Reduced expression of P120 catenin in cholangiocarcinoma correlated with tumor clinicopathologic parameters

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INTRODUCTION

P120-catenin is a member of the Armadillo (ARM)/β-catenin gene family and is essential for mesenchymal cadherin-mediated regulation of cell motility and invasiveness

AIM: To investigate the relationship between the expression of P120 and the clinicopathologic parameters in intrahepatic cholangiocarcinoma (ICC).

METHODS: An immunohistochemical study of E-cadherin and P120 catenin was performed on 42 specimens of ICC with a Dako Envision kit.

RESULTS: The expression of E-cadherin and P120 was reduced in 27 cases (64.3%) and 31 cases (73.8%), respectively. Both E-cadherin and P120 expressions were significantly correlated with the tumor histological grade ($\chi^2 = 9.333$, $P = 0.009$ and $\chi^2 = 11.71$, $P = 0.003$), TMN stage ($\chi^2 = 8.627$, $P = 0.035$ and $\chi^2 = 13.123$, $P = 0.004$), intrahepatic metastasis ($\chi^2 = 7.292$, $P = 0.007$ and $\chi^2 = 4.657$, $P = 0.041$, respectively) and patients’ survival ($\chi^2 = 6.351$, $P = 0.002$ and $\chi^2 = 4.023$, $P = 0.000$, respectively).

CONCLUSION: Down-regulated expression of E-cadherin and P120 occurs frequently in ICC and contributes to the progression and development of tumor. Both of them may be valuable biologic markers for predicting tumor invasion, metastasis and patients’ survival, but only P120 is an independent prognostic factor for ICC.
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The expression of E-cadherin and P120 tended to be reduced in poorly-differentiated tumors compared with well- and moderately-differentiated tumors. In addition, the expression of E-cadherin and P120 was inversely associated with the pTNM stage of tumors ($P = 0.035$ and $P = 0.004$, respectively).

**Relationship between expression of E-cadherin and P120 in ICC**

As shown in Table 3, positive and negative expression of E-cadherin and P120 was found in 9 and 25 cases, respectively. However, negative expression of P120 was observed in 7 cases. There was a significant concordance between the expressions of E-cadherin and P120 ($P = 0.000$).

**Relationship between expression of E-cadherin/P120 and survival of ICC patients**

The patients were followed up for 4-67 months. The overall survival rate of patients according to the expression of E-cadherin and P120 in tumor is shown in Figure 2. Analysis of the survival of all patients showed that abnormal expression of E-cadherin and P120 was

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**Table 1 Relationship between expressions of E-cadherin/P120 catenin and histological features of ICC $n$ (%)**

|                  | $n$ | +  | -  | $P$ value | +  | -  | $P$ value |
|------------------|-----|----|----|-----------|----|----|-----------|
| **Differentiation grade** |     |    |    |           |    |    |           |
| Well             | 3   | 3  | 0  | 0.009     | 3  | 0  | 0.003     |
| Moderate         | 14  | 7  | 7  |           | 5  | 9  |           |
| Poor             | 25  | 5  | 20 | 0.035     | 3  | 22 |           |
| **pTNM**         |     |    |    |           |    |    |           |
| I                | 2   | 2  | 0  | 0.035     | 2  | 0  | 0.004     |
| II               | 9   | 5  | 4  |           | 5  | 4  |           |
| III              | 25  | 8  | 17 |           | 4  | 21 |           |
| IV               | 6   | 0  | 6  |           | 0  | 6  |           |

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**Figure 1** Immunoreactivity of E-cadherin and P120 in intrahepatic cholangiocarcinomas. "Preserved type" (+) (A, D), "reduced type" (-) (B, E), and "complete absent" (C, F) of E-cadherin and P120 induced type (-) and staining, respectively ($\times$ 200).
significantly correlated with the poor survival of patients (\(P = 0.024\) and \(P = 0.004\), respectively). However, when the expression of E-cadherin or P120 and the clinicopathological parameters were analyzed by the Cox regression model, abnormal expression of P120 was found to be an independent prognostic factor for ICC patients (\(P = 0.049\)) (Table 4).

