Abstract: P458

Cardiac fibroblasts as inflammatory supporter cells trigger cardiac inflammation in heart failure - Influence of Heart Rate on Pathophysiological Fibroblast Activation

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Purpose

Cardiac remodeling and inflammation are hallmarks of cardiac failure and correlate with outcome in patients. However, the basis for the development of both remains unclear. We have previously reported that cardiac inflammation triggers transdifferentiation of fibroblasts to activated myofibroblasts and increase cardiac collagen deposition, one key pathology in cardiac remodeling. Our findings also reveal that cardiac fibroblasts are chemoactive sentinel cells, activated by increasing stretch intensities, and are able to recruit inflammatory cells into the cardiac tissue. Therefore, we examined the cross-talk between fibroblasts and inflammatory cells. Furthermore, pathophysiological increased heart rates were already shown to be associated with increased mortality rates in heart failure. Therefore, we aim to investigate, whether simulated increased heart rate affects cell morphology, ECM structure and proinflammatory pathways in vitro.

Methods and Results

We used primary cardiac fibroblasts in a specialized cell culture system. To stimulate cardiac fibroblasts, we used the flexcell system either with increasing stretch intensities mimicking cardiac dilation or with increasing stretch frequencies. We found that not only increasing stretch intensities but also increasing stretch frequencies induced activation of fibroblasts. Both types of mechanical activation lead to up-regulated chemokine production and triggers typical inflammatory pathways in vitro. Furthermore, we investigated the composition of the secretom of human cardiac fibroblasts using mass spectrometric analysis of the cell culture supernatant. We clearly demonstrated that besides ECM proteins different chemokines could be identified. Next, we used this conditioned medium derived from cardiac fibroblasts to perform co-culture experiments to investigate the cross-talk between fibroblasts and inflammatory cells which further revealed that activated fibroblasts support cardiac inflammation.

Conclusion

Exposure of cardiac fibroblasts to mechanical stretch, either with high elongation or high frequency, results in elevated gene expression of chemokines and an elevated expression of ECM-forming genes. The transdifferentiated myofibroblasts thereby plays a crucial role in promoting inflammation and fibrosis, the main pathological processes during cardiovascular diseases. Therefore, cardiac fibroblasts serve as supporter cells for cardiac inflammation. Due to different stimuli such as increased mechanical stretch, mimicking dilation, or increased stretch frequencies, mimicking tachycardia, fibroblasts secrete cytokines and chemokines.

In the present work we show, that a pathophysiological increased heart rate affects cell morphology, ECM structure and proinflammatory pathways in the myocardium. Here, we investigate the role of fibroblasts in the
inflammatory process as well as the cross-talk between fibroblasts and inflammatory cells.