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ORAL

Precision-cut tissue slices as a novel ex-vivo model for evaluating the efficacy of potential drugs

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Abstract

Background: Recently, we developed a novel model for drug screening by culturing ex-vivo precision-cut tissue slices (PCTS). The tissue slice consists of multiple cell types still in their normal matrix environment and structure provides numerous advantages compare to other models. Our objective was to use this model to investigate the effect of various potential compounds. In this study precision-cut intestinal slices (PCIS) were used to evaluate some transforming growth factor (TGF- β) and platelet-derived growth factor (PDGF) pathway inhibitors. TGF-β and PDGF are key cytokines in fibrotic and cancer diseases and are the main targets for treatment.

Methods: Murine PCIS were cultured for 48 h in the presence of profibrotic and/or antifibrotic compounds. The fibrotic process was studied on gene and protein level using a variety of markers including (pro)collagen 1a1 (Col1a1), heat shock protein 47 (Hsp47), fibronectin (Fn2) and plasminogen activator inhibitor-1 (PAI-1). The effects of potential drugs mainly inhibiting the TGFb pathway i.e. valproic acid, tetrandrine, pirfenidone, SB203580 and LY2109761 as well as compounds mainly acting on the PDGF pathway i.e. imatinib, sorafenib and sunitinib were assessed in the model at maximum non-toxic concentrations.

Results: Murine PCIS remained viable for 48 h and the onset of fibrosis was observed during culture, as demonstrated by an increased expression of, amongst others, Hsp47, Fn2 and Pai-1. Furthermore, TGFb1 stimulated fibrogenesis while PDGF had no effect. Regarding the tested antifibrotics, pirfenidone, LY2109761 and sunitinib had the most pronounced impact on fibrogenesis, both in the absence and presence of profibrotic factors, as illustrated by reduced levels of Col1a1, Hsp47, Fn2 and Pai-1 following treatment. Moreover, LY2109761 significantly reduced fibronectin protein expression in the presence of TGFb1.

Conclusion: PCIS can successfully be used to test drug efficacy. Using the model we demonstrated that tetrandrine, pirfenidone, LY2109761 and sunitinib showed potential antifibrotic effects on a gene level, warranting further evaluation of these compounds for the treatment of fibrosis disease. By using tissue extracted from patient, PCIS could also be a promising model to screen drug for personalized treatment in fibrotic and cancer disease.

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