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研究課題名（和文）

肝細胞癌の発癌・進展の分子機構：造影超音波クッパー相と遺伝子発現を用いた融合解析

研究課題名（英文）

Molecular mechanism of Hepatocarcinogenesis and Development : Combined Analysis with Kupffer phase Contrast-enhanced US and Gene Expression.

研究代表者

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研究成果の概要（和文）：

肝細胞癌の多段階発癌は、異型結節から早期肝癌を経て、多血性の中分化型肝炎に至る。その過程における造影超音波クッパー相の所見と遺伝子発現を検討した。その結果、異型結節ではほぼ全例に OATP8 が発現するが、造影超音波クッパー相で低信号を呈す早期発癌ではほぼ全例において OATP8 の発現を認めなかった。また異型結節では Glypican3, HSP70, CAP2, GS, Bmi-1 の発現を認める例はなかったが、造影超音波クッパー相で低信号を呈す早期肝癌ではこれらの遺伝子群の発現を認めた。以上より、臨床的には造影超音波クッパー相で低信号を呈す結節は治療対象とすべき結節であることが確認された。

研究成果の概要（英文）：

OATP8 expression is observed in dysplastic nodule, but not in early hepatocellular carcinoma (e-HCC), which is shown as low intense on kupffer phase contrast-enhanced US. In addition, Glypican3, HSP70, GS, CAP2, Bmi-1 are highly expressed in e-HCC during multistep hepatocarcinogenesis.

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研究分野：総合領域

科研費の分科・細目：人間医工学・医用システム

キーワード：①超音波医科学 ②ソナゾイド造影超音波 ③肝細胞癌 ④クッパー細胞  
⑤遺伝子多型

## 1. 研究開始当初の背景

肝細胞癌は異型結節、早期肝癌、進行肝癌とた段階的に発癌進展していくが、異型結節、早期肝癌の遺伝子発現が進行癌のそれと差があるがどうかについてはいまだ明らかにされていない。

## 2. 研究の目的

造影超音波クッパー相で低信号となる乏血性結節に対し、さまざまな遺伝子を染色し、多段階発癌のどの段階でこれらの遺伝子発

現の消失、出現が現れるかを検討する。

## 3. 研究の方法

組織学的に異型結節、早期肝癌と診断された結節に対し、OATP8, GS, Glypican3, HSP70, CAP2, Bmi-1 の発現を検討し、どの時点でこれらの遺伝子変化が生じているかを検討する。

## 4. 研究成果

ソナゾイド超音波クッパー相で低信号を

呈する結節は、異型結節の場合はこれらの遺伝子群に変化は見られず、早期肝臓になって始めて OATP8 の発現低下、Glypican3, HSP70, CAP2, Bmi-1 の発現がみられることが明らかとなった。

#### 5. 主な発表論文等

(研究代表者、研究分担者及び連携研究者には下線)

[雑誌論文] (計 41 件)

