The role of thrombospondin-1 in hypoxia-induced migration of human vascular smooth muscle cells

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[Object] When the arterial wall becomes to be thickened and blood-diffusion capacity to be lowered in atherosclerotic lesions, hypoxia would be a key factor for the development of atherosclerosis. Under hypoxic condition more than 100 genes, including many growth factors, are known to be induced by transcriptional factor, hypoxia-inducible factor-1α (HIF-1α). In this study, to examine whether or not HIF-1α-dependent induction of many growth factors is associated with the proliferation and migration of vascular cells in atherosclerotic lesions, we studied the implication of thrombospondin-1 (TSP-1), which is induced by hypoxia, in the pathogenesis of the progression of atherosclerosis in human coronary artery smooth muscle cells (CASMC).

[Results and conclusion] Under hypoxic conditions, the expression of HIF-1α increased time-dependently in human CASMC with concomitant increase in the mRNA and protein levels of TSP-1 and the mRNA level of TSP-1 receptor, integrin β_3. Moreover, the proliferation and migration of the cells were enhanced under hypoxia. The neutralizing antibody against TSP-1 reduced the hypoxia-induced migration, but not the proliferation. Similarly, the RGD peptide, which binds to integrin β_3, inhibited cell migration under hypoxia. The hypoxia-induced proliferation and migration were markedly reduced in HIF-1α-knockdown CASMC. In conclusion, hypoxia that appears in atherosclerotic lesions induces TSP-1, which plays an important role in acceleration of the migration of human CASMC and in progression of further atherosclerosis.