7 Summary

Pancreatic cancer is one of the most aggressive diseases. Sequential stages of disease initiation and progression are characterized by activating mutations in oncogenes (e.g. *K-Ras*) and functional inactivation of tumor suppressor genes (e.g. *p16*, *p53*, *DPC4*), which may be inherited or acquired. At least one of these genes is altered in pancreatic ductal carcinomas. Because of these alterations important regulatory functions such as cell cycle control, maintenance of genome integrity, expression of growth factors and their receptors are severely perturbed, allowing pancreatic cell transformation to occur. Mutations in the proto-oncogene *K-Ras* and in the tumor suppressor gene *p53* play an important role and their effects on tumorigenecity, invasiveness, angiogenesis and metastasis have been difficult to determine for pancreatic adenocarcinoma in the organ context. The current work has therefore adapted an inducible strategy of stage specific reexpression of the tumor suppressor p53 with an *in vivo* orthotopic mouse model of pancreatic cancer. The first part of this thesis focused on establishing stable pancreatic carcinoma cell lines with inducible expression of wild type (wt) p53 protein by adding doxycycline (dox) to the media of the cells. This approach resulted in controlled reconstitution of wt p53 function in DanG- and MiaPaCa-2-cells, causing a G1 cell cycle arrest with prominent induction of the cell cycle inhibitor p21 and no evidence of apoptosis induction. In the second part of this thesis the effects of inducible wt p53 expression of growth of MiaPaCa-2 orthotopic xenografts in nu/nu mice was studied. Dox treatment of mice directly after cell implantation as well as in already established tumors significantly inhibited the growth of orthotopic tumors. Furthermore a reduction of macroscopically detected abdominal metastasis was noted in dox treated animals during autopsy. In addition, dox treatment at an early time point of tumor growth led to a significant increase in the number of CD31 and Lyve1 stained vessels, suggesting a pro-angiogenic effect of wt p53 induction. This observation was in good agreement with an increased rate of micro-metastases in liver hilus lymph nodes in dox treated animals. Dox treatment of mice at a later time point of tumor development did not significantly affect the number of CD31 reactive vessels, but again increased lymphatic vessel density. Taken together our observations confirm the established tumor suppressive function of p53 in an orthotopic model of pancreatic cancer. In addition, the increased number of lymphatics and a concomitant increase of micrometastases suggest, that p53 induction affected the biology of different tumor constituents of pancreatic cancer in a complex manner. Our observation suggests that the combination of the inducible system with an orthotopic model can yield important insights into the in vivo tumor biology of pancreatic cancer.