**DISCUSSION**

Usually, ICC is an adenocarcinoma and may arise from the large intra-hepatic bile ducts near the hepatic hilus or from the bile ducts at the border of hepatic parenchyma. It was reported that altered expression of E-cadherin/catenins complex in ICC occurs frequently and is significantly correlated with tumor histological features and/or vascular invasion and metastasis\(^{[9-14]}\).

It was recently reported that P120 plays a role in the occurrence of various cancers, and that P120 may behave either as a tumor suppressor or as a metastasis promoter, depending on the loss of E-cadherin and P120. If E-cadherin is lost first, P120 may directly and actively promote metastasis. If P120 is lost first, E-cadherin levels would fall significantly, which is likely to be parallel to

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**Table 2** Relationship between expressions of E-cadherin/P120 catenin and clinical parameters of ICC

|        | E-cadherin | P120 catenin |
|--------|------------|--------------|
|        | +          | -            | \(P\) value | +          | -            | \(P\) value |
| Size   |            |              |             |            |              |             |
| < 5 cm | 7 (41.2)   | 10 (58.8)    | 0.826       | 6 (35.3)   | 11 (64.7)    | 0.584       |
| 5-10 cm| 5 (31.3)   | 11 (68.7)    |             | 3 (18.8)   | 12 (81.2)    |             |
| > 10 cm| 3 (33.3)   | 6 (66.7)     |             | 2 (22.2)   | 7 (77.8)     |             |
| Capsular invasion |            |              |             |            |              |             |
| +      | 4 (66.7)   | 2 (33.3)     | 0.164       | 3 (50)     | 3 (50)       | 0.391       |
| -      | 11 (30.6)  | 25 (69.4)    |             | 8 (22.2)   | 28 (77.8)    |             |
| Satellite nodules |            |              |             |            |              |             |
| +      | 4 (36.4)   | 7 (65.6)     | 1           | 3 (27.3)   | 8 (72.7)     | 0.314       |
| -      | 11 (35.5)  | 20 (64.5)    |             | 8 (25.8)   | 23 (74.2)    |             |
| Vascular invasion |            |              |             |            |              |             |
| +      | 13 (45.4)  | 16 (55.2)    | 0.089       | 1 (7.7)    | 12 (92.3)    | 0.127       |
| -      | 29 (13.6)  | 16 (86.4)    |             | 10 (34.5)  | 19 (65.5)    |             |
| L.N.P  |            |              |             |            |              |             |
| +      | 7 (14.3)   | 6 (85.7)     | 0.39        | 0 (0)      | 7 (100)      | 0.161       |
| -      | 35 (14.0)  | 21 (86.0)    |             | 11 (31.4)  | 24 (68.6)    |             |
| I.M.   |            |              |             |            |              |             |
| +      | 10 (0)     | 10 (100)     | 0.007       | 0 (0)      | 10 (100)     | 0.041       |
| -      | 32 (14.9)  | 17 (53.1)    |             | 11 (34.4)  | 21 (65.6)    |             |

**Table 3** Relationship between expression of E-cadherin and P120 catenin in ICC

| E-cadherin | P120   |
|------------|--------|
| +          | 9      |
| -          | 2      |

**Figure 2** Kaplan-Meier survival curves. **A**: Expression of P120 induced type (\(-\)) and **B**: Expression of E-cadherin.

* Sig: Significance; RR: Relative risk; CI: Confidence interval.*

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**Table 4** Cox multivariate analysis for survival of 37 patients

| E-cadherin expression | Sig  | RR    | 95% CI |
|-----------------------|------|-------|--------|
|                       |      |       |        |

*Significantly correlated with the poor survival of patients (\(P = 0.024\) and \(P = 0.004\), respectively). However,*
the reduced levels of α- and β-catenins[15]. P120 down-regulation results in a striking dose-dependant loss of endogenous cadherins, indicating that P120 is essential for cadherin stability. Moreover, P120 down-regulation occurs frequently in almost all carcinomas[16]. P120 loss is often associated with the stage and poor prognosis of tumors, suggesting that its loss may be associated with biological aggressiveness and progression of tumors. Nevertheless, to our knowledge, no report is available on the expression of P120 in human intrahepatic cholangiocarcinoma.

