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Dr. sc. hum.

Development of a prognostic model for pancreatic cancer on fertilized chicken eggs

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Pancreatic adenocarcinoma is one of the deadliest cancers worldwide with poor prognosis and insufficient therapeutic options. Therefore, new personalized diagnostic models are urgently needed. Mouse xenograft models for personalized tumor copies derived from patient tissue are widely used for therapy studies, but the tumor growth often needs months, animal experiments have high administrative barriers and are expensive. I examined xenotransplantation of freshly resected pancreatic cancer tissue to fertilized chicken eggs as a promising mammalian replacement method. I transplanted 58 freshly resected pancreatic patient tissues on chicken eggs including 38 PDAs, 2 neuroendocrine tumors, 7 IPMNs, 3 malignant IPMNs, one PanIN, one chronic pancreatitis, one Franz tumor and 5 benign cystadenomas. Therein, a significant correlation between the grafting efficiency of malignant and benign tissue was observed, when the overall data from my colleagues and me were evaluated. For expansion of the primary tissue for therapeutic screening I developed different strategies. For the first subtransplantation strategy, freshly resected patient tissue was digested to obtain spheroids before transplantation on eggs. This step was repeated for further expansion of egg xenografts. But the engraftment stopped at serial passage 3 and no increase in the tumor volume over the passages was observed. With the second strategy an increase in total tumor volume during serial subtransplantation and also an increase in the copy numbers of the primary tissue on chicken eggs were achieved. In the first step of the second strategy, freshly resected patient tissue was digested and incubated as organoids to obtain the first passage, followed by direct subtransplantation of egg xenografts from egg to egg, without intermediate incubation steps. This was a breaktrough, because it provided sufficient material of patient tumor copies. The efficacy of the treatment experiments was analyzed by immunohistochemical stainings, BrdU detection of proliferating cells and tumor volume examination of the egg xenografts. These analyses confirmed that the tumor properties were kept over the passages and also that the treatment of the egg xenograft was effective. Additionally, molecular methods confirmed the suitability of this model for treatment

experiments due to a high correlation of the egg xenograft gene expression and mutation status compared to the primary tumor.

All in all, the results of this thesis verified the xenotransplantation of freshly resected PDA tissue from patients to fertilized chicken eggs as model for personalized drug screening. Importantly, the small tissue amount needed for xenografting indicates this model also suitable for inoperable patients undergoing fine needle biopsy.