

## Differential expression of junctional adhesion molecules in different stages of systemic sclerosis: pathogenetic implications

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Systemic sclerosis (SSc, scleroderma) is characterized by early perivascular inflammation, microvascular endothelial cell (MVEC) activation/damage and defective angiogenesis. Junctional adhesion molecules (JAMs) regulate leukocyte recruitment to sites of inflammation and ischemia-reperfusion injury, vascular permeability and angiogenesis. In the present study, we investigated the possible role of JAMs in SSc pathogenesis. The expression of JAM-A and JAM-C in skin biopsies from 25 patients with SSc (14 early-stage SSc, 11 late-stage SSc) and 15 healthy subjects was investigated by immunohistochemistry and western blotting. Subcellular localization of JAMs in cultured dermal healthy MVECs (H-MVECs) and early-stage SSc-MVECs was assessed by confocal laser scanning microscopy. Serum levels of soluble JAM-A (sJAM-A) and JAM-C (sJAM-C) from 64 SSc patients (25 early-stage SSc, 39 late-stage SSc) and 32 healthy subjects were examined by ELISA. In control skin, constitutive JAM-A expression was observed in dermal MVECs and fibroblasts. In early-stage SSc skin, JAM-A expression was strongly increased in MVECs, fibroblasts and perivascular infiltrating inflammatory cells. In late-stage SSc, JAM-A expression was decreased compared with healthy controls. JAM-C was weakly expressed in control and late-stage SSc skin, while it was strongly expressed in MVECs, fibroblasts and inflammatory cells from early-stage SSc skin. Cell surface expression of JAM-A was higher in early-stage SSc-MVECs and increased in H-MVECs upon stimulation with early-stage SSc sera. JAM-C was cytoplasmic in resting H-MVECs, while it was rapidly recruited to the cell surface upon challenging with early-stage SSc sera. Early-stage SSc-MVECs exhibited increased expression and constitutive localization of JAM-C on the cell surface. Circulating levels of sJAM-A and sJAM-C were significantly increased in early-stage SSc compared with healthy controls and late-stage SSc. In addition, sJAM-A and sJAM-C levels were significantly raised in SSc patients with 'early/active' nail-fold capillaroscopic pattern compared with those with 'late' capillaroscopic pattern.

Collectively, the results of our study suggest that JAMs may participate in dermal MVEC activation, inflammatory processes and impaired angiogenesis in different stages of SSc.

Keywords: Junctional adhesion molecules, microvascular endothelial cells, skin, systemic sclerosis.