The role of the EMT transcription factor Zeb1 in early and late steps of pancreatic cancer

Isabell Frisch[1]
[1]***AG Brabletz, Experimentelle Medizin I, Nfz Erlangen, FAU Erlangen Nürnberg, Erlangen, Germany***

Pancreatic ductal adenocarcinoma (PDAC) is one of the deadliest human cancers with a 5-year survival rate of 3%. PDAC is characterized by rapid progression, metastasis and resistance to treatment. The early mechanisms in pancreatic cancer development still need to be determined in order to understand the rapid progression of PDAC and to establish more effective regimens. Activation of the epithelial-mesenchymal transition program (EMT) is a major driver of tumor progression from initiation to metastasis. We have recently shown that the EMT transcription factor Zeb1 is driving the formation of precursor lesions, invasion and metastasis in a genetic mouse model of PDAC with mutant Kras and p53 expression (KPC mice). We observed that additional Zeb1 deletion reduced grading, invasion and distant metastasis in KPC mice. To further address the role of Zeb1 during tumor initiation and formation of precancerous lesions we now utilize a mouse model with only mutant Kras but wild type p53 (KC mice) which results in a slower tumor progression and limits acquisition of hypermutations. These mice recapitulate the formation and progression of human pancreatic intraepithelial neoplasias (PanINs), which are thought to be direct precursors to PDAC. Histological analysis of KC mice show that the number and grade of PanINs increase over time and a low number of spontaneously progressed PDACs could be observed after one year of age. Interestingly, additional pancreas-specific depletion of Zeb1 in KC mice results in significantly fewer and lower grade PanINs compared to KC controls indicating that Zeb1 not only promotes EMT in full-blown tumors but also facilitates the formation and progression of precancerous lesions. The underlying EMT independent molecular mechanisms are currently investigated.