

行政院國家科學委員會專題研究計畫 成果報告

細胞角質-19 於肝癌之表現及其與肝癌轉移特性之關係 研究成果報告(精簡版)

計畫類別：個別型
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執行期間：95年08月01日至96年07月31日
執行單位：國立臺灣大學醫學院內科

計畫主持人：黃冠棠

計畫參與人員：臨時人員：林淑月

處理方式：本計畫可公開查詢

中華民國 96 年 10 月 27 日

行政院國家科學委員會補助專題研究計畫 成果報告
 期中進度報告

細胞角質-19 於肝癌之表現及其與肝癌轉移特性之關係

計畫類別： 個別型計畫 整合型計畫

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計畫主持人：黃冠棠

共同主持人：

計畫參與人員：

成果報告類型(依經費核定清單規定繳交)： 精簡報告 完整報告

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執行單位：台大醫學院內科部

中 華 民 國 96 年 10 月 27 日

中文摘要（關鍵詞：肝臟前驅細胞、細胞角質-19、肝細胞癌）

我們之前的研究顯示肝臟前驅細胞，或叫卵圓細胞，可以其特殊表現之蛋白如細胞角質(cytokeratin)-19、aldolase、deleted in malignant brain tumor、platelet-derived growth factor binding protein、pancreatitis-associated protein、及 jagged-1。幹細胞或前驅細胞具有一些與癌細胞類似的特性，如 Wnt、Shh、與 Notch 訊息路徑的活化，及繁殖與移行之特性。本研究將探討卵圓細胞特殊表現之蛋白（著重於細胞角質-19）於肝癌組織之表現情形，以了解其與肝癌惡化情況之關連。

我們以 107 個接受肝癌切除手術病人的肝組織進行細胞角質-19 的組織免疫染色，分析肝癌組織表現細胞角質-19 與否與臨床病理學的關係如何。結果 107 個病患切片中，有 6 個表現細胞角質-19，臨床上這些病人的年紀比較輕，平均 45.3 歲 vs. 58.1 歲；有比較高的胎兒蛋白值（13761 ng/ml vs. 5884 ng/ml）；比較不良的癌細胞分化（grade3-4:100% vs. 49%）。兩年的存活率比未表現 CK-19 的病人比較低（50% vs. 69%，但是 $P>0.05$ ）。

由以上之研究可發現，表現細胞角質 19 之肝癌發生於年紀比較輕的病人，腫瘤的分化度也比較不良，而且存活率也比較差。

英文摘要（Keywords：liver progenitor cells、cytokeratin-19、hepatocellular carcinoma）

In our previous studies, liver progenitors, oval cells, were shown to be marked by their expression of cytokeratin-19, in addition to other proteins such as aldolase, deleted in malignant brain tumor, platelet-derived growth factor binding protein, pancreatitis-associated protein, and jagged-1, etc. Stem cells share with cancer cells in several behaviors, for example, Wnt, Shh, and Notch signal cascades and the abilities to proliferate and migrate. This work is to study the expression of oval cell markers, especially cytokeratin-19, in HCCs and the relevance of its expression to the progressiveness of this cancer.

In this study, we performed cytokeratin (CK)-19 immunohistochemistry staining on liver cancer sections from 107 patients who have undergone surgical resection. The clinico-pathological analyses revealed CK-19-positive patients tend to be younger, having higher serum alpha-fetoprotein value. The tumors were more poorly differentiated, and the prognosis of patients was poorer.

From current study, we identified this CK-19-positive group to be a distinct group with earlier occurrence, poorer tumor differentiation and poorer prognosis.

報告內容：

前言：

Current knowledge indicates that liver oval cells might be an important candidate lineage of hepatic cells responsible for hepatocarcinogenesis. Oval cells share several similar characteristics with hepatocellular carcinoma (HCC) cells. Cytokeratin-19 is a well-known marker for both bile duct cells and oval cells in the liver. Cytokeratins are not just inert components as skeletons in cells. Recently they were found to have potential roles in mediating phenotypic changes of cells. For example, cytokeratin-19 was shown to be highly expressed in prostate intraepithelial neoplasia and invasive prostate carcinoma compared with normal or hyperplastic prostatic epithelium. Also, by comparative proteome analysis, dedifferentiated human retinal pigment epithelial cells displayed a strong shift toward increased expression of proteins associated with cell shape, cell adhesion, and stress fiber formation, including cytokeratin-19, gelsolin and tropomyosins. By using micro-chemotaxis chambers, human retinal pigment epithelial cells expressing cytokeratin-19 and -18 were more actively migrating.

