The thrombospondin-1 acts as a fence to inhibit angiogenesis that occurs during cervical carcinogenesis

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摘要

Abstract

PURPOSE The acquisition of an angiogenic phenotype (angiogenic switch) is essential for cervical carcinogenesis. This study was aimed to examine the spatial and temporal relationship ofthrombospondin-1 (TSP-1) expression in patients with precursor lesions and squamous cell carcinoma of uterine cervix and to correlate its expression with tumor angiogenesis. PATIENTS AND METHODS TSP-1 expression and microvessel density were assessed by immunohistochemistry in samples obtained from patients with pathological diagnoses of cervical intraepithelial neoplasm I, carcinoma in situ, invasive squamous cell carcinoma (SCC), and benign disease (N = 12 from each group). Two representative blocks that contained serial changes of cervical lesions from these 48 subjects were examined, and the pathological findings were categorized into the four groups of (1) normal cervical epithelia, (2) low-grade squamous intraepithelial lesions (LSILs), (3) high-grade SILs (HSILs), and (4) SCC. RESULTS A total of 120 foci with various cervical lesions from 98 slides were examined and classified into normal (48), LSIL (36), HSIL (24), and SCC epithelium (12). Immunohistochemical studies showed that TSP-1 was mainly localized at the basal epithelial cells, and we named it as the "TSP-1 fence." The mean microvessel density counts and TSP-1 scores for normal, LSIL, HSIL, and SCC epithelium were 7.3 ´ 2.9, 9.9 ´ 3.4, 17.7 ´ 5.1, and 22.8 ´ 8.6, and 3.8 ´ 0.4, 3.8 ´ 0.4, 1.8 ´ 0.4, and 1.5 ´ 0.5, respectively. The TSP-1 intensities were significantly higher and the MVD counts lower in the groups of normal and LSIL epithelium than in those with HSIL and SCC epithelium. In addition, microvessel density count was negatively associated with the intensity of TSP-1. DISCUSSION Our results indicate that the disruption of TSP-1 fence and the switch to angiogenic phenotype occurred during the transition from LSIL into HSIL. This concordance suggests that TSP-1 plays a role in the regulation of angiogenic switch. We conclude that the onset of angiogenesis is an early event in cervical carcinogenesis due, in part, to the down-regulation of TSP-1 by the dysplastic epithelium.