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Expression of lung resistance protein in patients with gastric carcinoma and its clinical significance

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INTRODUCTION

The efficacy of chemotherapy in the treatment of cancer patients is often hampered by the presence or appearance of multidrug resistance (MDR) of tumor cells. One of the most important mechanisms of MDR is overexpression of P-glycoprotein (Pgp) which is encoded by mdr1 gene[1]. Recently, another MDR-related protein, lung resistance protein (LRP), has been identified[2]. Our primary study indicated that LRP overexpressed in gastrointestinal carcinoma[3]. In this paper, the expression of LRP in human gastric carcinoma and its significance were studied.

MATERIALS AND METHODS

Patients

All the 36 patients (21 men, 15 women; aged 32-78 years, mean age 54.6 years) were in-patients of our hospital admitted between September 1997-August 1998 and surgically resected specimens were diagnosed as adenocarcinoma by pathologi sts. No patients received chemotherapy before operation.

Methods

The expression of LRP in tumor tissues was detected by SABC (streptavidin-biotin complex) immunohistochemical staining as described before[4], and in 14 of 36 specimens, the LRP was also analysed by flow cytometry (FCM), the matched mucosas served as normal controls, and peripheral blood lymphocytes as negative controls. The specific LRP monocolonal antibody LRP-56 was kindly supplied by Dr. R.J. Scheper (Department of Pathology, Free University Hospital, Amsterdam, the Netherlands), and the SABC immunohisto-chemical kit was purchased from Boster Biotechnology Company (Wuhan).

RESULTS

Expression of LRP in gastric carcinoma tissues

The LRP positive rate was 72.2% (26/36). LRP immunoreactivity was cytoplasmic, and in some specimens, the interstitial cells were also LRP immunostained. The intensity of the reactions was frequently strong and, in general, most of the cancer cells were LRP-positive in LRP-positive tissues.

Expression of LRP and pathologic parameters

The relationship between LRP expression and pathologic parameters is shown in Table 1. The LRP expression in highly and moderately differentiated carcinoma (9/9) was higher than that in mucoid carcinoma (6/11). There was no association between LRP expression and tumor size, lymph nodal involvement, serosal invasion, or TNM stages.

Expression of LRP detected by FCM

LRP expression was at low to moderate levels in gastric cancer tissues (0%-20% in 10 patients, 21%-40% in 2 patients, and 41%-60% in 2 patients), and the mean LRP positivity rate was 29.9% ± 9.8%, significantly higher than that in normal (16.9% ± 7.5%, $t = 3.94$, $P<0.01$) and negative controls (1.72% ± 0.23%, $t = 5.63$, $P<0.01$).

Table 1 The pathologic parameters and expression of LRP

Pathologic parameters	LRP(+) *n*	LRP(-) *n*
Tumor size		
<3 cm	7	2
3 cm-5 cm	11	3
>5 cm	8	5
Differentiation		
well	1	0
moderate	8	0
poor	11	5
mucoid	6	5[a]
Nodal metastasis		
(-)	15	2
(+)	11	8
Serosal invasion		
(-)	7	3
(+)	19	7
TNM stage		
I	6	1
II	8	3
III	9	3
IV	3	3
N	26	10

[a]$P<0.05$, *vs* well and moderately differentiated carcinoma. *n*: number of cases

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DISCUSSION

LRP is the human major vault transporter protein and is suggested to confer anticancer drug resistance. The mechanism that LRP confers MDR is unknown, but concerning the reduced nuclear accumulation of daunorubicin in the LRP-overexpressing MDR cell line 2R120 and the evidence supporting a role of vaults as transporter unit of the nuclear pore complexes, it is tempting to hypothesize that LRP can mediate drug resistance by regulating both the cytoplasmic redistribution and the nucleocytoplasmic transport of drugs[5]. LRP was overexpressed in ovarian cancer, leukemia, and several cancer cell lines of MDR phenotype, and LRP is of high predictive value for response to chemotherapy and prognosis[6,7]. Ikeda *et al*[8] quantitated the level of LRP mRNA expression in 10 gastric cancer cell lines by RT-PCR, and examined the relationship between its level in these cells and their sensitivities to anticancer drugs. LRP mRNA was expressed in all cell lines, and LRP correlated with the resistance to cisplatin. But up to now, there has been no study about LRP expression in specimens of gastric cancer and the relationship between LRP expression and pathologic parameters. Our study revealed that LRP was frequently overexpressed in untreated gastric cancer, suggesting that gastr ic carcinoma holds high intrinsic resistance. Analysis of LRP can help evaluate the chemosensitivity of patients to anticancer drugs, and choose more effective drugs.

Meanwhile, our results disclosed that LRP positivity rates in well and moderat ely differentiated carcinomas were 100%, in poorly differentiated cancer was 11/16, and in mucoid carcinoma was 6/11, showing the descending tend ency, and LRP positivity rate in patients with well and moderately differentiated adenocarcinoma was higher than that in mucoid carcinoma, which was consistent with the clinical observation that well-differentiated cancer cells have less satisfactory chemosensitivity than poorly differentiated. LRP expression was independent on tumor size, lymph nodal involvement, serosal invasion, and TNM stage, indicating that these parameters represent the progression of the tum or only, and have no correlation to chemotherapy drug sensitivity. Our previous studies showed that mdr1 mRNA and MRP were overexpressed in gastric carcinoma[9,3], and the present study demonstrated that LRP overexpressed in gastric cancer, suggesting that MDR can be mediated by all of them simultaneously, and combined administration of different MDR reversing agents, which can overcome MDR by increasing the intracellular drug accumulation of cancer cells, could achieve a better effect.

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