1. Minami Y, Okumura N, Yamamoto N, Tsuji N, Kono Y, Kudo M\*: Quantification of tumor vascularity with contrast-enhanced ultrasound for early response of transcatheter arterial chemoembolization for hepatocellular carcinoma: a report of three cases. **J Med Ultrason** 28: 15-19, 2012. (査読あり)
2. Clavien PA, Lesurtel M, Bossuyt PM, Gores GJ, Langer B, Perrier A, Abecassis M, Balabaud C, Barritt GJ, Belghiti J, Bhoori S, Bossuyt P, Breitenstein S, Broelsch C, Bruix J, Burra P, Burroughs A, Busuttil R, Charlton M, Cherqui D, Colombo ML, d'Albuquerque C, D'Alessandro A, de Santibanez EJ, Dufour F, Durand F, Dutkowski P, Duvoux C, El-Serag H, Fan ST, Finn RS, Fisher R, Forner A, Freeman R, Fung J, Geier A, Germani G, Gores G, Gouw AS, Grant D, Greig P, Gurusamy K, Hanto D, Heaton N, Heim M, Hemming A, Hippen B, Hisham A, Hubscher S, Ichida T, Kahn D, Kew M, Kita Y, Kiuchi T, Klintmalm GB, Kneteman N, Kojiro M, Kudo M, Langer B, Lee JM, Lee SG, Lencioni R, Lerut J, Lesurtel M, Livraghi T, Llovet JM, Lo CM, Lodge P, MacCaughan G, Madoff D, Majno P, Marcellin P, Marrero J, Mazzaferro V, Mergental H, Merle P, Miksad R, Mornex F, Mullhaupt B, Olthoff K, Paradis V, Perrier A, Pestalozzi B, Pomfret E, Poon R, Porte R, Greig P, Prasad KR, Raptis D, Roskams T, Rossi M, Samuel D, Schlitt H, Schwartz M, Sexton Dobby AM, Shaked A, Sherman M, Siegler M, Suh KS, Todo S, Toso C, Trevisani F, Trotter JJ, Veldecasas GJ, Vauthey N, Vilgrain V, Villamil F, Vonlanthen R, Wald C, Weber A, Wiesner R, Wright L, Yao F, Zheng SS, Zucman-Rossi J: Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report. **Lancet Oncol** 13: e11-22, 2012. (査読あり)
3. Minami Y, Kitai S, Kudo M\*: Treatment response assessment of radiofrequency ablation for hepatocellular carcinoma: Usefulness of virtual CT sonography with magnetic navigation. **Eur J Radiol** 81: e277-280, 2012. (査読あり)
4. Takayasu K, Arai S, Kudo M, Ichida T, Matsui O, Izumi N, Matsuyama Y, Sakamoto M, Nakashima O, Ku Y, Kokudo N, Makuuchi M: Superselective transarterial chemoembolization for hepatocellular carcinoma. Validation of treatment algorithm proposed by Japanese guidelines. **J Hepatol** 56: 886-892, 2012. (査読あり)
5. Kudo M\*, Tateishi R, Yamashita T, Ikeda M, Furuse J, Ikeda K, Kokudo N, Izumi N, Matsui O: Current status of hepatocellular carcinoma treatment in Japan: Case study and discussion-voting system. **Clin Drug Invest** 32;suppl.2:37-51, 2012. (査読あり)
6. Saito J, Kim SR, Kuod M, Imoto S, Ando K, Nakajima T, Fukuda K, Otono Y, Kim SK, Komaki T, Yano H, Nakashima O, Sugimoto K, Matsuoka T: Well-differentiated hepatocellular carcinoma detected as hypovascularity by only CT during hepatic arteriography. **Intern Med** 51:885-890, 2012. (査読あり)
7. Lencioni R, Kudo M, Ye SL, Bronowicki JP, Chen XP, Dagher L, Furuse J, Geschwind JF, Guevara LL, Papandreou C, Sanyal AJ, Takayama T, Yoon SK, Nakajima K, Cihon F, Heldner S, Marrero JA: First interim analysis of the GIDEON (Global Investigation of therapeutic DEcisions in hepatocellular

- carcinoma and Of its treatment with sorafeNib) non-interventional study. **Int J Clin Pract** 66:675-683, 2012. (査読あり)
8. Okada M, Ishii K, Numata K, Hyodo T, Kumano S, Kitano M, **Kudo M**, Murakami T: Can the biliary enhancement of Gd-EOB-DTPA predict the degree of liver function? **Hepatob Pancreatic Dis Int** 11:307-313, 2012. (査読あり)
  9. Hagiwara S, **Kudo M**, Nagai T, **Inoue T**, Ueshima K, Nishida N, Watanabe T, Sakurai T: Activation of JNK and high expression level of CD133 predict a poor response to Sorafenib in hepatocellular carcinoma. **Brit J Cancer** 106:1997-2003, 2012. (査読あり)
  10. Shiina T, Maki T, Yamakawa M, Mitake T, **Kudo M**, Fujimoto K: Mechanical model analysis for quantitative evaluation of liver fibrosis based on ultrasound tissue elasticity imaging. **Jpn J Appl Phys** 51:07GF11-1-8, 2012. (査読あり)
  11. Hagiwara S, Sakurai T, Nishina S, Tanaka K, Ikeda M, Ueshima K, Minami Y, **Inoue T**, Yada N, Kitai S, Takita M, Nagai T, Hayaishi S, Arizumi T, Park AM, Munakata H, Nishida N, **Kudo M**: Characteristic pattern of reactivation of hepatitis B virus during chemotherapy for solid cancers. **Digest Dis** 30:541-546, 2012. (査読あり)
  12. Nishida N, Arizumi T, Hayaishi S, Takita M, Kitai S, Yada N, Hagiwara S, **Inoue T**, Minami Y, Ueshima K, Sakurai T, Ikai I, **Kudo M**: Gender differences in the livers of patients with hepatocellular carcinoma and chronic hepatitis C infection. **Digest Dis** 30:547-553, 2012. (査読あり)
  13. Ueda T, Tsuchiya K, Hashimoto S, **Inoue T**, Inao M, Tanaka A, Kaito M, Imazaki F, Nishiguchi S, Mochida S, Yokosuka O, Yatsushashi H, Izumi N, **Kudo M**, for RETRY study group: Retreatment with peginterferon alfa-2a plus ribavirin in patients who failed previous peginterferon alfa-2b plus ribavirin combination therapy. **Digest Dis** 30:554-560, 2012. (査読あり)
  14. Hagiwara S, Sakurai T, Takita M, Ueshima K, Minami Y, **Inoue T**, Yada N, Kitai S, Nagai T, Hayaishi S, Arizumi T, Nishida N, **Kudo M**: Risk of HCC development in cases of hepatitis C treated by long-term, low-dose PEG-IFN  $\alpha$ 2a. **Digest Dis**, 30:561-567, 2012. (査読あり)
  15. Kobayashi S, Kim SR, Imoto S, Ando K, Hirakawa M, Saito J, Fukuda K, Otono Y, Sakaki M, Tsuchida S, Kim SK, Hayashi Y, Nakano M, **Kudo M**: Histopathological diagnosis of early HCC through biopsy -efficacy of victoria blue and cytokeratin 7 staining-. **Digest Dis** 30:574-579, 2012. (査読あり)
  16. Tsuchida S, Fukumoto T, Toyokawa A, Awazu M, Kusunoki N, Kido M, Takahashi M, Tanaka M, Kuramitsu K, Kim SR, **Kudo M**, Ku Y: Novel non-trocar technique for laparoscopic radiofrequency ablation. **Digest Dis** 30:588-591, 2012. (査読あり)
  17. Minami Y, **Kudo M**\*: Hepatocellular carcinoma with obstructive jaundice: endoscopic and percutaneous biliary drainage. **Digest Dis** 30:592-597, 2012. (査読あり)
  18. **Kudo M**\*, Ueshima K, Arizumi T: Real-life clinical practice with sorafenib in advanced hepatocellular carcinoma: a aingle center experience. **Digest Dis** 30:609-616, 2012. (査読あり)
  19. Katsube T, Okada M, Kumano S, Imaoka I, Kagawa Y, Horii M, Ishii K, Tanigawa N, Imai Y, **Kudo M**, Murakami T: Estimation of liver function using T2\* mapping on gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid enhanced magnetic resonance imaging. **Eur J Radiol** 81:1460-1464, 2012. (査読あり)