研究目的：

To determine how often the HCCs express CK-19, and what are the clinicopathological correlations.

文獻探討：

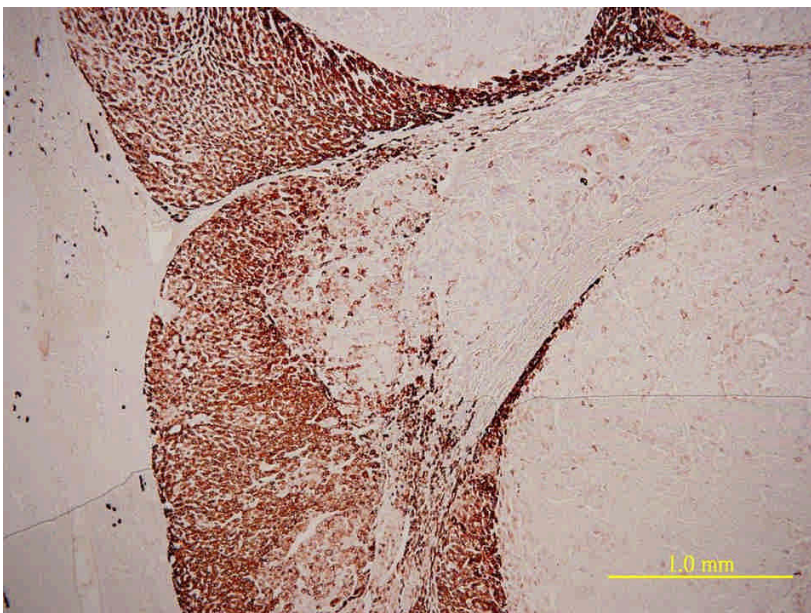
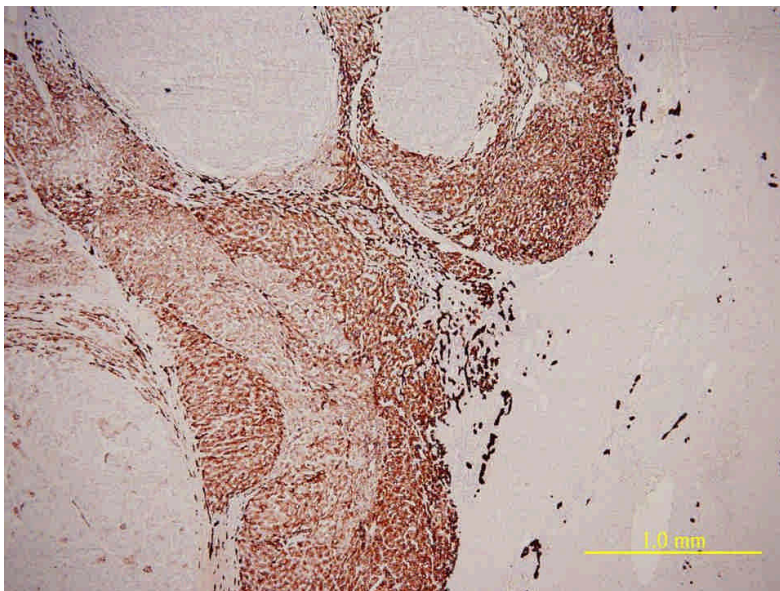
In HCCs, cytokeratin-19 expression has been shown to be a predictor of early postoperative recurrence due to increased invasiveness (Uenishi T, Kubo S, Yamamoto T, Shuto T, Ogawa M, Tanaka H, Tanaka S, Kaneda K, Hirohashi K. Cytokeratin 19 expression in hepatocellular carcinoma predicts early postoperative recurrence. *Cancer Sci* 2003;94:851-857.). By proteomic analysis, cytokeratin-19 was found overexpressed in a HCC cell strain with high metastatic potential in comparison to another strain with low metastatic potential. Furthermore, immunohistochemical study of cytokeratin-19 on HCC specimens revealed that more patients in the cytokeratin-19-positive group have overt intrahepatic metastases, i.e., satellite nodules, vascular tumor emboli and nodal metastasis (Ding SJ, Li Y, Tan YX, Jiang MR, Tian B, Liu YK, Shao XX, Ye SL, Wu JR, Zeng R, Wang HY, Tang ZY, Xia QC. From proteomic analysis to clinical significance. Overexpression of cytokeratin 19 correlates with hepatocellular carcinoma metastasis. *Molecular & Cellular Proteomics* 2004; 3:73-81.).

