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Title: Development of an invasive 3D lung tumor model for oncological research

David 12498 Fecher david.fecher@uni-wuerzburg.de [1], Prof. Dr Heike 12499 Walles heike.walles@uni-wuerzburg.de [1], Prof. Dr Thorsten 12500 Walles Walles_T.htc@klinik.uni-wuerzburg.de MD [2], Dr. Sarah 12501 Nietzer sarah.nietzer@uni-wuerzburg.de [1] and Dr. Gudrun 12502 Dandekar gudrun.dandekar@uni-wuerzburg.de [1]. [1] Chair of Tissue Engingeering and Regenrative Medicine, University Wuerzburg, Wuerzburg, Bavaria, Germany, 97070 and [2] Department of Cardiothoracic Surgery, University Hospital Wuerzburg, Wuerzburg, Bavaria, Germany, 97080 .

Body: Objective: The high mortality of lung cancer is mainly often associated with tumor recurrences and distant metastases. One fundamental oncologic mechanism involved in tumor cell invasion is the epithelial-to-mesenchymal transition (EMT). However, no established models exist to study this process. Methods: To generate a 3D lung tumor model, A549 and HCC-827 cells were cultivated on acellular porcine small intestinal submucosa (SIS) segments and stimulated with TGF-β1 at concentrations of 0.05, 0.5 and 5 ng/ml for 14 days. Immunohistology and RT-PCR were applied to characterize cellular phenotypic changes. Invasive potential was quantified by assessing the number of single cells inside the SIS. Results: Both cell types formed a cell layer on the apical side of the SIS. While HCC-827 exhibited a polarized expression of Mucin-1, E-cadherin and β-catenin, A549 expressed these proteins in a diffuse pattern. When stimulated with TGF-β1, both cell types displayed a concentration-dependent change in morphology, gene expression and invasive behavior. While only 5 – 10% of single cells were found inside the SIS under control conditions, treatment with 5 ng/ml TGF-β1 led to invasion of 35 – 50% of the cells. Expression of epithelial markers was lost, whereas expression of mesenchymal markers was upregulated after TGF-β1 stimulation. Conclusion: Our in vitro tumor model provides a polarised epithelial layer that exhibits upregulation of tumor relevant genes and affords induction of EMT and invasion. It may open the door for studying this process in greater detail and for testing drug candidates targeting EMT and cell invasion.