POSTER NUMBER: 2006

Decreased fibrogenesis upon pirfenidone in a newly developed mouse model of intestinal fibrosis

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Background: Fibrosis as a common problem in patients with Crohn's disease (CD) is a result of an imbalance towards excessive tissue repair. At present there is no specific treatment option for CD patients with recurrent intestinal fibrosis. Pirfenidone is a small molecule approved for the treatment of idiopathic pulmonary fibrosis with both anti-fibrotic and anti-inflammatory effects. We subsequently investigated the impact of pirfenidone treatment upon development of fibrosis in a new mouse model of intestinal fibrosis.

Methods: Small bowel resections from donor-mice were transplanted subcutaneously into the neck of recipients. Animals received either pirfenidone (100 mg/kg administered three times a day orally) or vehicle. Intestinal grafts were examined for collagen layer thickness, expression of mediators of fibrosis and cytokines.

Results: Upon pirfenidone a significantly decreased collagen layer thickness was revealed as compared to vehicle (9.7 ± 1.0 vs. 13.5 ± 1.5 µm, respectively, ** $p < 0.001$). Important mediators of fibrosis such as TGF-ß and MMP-9 were significantly decreased upon administration of pirfenidone as confirmed by qPCR (0.42 ± 0.13 vs. 1.00 ± 0.21 and 0.46 ± 0.24 vs. 1.00 ± 0.62 mRNA expression level relative to GAPDH, respectively, * $p < 0.05$). Significantly decreased TGF-ß upon administration of pirfenidone was confirmed by Western blot.

Conclusion: In our new established mouse model intestinal fibrosis can be reliably induced and is developed within 7 days. Pirfenidone partially prevented development of fibrosis making it a potential treatment option against CD associated fibrosis. Further studies will be necessary to develop this option.

POSTER NUMBER: 2007

Measuring Changes in Matrix Stiffness Using a Force Conditioning Model

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The role of a stiffening extra-cellular matrix (ECM) in the development of organ fibrosis and a range of other illness, including cancer and autoimmune/inflammatory diseases, can be difficult to study and interpret. Measuring changes in matrix stiffness can be complicated, involving complex mathematical models and physically complex methodology. Current methods for measuring matrix stiffness involve exposing a sample to a physical strain such as stretching or indentation. However, very few directly measure matrix stiffness while allowing for a global and dynamic response to strain. Here we developed a conditioning stretch protocol to measure the stiffness of collagen matrices and how these biophysical changes are regulated by cellular and matrix cues. Using this assay, we determined the stiffness of matrices arranged by MDA-MB-231 cells, with or without nonmuscle myosin II isoforms, major regulators of actin contractility in nonmuscle cells. We found that inclusion of MDA-MB-231 cells remarkably enhanced the stiffness of the collagen matrix, increasing the elastic modulus from 0.40 Pascals (Pa) to 9.22 Pa. Myosin IIA and IIB were shown to have separate functions in matrix remodeling by MDA-MB-231 cells, as cells lacking these isoforms generated matrices with significantly different elastic moduli (3.42 and 7.20 for IIA and IIB KD cells, respectively). Specific cell and matrix contributions to the overall sample elastic modulus were calculated. These results reveal that Myosin IIA and IIB play distinct and non-redundant roles in matrix remodeling by breast cancer cells. Thus, this stretch conditioning model allows both the direct measurement of ECM stiffness and molecular analysis of impacts of specific cellular components and signaling molecules on ECM remodeling in a controlled environment. We expect this force conditioning protocol to be applicable to the study of diverse diseases involving changes in matrix stiffness.

POSTER NUMBER: 2008

Direct adhesion of macrophages promotes myofibroblast differentiation by establishing a niche of active TGF-ß1

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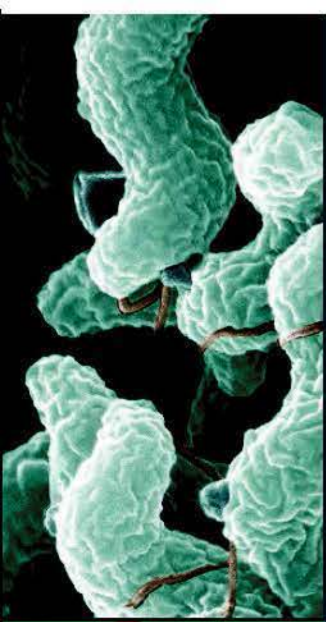
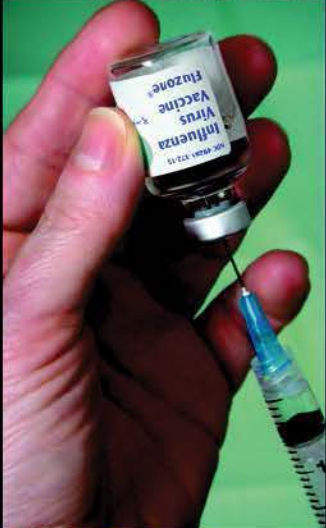
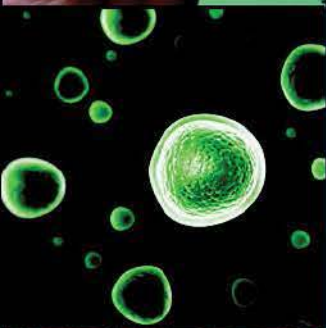
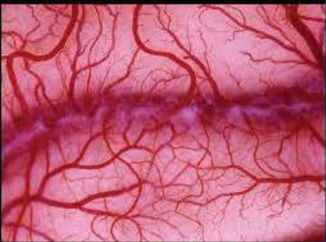
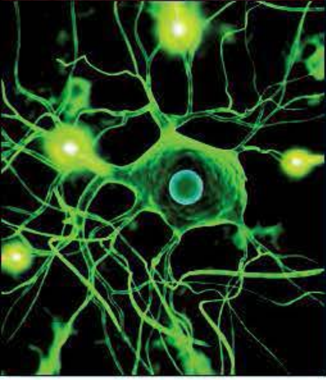
**EC and ML contributed equally*

Fibrosis: From Basic Mechanisms to Targeted Therapies

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