研究方法：

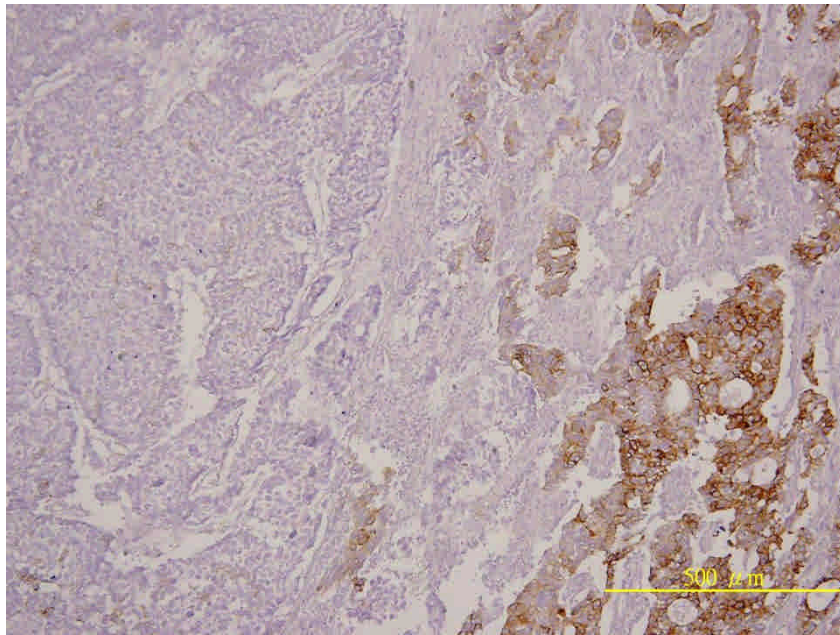
We have collected 107 HCC slides sectioned from paraffin-embedded blocs. The clinical information has been well recorded and the pathological status has been determined by a pathologist of hepatology specialist. The slides were immunohistochemically stained using CK-19 antibody and the nuclei were counterstained by hematoxylin. The slides were observed under a microscope and photos taken using a CCD camera. The statistics were performed using Mann-Whitney U test or Chi-Square test.

結果與討論：

CK-19 was successfully stained on the slides. Six among the 107 samples were positively stained. In non-tumor portion, only bile ducts within the portal tracts could be stained. In most cases, only part of the tumor was positive. An example below shows CK-19-positive cancer cells are located on the periphery of tumor nodules. New emerging cancer clusters at the center are negatively stained.



The CK-19 staining is more likely on the cancer cells with infiltrating property compared with neighboring cancer cells in nodules.



The clinicopathological correlations with CK-19 staining are as follow:

	CK - 19 ⁺	CK - 19 ⁻	P-value
Sex (M:F)	6 : 0	90 : 11	> 0.05
Age	45.3 ± 6.5	58.1 ± 13.2	< 0.05
AFP	13761 ± 13346	5884 ± 15659	< 0.05
Tumor size	8.7 ± 2.7	6.5 ± 4.0	> 0.05
Advanced tumor grade (3 & 4)	100 %	49 %	< 0.05
2-year survival rate	50 %	69 %	> 0.05

From current study, we identified this CK-19-positive group to be a distinct group with earlier occurrence, poorer tumor differentiation and poorer prognosis.