20. Nishida N, **Kudo M**, Nagasaka T, Ikai I, Goel A: Characteristic patterns of altered DNA methylation predict emergence of human hepatocellular carcinoma. **Hepatology** 56:994-1003, 2012. (査読あり)
21. **Kudo M**: Signaling pathway/molecular targets and new targeted agents under development in hepatocellular carcinoma. **World J Gastroenterol** 18:6005-6017, 2012. (査読あり)
22. **Kudo M**: Japan's successful model of nationwide hepatocellular carcinoma surveillance highlighting the urgent need for global surveillance. **Liver Cancer** 1(3):141-143, 2012. (査読あり)
23. Okusaka T, Kasugai H, Ishii H, **Kudo M**, Sata M, Tanaka K, Shioyama Y, Chayama K, Kumada H, Yoshikawa M, Seki T, Saito H, Hayashi N, Shiratori K, Okita K, Sakaida I, Honda M, Kusumoto Y, Tsutsumi T, Sakata K: A randomized phase II trial of intra-arterial chemotherapy using SM-11355 (Miriplatin) for hepatocellular carcinoma. **Invest New Drug** 30: 2015-2025, 2012. (査読あり)
24. Hagiwara S, **Kudo M**, Chung H, Ueshima K, **Inoue T**, Haji S, Watanabe T, Park AM, Munakata H, Sakurai T: Activation of c-Jun N-terminal kinase in non-cancerous liver tissue predicts a high risk of recurrence after hepatic resection for hepatocellular carcinoma. **Hepatol Res** 42: 394-400, 2012. (査読あり)
25. **Kudo M\***: Targeted therapy for liver cancer: updated review in 2012. **Curr Cancer Drug Tar** 12: 1062-1072, 2012. (査読あり)
26. Kaneko S, Furuse J, **Kudo M**, Ikeda K, Honda M, Nakamoto Y, Onchi M, Shiota G, Yokosuka O, Sakaida I, Takehara T, Ueno Y, Hiroishi K, Nishiguchi S, Moriwaki H, Yamamoto K, Sata M, Obi S, Miyayama S, Imai Y: Guideline on the use of new anticancer drugs for the treatment of hepatocellular carcinoma 2010 update. **Hepatol Res** 42: 523-542, 2012. (査読あり)
27. **Inoue T**, **Kudo M\***, Komuta M, Hayaishi S, Ueda T, Takita M, Kitai S, Hatanaka K, Yada N, Hagiwara S, Chung H, Sakurai T, Ueshima K, Sakamoto M, Maenishi O, Hyodo T, Okada M, Kumano S, Murakami T: Assessment of Gd-EOB-DTPA-enhanced MRI for HCC and Dysplastic nodule and comparison of detection sensitivity versus MDCT. **J Gastroenterol** 47: 1036-1047, 2012. (査読あり)
28. Nagai T, Arao T, Furuta K, Sakai K, Kudo K, Kaneda H, Tamura D, Aomatsu K, Kimura H, Fujita Y, Matsumoto K, Saijo N, **Kudo M**, Nishio K: Sorafenib inhibits the hepatocyte growth factor-mediated epithelial mesenchymal transition in hepatocellular carcinoma. **Mol Cancer Ther** 10: 169-177, 2011. (査読あり)
29. **Kudo M**, Hatanaka K, Kumada T, Toyoda H, Tada T: Double-contrast ultrasound: a novel surveillance tool for hepatocellular carcinoma. **Am J Gastroenterol** 106: 368-370, 2011. (査読あり)
30. Kudo K, Arao T, Tanaka K, Kaneda H, Matsumoto K, Tamura D, Aomatsu K, Velasco M, Fujita Y, Saijo N, **Kudo M**, Nishio K: Antitumor activity of BIBF 1120, a vascular endothelial growth factor-2 inhibitor and use of VEGR2+pTYR+leucocyte as a pharmacodynamic biomarker. **Clin Cancer Res** 17: 1373-1381, 2011. (査読あり)
31. Hagiwara S, **Kudo M\***, Ueshima K, Chung H, Yamaguchi M, Takita M, Haji S, Kimura M, Arao T, Nishio K, Park AM, Munakata H: The cancer stem cell marker CD133 is a predictor of the effectiveness of S1+pegylated interferon  $\alpha$ -2b therapy against advanced hepatocellular carcinoma. **J Gastroenterol** 46: 212-221, 2011. (査読あり)
32. Kagawa Y, Okada M, Kumano S, Katsube T, Imaoka I, Tanigawa N, Ishii K,

