenesis. The effect of miRNA expression on target expression was evaluated by qRT-PCR and Western blotting for miRNA and protein expression, respectively. Functionally, migration was assessed using the wound healing assay, and the ability of single cells to form colonies was assessed in soft agar. Wt experiments were performed with the chick embryo model. ASANPACA cells transfected with 50nM miR-XYZ and treated with 1μM DEX, transplanted on day 9 into eggs, injected IV on day 14 with mimics and lipofectamin to maintain miRNA expression.

Conclusion: miR-XYZ is the most significantly DEX deregulated miRNA in pancreatic cancer cell lines and targets key members of the TGF-beta pathway, specifically TGFβ-2. miR-XYZ significantly reduced proliferation, migration and colony formation of pancreatic cancer cells in vitro and in vivo. It reduced tumor xenograft growth. miR-XYZ is a potential tumor suppressor miRNA in pancreatic cancer.

Outlook: We are working on assessing the expression of miR-XYZ in patient tissues and identifying the impact of miR-XYZ on drug resistance. Furthermore we are working towards confirming our in vitro findings in a mouse model.

Acknowledgment: We thank the microarray unit of the DKFZ Genomics and Proteomics Core Facility for providing the miRNA profiling and related services. This study was supported by Heidelberger Stiftung Chirurgia.

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