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Pathology

Cholangiolocellular Component Predicts a Biologically Distinct Subgroup of Mass-Forming Intrahepatic Cholangiocarcinoma

Naoto Kubota[1,2,3,4] | Ken Yamazaki[1] | Yasuhito Arai[4] | Minoru Esaki[5] | Nobuyoshi Hiraoka[6,7] | Hirofumi Shirakawa[3,8] | Moriaki Tomikawa[8] | Taisuhiro Shibata[4,9] | Michiie Sakamoto[3,10] | Hidenori Ojima[1,2,3,4]

[1]Department of Molecular Pathology, Research Institute, Tochigi Cancer Center, Tochigi, Japan | [2]Department of Pathology, Tochigi Cancer Center, Tochigi, Japan | [3]Department of Pathology, Keio University School of Medicine, Tokyo, Japan | [4]Division of Cancer Genomics, National Cancer Center Research Institute, Tokyo, Japan | [5]Hepatobiliary Pancreatic Surgery Division, National Cancer Center Hospital, Tokyo, Japan | [6]Division of Molecular Pathology, National Cancer Centre Research Institute, Tokyo, Japan | [7]Department of Diagnostic Pathology, National Cancer Center Hospital, Tokyo, Japan | [8]Department of Hepato-Biliary-Pancreatic Surgery, Tochigi Cancer Center, Tochigi, Japan | [9]Laboratory of Molecular Medicine, the Institute of Medical Science, The University of Tokyo, Tokyo, Japan | [10]School of Medicine, International University of Health and Welfare, Chiba, Japan

Correspondence: Hidenori Ojima (hojima@keio.jp)

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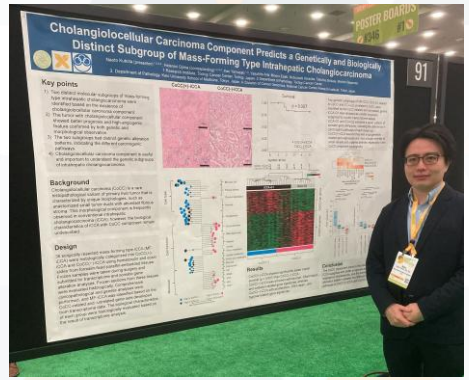
ABSTRACT

Cholangiolocellular carcinoma (CLC) is a histopathological variant of primary liver tumor with unique morphologies, and intrahepatic cholangiocarcinomas (ICCAs) frequently contain a CLC component; however, the biological characteristics of ICCA with CLC remain undescribed. In this study, 36 mass-forming ICCAs (MF-ICCAs), histologically small-duct type ICCA, were classified into CLC(+) ICCAs and CLC(−) ICCAs by the presence/absence of the CLC component. Two genetic subgroups were generated using highly expressed genes in CLC(+) ICCA and CLC(−) ICCA. As the results of clinicopathological and genetic analyses, CLC(+) ICCA had better overall survival and upregulation of stromal- and oxidation-related genes, whereas CLC(−) ICCA showed upregulation of proliferation- and hypoxia-related genes. Two genetic subgroups of ICCA were identified: ICCA-G1, which was related to CLC, and ICCA-G2, which was unrelated to CLC. ICCA-G1 comprised all 14 CLC(+) ICCAs [CLC(+)G1] and 7 of 19 CLC(−) ICCAs [CLC(−)G1], whereas ICCA-G2 was composed only of CLC(−) ICCAs [CLC(−)G2]. CLC(+)G1 and CLC(−)G1 exhibited similar patterns of somatic gene alterations compared with CLC(−)G2. Angiogenesis-related genes were upregulated in CLC(+)G1, and the number of tumor vessels was larger in CLC(+)G1, followed by CLC(−)G1, compared with CLC(−)G2. Further, *SPP1* (encoding osteopontin) was identified as a highly expressed angiogenesis-related gene in CLC(+) ICCA. Immunohistochemical expression of osteopontin was high in CLC(+) ICCA, showing apical and/or cytoplasmic expression patterns, which should facilitate the histopathological classification of ICCA-G1 and ICCA-G2. CLC component is useful for predicting a distinct genetic subgroup of MF-ICCA with better prognosis, high angiogenesis, and different gene alteration patterns, indicating different carcinogenic pathways of MF-ICCA.

本研究では、腫瘤形成型肝内胆管癌の一部にみられる細胆管細胞癌(CLC)成分に注目し、これまで一括りに語られることの多かった肝内胆管癌が、生物学的性質の異なる2つのサブタイプに分類されることが明らかになりました。特にCLC成分を有する肝内胆管癌は特徴的な遺伝子発現、遺伝子異常を示すとともに腫瘍内血管新生が亢進した予後良好なサブタイプであり、実臨床的にはOsteopontinの発現を免疫染色で確認することで精度の高い病理組織学的な分類が可能であることがわかりました。本研究成果により、エビデンスに基づいた肝内胆管癌病変の予後層別化が可能となり、将来的には治療の層別化による更なる予後の改善が期待されます。なお、本成果の一部はUSCAP（The United States and Canadian Academy of Pathology）2024でも発表されています。（尾島）



オープンアクセス

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