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Angiogenesis in systemic sclerosis: impaired expression of vascular endothelial growth factor receptor 1 in endothelial progenitor-derived cells under hypoxic conditions

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Abstract

Objective: To assess angiogenesis and explore the expression and regulation of vascular endothelial growth factor (VEGF), VEGF receptor 1 (VEGFR-1), and VEGFR-2, the leading mediators of angiogenesis, in SSc patients and controls.

Methods: Late-outgrowth endothelial progenitor cells (EPCs), isolated from the peripheral blood of systemic sclerosis (SSc) patients and controls, and human umbilical vein endothelial cells (HUVECs) were assessed under normal and hypoxic conditions. Genomic background was evaluated in a large case-control study (including 659 patients with SSc and 511 controls) using tag single-nucleotide polymorphisms on VEGFR1 and VEGFR2 genes.

Results: EPCs from SSc patients had the phenotype of genuine endothelial cells and displayed in vitro angiogenic properties similar to those of HUVECs and control EPCs under basal conditions, as determined by flow cytometry, tube formation, and migration assay. However, after 6 hours of hypoxic exposure, EPCs from SSc patients exhibited lower induced expression of VEGFR-1 at the messenger RNA and protein levels, but similar VEGF and VEGFR-2 expression, compared with HUVECs or EPCs from healthy controls. There was no evidence of defective expression of hypoxia-inducible factor 1alpha. These results were supported by the lower serum levels of soluble VEGFR-1 found in SSc patients (n = 187) compared with healthy controls (n = 48) (mean +/- SD 163.7 +/- 98.5 versus 210.4 +/- 109.5 pg/ml; P = 0.0042). These abnormalities did not seem to be related to genomic background.

Conclusion: Our findings shed new light on the possible role of VEGFR-1 in the main vascular disturbances that occur in SSc and lead to more severe disease.

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