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Expression of nm23 gene in hepatocellular carcinoma tissue and its relation with metastasis

HUANG Bei, WU Zhong-Bi and RUAN You-Bing

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INTRODUCTION

Among the mostly expressed 23 genes in nonmetastatic tumors, *nm23* had the highest frequency. Steeg *et al*[1] first identified and cloned its complementary DNA and confirmed that its lower expression was related to the high metastatic activity of melanoma cell lines. Many studies found afterwards that the expression of *nm23* at the RNA or protein level was inversely correlated with the development of metastasis or poor clinical course in cohorts of several human tumor types, including breast, colorectal and gastric carcinomas. But the effects of *nm23* on metastasis of hepatocellular carcinoma (HCC) is still unclear. In this study we have investigated *nm23* expression in HCC with immunohistochemical techniques and the correlation between its expression level and metastatic progression.

MATERIALS AND METHODS

Subjects

Specimens of 24 cases of human HCC were obtained from surgical resections in Tongji Hospital. Observations were carried out on tissues from tumor areas, nonneoplastic areas and their boundary areas when available. Ten of them showed cancer cell emboli in portal vein or metastasis in portal lymph nodes or in distant organs, e.g. in the lung. Fourteen cases without metastasis were characterized by no findings of tumor invasion into the surrounding tissues at operation or no metastasis outside the liver by X-ray and sonography. The samples were fixed with 4% paraformaldehyde and embedded with paraffin. Successive sections were stained with HE, as well as immunohistochemically with the SP method. The staining was considered negative (-) when no cells were stained on the section, and weakly (+), moderately (++) and strong (+++) positive, when a few, more and a lot of cancer cells were darkly stained, respectively.

RESULTS

The positive signal revealed brown grains in cytoplasm of tumor cells. *nm23* protein expressed highly in HCC, but was not obviously related to the degree of malignancy histologically. The positive rate was 67% (16/24). The expression of *nm23* was heterogeneitic in different cancer cell nodules and in the same nodule. The positive cells presented focal distribution or scattered through the cancer nodules. *nm23* protein also expressed in the normal liver tissues around the carcinoma. The positive rate of *nm23* was 86% in the group without metastasis, and 40% in the group with metastasis. The *nm23* expression level in metastatic HCC was significantly lower than that in nonmetastatic HCC ($P<0.05$, Table 1).

Table 1 Relationship between [a]«nm23[a]« expression and metastasis of HCC

Groups	*n*	*nm23* expression				Positive rate(%)
		-	+	++	+++	
Nonmetastatic	14	2	3	3	6	85
Metastatic	10	6	2	1	1	40[a]

[a]$P<0.05$ compared with metastatic group.

DISCUSSION

nm23 is a suppressor gene for tumor metastasis that encodes nucleoside diphosphokinase (NDPK). NDPK causes activation of a G protein pathway involved in the signal transduction of many growth factors and hormones. Expression of *nm23* at the RNA or protein level was shown to be inversely correlated with the staging and differentiation of human breast cancer. In later period of poorly differentiated tumors, *nm23* showed in general a lower expression and their recidive rate was higher, and survival rate was low[2]. Similar results were obtained by prostate and thyroid carcinoma[3]. Our data showed that the expression level of *nm23* was

Department of Ultrastructural Pathology, Research Center of Experimental Medicine, Tongji Medical University, Wuhan 430030, Hubei Province, China

Dr. HUANG Bei, female, was born on Feb. 13, 1964 and graduated from Tongji Medical University in 1987.

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Correspondence to: Dr. HUANG Bei, Department of Ultrastructural Pathology, Research Center of Experimental Medicine, Tongji Medical University, Wuhan 430030, Hubei Province, China

Tel. +86 • 27 • 3692639

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significantly lower in cases of HCC with metastasis than that without metastasis, suggesting that *nm23* had some effects of inhibiting metastasis of HCC. However, no relation between expression of *nm23* and lymph node metastasis was reported by Haut *et al*[4]. However, Cohn *et al*[5] found that nm23 was associated with distant metastasis after operation in colorectal carcinoma. Moreover, *nm23* was reported to be related with lymph node metastasis in pulmonary squamous cell carcinoma, but not in pulmonary adenocarcinoma[6]. Our preliminary study also showed that there was no nm23 expression in 2 nonmetastatic HCC tissues, but stronger expression in 1 metastatic HCC. These suggested that some other regulatory factors may exist evidently in the process of metastasis of HCC.

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