

**A novel role of thrombospondin-1 in  
cervical carcinogenesis. Inhibit stroma  
reaction by inhibiting activated fibroblasts  
from invading cancer**

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摘要

**Abstract**

Thrombospondin (TSP)-1, a potent angiogenesis inhibitor, has been shown to exert different biological functions on various cell types. Here, we investigate the role of TSP-1 in tumor – stroma reaction, which is mainly characterized by fibroblast activation to create a permissive microenvironment for tumor progression. Immunohistochemistry examinations in the human surgical specimens have shown that a downregulation of TSP-1 during the progression of cervical carcinogenesis was accompanied by an emergence in the upregulation of stroma markers, -smooth muscle actin (-SMA) and desmin. Transfection of SiHa cervical cancer cells with a plasmid expressing the TSP-1 protein exhibited antiangiogenic activity in vitro and resulted in reduced tumor growth in severe combined immunodeficiency (SCID) mice, which was accompanied by a decrease in tumor vascularization and lower expressions of -SMA and desmin than those in the vector controls. Transfection with TSP-1 and purified TSP-1 added to NIH3T3 cells did not alter the protein levels of -SMA and desmin but significantly inhibited matrix metalloprotease-2 activity. Transforming growth factor- $\beta$  (TGF- $\beta$ ), a major factor in the activation of fibroblasts, increased -SMA and desmin expression and the ability of cell migration and invasion in NIH3T3 cells. The increased migration ability and the invasive ability into tumor cluster of TGF- $\beta$ -treated NIH3T3 cells were dose dependently inhibited by TSP-1. In contrast, ectopic TSP-1 expression in SiHa cells has little effect on the invasive ability of the NIH3T3 cells. Together, our findings demonstrate a novel role of TSP-1 to inhibit tumor – stroma reaction that could be attributed to the blockage of activated fibroblasts

from invading cancer cells