The present study showed that reduced or absent expression of E-cadherin and P120 was associated with the histological grade of tumors, which is consistent with reported data[17-21]. In well-differentiated tumors, there were obvious and strong staining along the cell-cell boundaries, whereas in poorly-differentiated tumors, the immunohistostaining was focally and heterogeneously distributed, with patchy or spotty features along the cell-cell boundaries, indicating that the staining of E-cadherin and P120 is related with the differentiation of ICC, namely both E-cadherin and P120 may be regarded as differentiation markers of tumor. In addition, the staining intensity of E-cadherin and P120 complex was gradually decreased, suggesting that P120 may play a critical role in ICC progression.

Microscopy revealed that E-cadherin was located on the membrane either in non-tumor tissues or in tumor cells, whereas P120 was expressed on the membrane or in cytoplasm of tumor cells. However, it was reported that P120 is also in nuclei[22], suggesting that P120 plays an important role in cell signal transduction. P120 has an intrinsic nucleocytoplasmic shuttling activity that is modulated, in part, by extrinsic factors such as cadherin binding and interactions with the microtubule network[23]. Julia and colleagues reported[24] that P120 displays up-regulation and nuclear expression in pancreatic cancer. No expression of P120 in nuclei of cancer cells, however, was observed in our study, suggesting that it is necessary to further investigate the mechanism underlying P120 expression in nuclei of cancer cells.

In this study, we observed the relationship between reduced expression of E-cadherin and P120 and several clinicopathologic parameters of ICC. The expression of P120 and E-cadherin was significantly associated with tumor pTNM stage and intrahepatic metastasis (IM), but not with tumor stage and size, capsular and vascular invasion, and lymph node invasion. Osaka and his colleagues[24] revealed that E-cadherin is involved in intra-hepatic metastasis of hepatocellular carcinoma. Asayama et al[13] detected the expression of E-cadherin in hepatocellular carcinoma and cholangiocarcinoma, and found that reduced expression of E-cadherin is significantly correlated with the grade and IM of ICC. Therefore, E-cadherin and P120 may be important mediators in tumor progression, and can be considered as invasion and metastasis markers of ICC.

Several studies on other cancers have evaluated the relationship between the expression of E-cadherin/P120 and the survival of patients, but the results remain debatable[25-29]. In the present study, reduced expression of both E-cadherin and P120 was significantly related with the survival of patients. However, when the expression of E-cadherin/P120 and the clinicopathological parameters of ICC were analyzed by the Cox regression model, only the abnormal expression of P120 was found to be an independent prognostic factor for ICC, suggesting that P120 can be considered a valuable biological marker for predicting the prognosis of ICC patients.

In summary, abnormal expression of E-cadherin and P120 catenin occurs frequently in intrahepatic cholangiocarcinoma. Reduced expression of P120 catenin and E-cadherin is correlated with tumor differentiation, pTNM stage, intrahepatic metastasis and survival of patients. Both P120 catenin and E-cadherin may play an important role in the development and progression of human intrahepatic cholangiocarcinoma.

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COMMENTS

Background
P120-catenin is a member of the E-cadherin/catenin complex family and may be associated with biological aggressiveness and progression of tumors. However, no report is available on the expression of P120 catenin in human intrahepatic cholangiocarcinoma.

Research frontiers
P120 down-regulation occurs frequently in almost all carcinomas. P120 loss is often associated with the stage and poor prognosis of tumors.

Innovations and breakthroughs
Our results suggest that down-regulated expression of E-cadherin and P120 catenin occurred frequently in intrahepatic cholangiocarcinoma (ICC) and contributed to the progression and development of tumors. Both E-cadherin and P120 catenin may be valuable biologic markers for predicting tumor invasion, metastasis and survival of patients, but only P120 catenin is an independent prognostic factor for ICC.

Applications
Because down-regulated expression of P120 contributes to the progression and development of ICC, P120 can be used as a valuable biologic marker for predicting the invasion and metastasis of ICC, and the survival of patients.

Peer review
This is an interesting report on E-cadherin and P120 catenin in human intra-hepatic cholangiocarcinoma. The study was performed on 42 specimens of ICC with a Dako Envision kit, indicating that. Both E-cadherin and P120 catenin may be valuable biological markers for predicting tumor invasion, metastasis and survival of patients. However, its clinical application should be further studied.

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