Overexpression of CCN3 in cervical cancer: correlation with clinicopathological features and prognosis

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Abstract

Objectives: Cervical cancer continues to be one of the major causes of cancer-related death in women worldwide. CCN3 plays important roles in growth, differentiation, angiogenesis and adhesion. Recently, the role of CCN3 in human carcinogenesis has become an area of great interest. However, little is known about the function of CCN3 in human cervical cancer. The aim of this study was to investigate the expression profile of CCN3 in cervical cancer and to assess its clinical significance.

Methods: In this study, qRT-PCR, immunohistochemistry and western blotting analysis were used in the detection of CCN3 mRNA and protein expression, both in cervical cancer and in corresponding normal tissue, respectively. The data was correlated with clinicopathological features. Survival analysis was performed to assess prognostic significance.

Results:

Expression profile of CCN3 mRNA in human cervical cancer and in corresponding normal cervical tissue

The qRT-PCR was carried out to identify transcripts that encoded human CCN3 in 15 pairs of cervical cancer tissue and corresponding normal tissue. The result showed that CCN3 mRNA expression level in cervical cancer tissue was markedly up-regulated (3.46 ± 0.83) when compared with corresponding normal tissue (1.21± 0.67), the difference between the two groups has statistical significance (P < 0.05).

Expression profile and subcellular location of CCN3 protein in human cervical cancer and in corresponding normal cervical tissue

We determined the expression profile and distribution of CCN3 by immunohistochemistry in 56 pairs of cervical cancer tissue and corresponding normal cervical tissue. There was no or low expression of CCN3 in normal cervical tissue. On the contrary, cervical cancer samples revealed intensive CCN3 staining, which was scored as positive where strong cytoplasmic staining was present. The positive rate of CCN3 expression in cervical cancer is 53.57% (30/56). Western blot analysis was also revealed that CCN3 was dramatically increased in cervical cancer tissue when compared with normal cervical tissue, which showed little or no expression of CCN3.

Correlation of CCN3 expression with clinicopathological parameters in cervical cancer

We aimed to explore the clinical significance of CCN3 expression in our patient samples. We evaluated the association between CCN3 expression and clinicopathological parameters. In all 56 patients, there was a higher percentage of positive CCN3 protein staining in disease stage III-IV (68.97%) when compared with stage I-II (37.04%) (P = 0.017). There was also a significant difference in the correlation of positive CCN3 protein staining and lymph node invasion (negative lymph node invasion vs positive lymph node invasion: 36.67% vs 73.08%) (P = 0.006). However, we found that the positive staining for CCN3 protein in patients <40 and >=40 years was 47.83% and 57.58%, respectively, which indicated no significant difference between ages in CCN3 positive staining with cervical cancer (P = 0.472). There were also no significant differences of positive CCN3 protein staining in histological G2 (56.25%) and G3 (61.90%) compared with G1 (42.11%) (P = 0.441). Meanwhile, the expression of CCN3 was not associated with tumor size (P = 0.197) and menses (P = 0.938), respectively. These results indicated that overexpression of CCN3 was related to disease stage and lymph node invasion in cervical cancer.

CCN3 protein expression associated with shorter overall survival

Survival analysis of the 56 studied patients was performed using information available on clinical follow-up. At the end of follow-up, 26 patients were still alive and 27 had died. The remaining three had been lost to follow-up, resulting in a follow-up rate of 94.64%. Of the remaining 53 evaluable patients, only 8 of the 24 (33.33%) in the negative CCN3 staining group died of the disease, compared with 19 of the 29 (65.52%) in the positive CCN3 staining group. CCN3 overexpression in patients with cervical cancer was related to reduced overall survival.
survival time by log-rank test (P = 0.021) (Figure 3). Our observations suggested that CCN3 overexpression in cervical cancer patients was associated with reduced overall survival.

Conclusions: We have shown that CCN3 expression was increased in cervical cancer and was positively correlated with poor prognosis. Our results suggest that CCN3 may play an important role in cervical carcinogenesis and therefore may have potential as a biomarker for prognosis and therapeutic target in cervical cancer.

Key words: CCN3; cervical cancer; clinicopathological parameters; prognosis;