Inactivation of urokinase-type plasminogen activator receptor induces dermal and pulmonary fibrosis and peripheral microvasculopathy in mice closely mimicking human systemic sclerosis

Mirko Manetti¹, Irene Rosa¹, Anna Franca Milia¹, Dalila Conte¹, Martina Ruffo¹, Peter Carmeliet², Marco Matucci-Cerinic¹ and Lidia Ibba-Manneschi¹

¹Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy
²Laboratory of Angiogenesis and the Neurovascular Link, Vesalius Research Center, VIB, Leuven, Belgium

Urokinase-type plasminogen activator receptor (uPAR, or CD87) is a key component of the fibrinolytic system involved in extracellular matrix remodeling and angiogenesis. The cleavage/inactivation of uPAR is a crucial step in fibroblast-to-myofibroblast transition and has been implicated in systemic sclerosis (SSc, scleroderma) peripheral microvasculopathy and impaired angiogenesis. In the present study, we investigated whether uPAR gene inactivation in mice could result in tissue fibrosis and peripheral microvasculopathy resembling human SSc. Skin and lung sections from uPAR-deficient mice and wild-type littermates at 12 and 24 weeks of age were stained with hematoxylin-eosin, Masson’s trichrome and Picrosirius red. Dermal thickness and hydroxyproline content were quantified. The number of myofibroblasts and microvessels were determined in skin sections immunostained for alpha-smooth muscle actin and the pan-endothelial cell marker CD31, respectively. Endothelial cell apoptosis was assessed by TUNEL/CD31 immunofluorescence assay. Dermal thickness, collagen content and myofibroblast counts were significantly greater in uPAR-deficient mice than in wild-type littermates. In uPAR-deficient mice, dermal fibrosis was paralleled by endothelial cell apoptosis and severe loss of microvessels. Lung specimens from uPAR-deficient mice exhibited non-specific interstitial pneumonia-like pathological features with large patchy areas of lung parenchyma displaying a uniform interstitial involvement characterized by both diffuse cellular inflammation and collagen deposition. In uPAR-deficient mice pulmonary pathology worsened significantly from 12 to 24 weeks of age, as shown by a significant increase in alveolar septal width and collagen content. The absence of uPAR induces dermal and pulmonary fibrosis and peripheral microvasculopathy in mice closely mimicking human SSc. uPAR-deficient mice might be a promising preclinical model to study the pathogenetic mechanisms of human SSc and enable testing of antifibrotic agents and drugs targeting small vessel vasculopathy simultaneously.

Key words
Systemic sclerosis, scleroderma, uPAR, fibrosis, peripheral microvasculopathy, animal models.