

## Systemic sclerosis-like histopathological features in the myocardium of uPAR-deficient mice

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Systemic sclerosis (SSc) is a complex connective tissue disease characterized by widespread microvascular damage and progressive fibrosis involving the skin and multiple internal organs, especially lungs, heart and gastrointestinal tract. Cardiomyopathy is among the leading causes of death in SSc patients. Urokinase-type plasminogen activator receptor (uPAR)-deficient mice have been recently reported to display important histopathological hallmarks of SSc, including dermal fibrosis, reduced dermal capillary density and pulmonary fibrosis (Manetti et al., 2014). Here, we investigated whether uPAR-deficient mice could display the histopathological features of SSc-related cardiomyopathy. Left ventricular myocardium specimens from uPAR-deficient and wild-type mice were processed for light and transmission electron microscopy. Myocardium sections were stained with hematoxylin-eosin and Picrosirius red for the analysis of collagen content. Myofibroblast and microvessel counts were determined by immunofluorescence for alpha-smooth muscle actin and CD31, respectively. Endothelial cell apoptosis was assessed by a combined TUNEL/CD31 immunofluorescence assay. The expression of uPAR in human SSc and control left ventricular myocardium samples was determined by immunohistochemistry. The myocardium of uPAR-deficient mice displayed focal ischemic lesions with cardiomyocyte hypertrophy, myofibril rarefaction and contraction band necrosis. Interstitial and perivascular collagen deposition and myofibroblast counts were significantly greater in myocardial tissue of uPAR-deficient than in wild-type mice. In uPAR-deficient mice, myocardial fibrosis was paralleled by microvascular endothelial cell apoptosis and reduced capillary density. uPAR expression was significantly downregulated in human SSc myocardium. Typical histopathological features of SSc-related cardiomyopathy are mimicked by uPAR-deficient mice. The downregulation of uPAR in the myocardium of SSc patients may suggest similar underlying pathogenetic mechanisms. uPAR-deficient mice might be a preclinical model to study the mechanisms and therapeutic approaches of myocardial involvement in SSc.

### References

- [1] Manetti et al. (2014) Inactivation of urokinase-type plasminogen activator receptor (uPAR) gene induces dermal and pulmonary fibrosis and peripheral microvasculopathy in mice: a new model of experimental scleroderma? *Ann Rheum Dis* 73: 1700-1709.

### Keywords

Systemic sclerosis; Animal model; Myocardium; uPAR.