Alia Abukiwan

Dexamethsone –Induced microRNA Regulation of Pancreatic Cancer Progression

Fach/Einrichtung: Chirurgie

Doktormutter: Prof. Dr. rer. nat. Ingird Herr

Summary

Glucocorticoids (GCs) like dexamethasone (DEX) are involved in the modulation of multiple signaling pathways and their use in pancreatic ductal adenocarcinoma (PDA) has been shown to enhance rather than curtail tumor progression. I hypothesized that miRNAs could be instrumental to the tumor supporting phenotype and towards this end, performed a genome wide miRNA profiling to discern the differentially regulated miRNAs and explore how they may impact the tumor phenotype in PDA. My miRNA microarray showed 268 microRNAs to be differentially expressed between DEX-treated and control PDA cell lines. Of these, miR-132 was found to be one of the most significantly downregulated miRNAs, which directly targeted TGFß-2 as confirmed by luciferase assay and Western blot analyses. Strikingly, TGFß-2 is a member of TGFß signaling pathway and is a master regulator of EMT progression. EMT characteristics were reversed through overexpression of miR-132 in PDA cell lines *in vitro* and *in vivo*. Moreover, enhanced expression of miR-132 inhibited migration, colony formation, and proliferation *in vitro*, as well as reduced the tumor size *in vivo*. Finally, I demonstrated that the DEX-induced suppression of miR-132 was achieved by hypermethylation of the miR-132 promoter. In conclusion, this study shows that miR-132 is a downstream mediator of DEX activity with resultant effects on tumor cell aggression. The co-administration of a miR-132 mimic could be used to curtail the pro-tumorigenic side effects of DEX activity in future co-medication to cancer patients.