- Kudo M**, Murakami T: Optimal scanning protocol of arterial dominant phase for hypervascular hepatocellular carcinoma with gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid-enhanced MR. **J Magn Reson Imaging** 33: 864-872, 2011. (査読あり)
33. Katsube T, Okada M, Kumano S, Hori M, Imaoka I, Ishii K, **Kudo M**, Kitagaki H, Murakami T: Estimation of liver function using T1 mapping on Gd-EOB-DTPA-enhanced magnetic resonance imaging. **Invest Radiol** 46: 277-283, 2011. (査読あり)
34. Eguchi S, Kanematsu T, Arai S, Omata M, **Kudo M**, Sakamoto M, Takayasu K, Makuuchi M, Matsuyama Y, Monden M, for the Liver Cancer Study Group of Japan: Recurrence-free survival more than 10 years after liver resection for hepatocellular carcinoma. **Brit J Surg** 98: 552-557, 2011. (査読あり)
35. **Kudo M\***, Izumi N, Kokudo N, Matsui O, Sakamoto M, Nakashima O, Kojiro M, Makuuchi M: Management of hepatocellular carcinoma in Japan: Consensus-based clinical practice guideline proposed by the Japan Society of Hepatology (JSH) 2010 updated version. **Digest Dis** 29: 339-364, 2011. (査読あり)
36. Yoshida H, Shiratori Y, **Kudo M**, Shiina S, Mizuta T, Kojiro M, Yamamoto K, Koike Y, Saito K, Koyanagi N, Kawabe T, Kawazoe S, Kobashi H, Kasugai H, Osaki Y, Araki Y, Izumi N, Oka H, Tsuiji K, Toyota J, Seki T, Osawa T, Masaki N, Ichinose M, Seike M, Ishikawa A, Ueno Y, Tagawa K, Kuromatsu R, Sakisaka S, Ikeda H, Kuroda H, Hokuryu H, Yamashita T, Sakaida I, Katamoto T, Kikuchi K, Nomoto M, Omata M: Effect of vitamin K2 on the recurrence of hepatocellular carcinoma. **Hepatology** 54: 532-540, 2011. (査読あり)
37. **Kudo M\***: Hepatocellular carcinoma in 2011 and beyond: From the pathogenesis to molecular targeted therapy. **Oncology** 81: 1-10, 2011. (査読あり)
38. Sakurai T, **Kudo M**: Signaling pathways governing tumor angiogenesis. **Oncology** 81: 24-29, 2011. (査読あり)
39. Alaboudy A, **Inoue T**, Hatanak K, Chung H, Hyodo T, Kumano S, Murakami T, Moustafa EFA, **Kudo M**: Usefulness of combination of imaging modalities in the diagnosis of hepatocellular carcinoma using Sonazoid-enhanced ultrasound, gadolinium diethylene-triamine-pentaacetic acid-enhanced magnetic resonance imaging, and contrast-enhanced computed tomography. **Oncology** 81: 66-72, 2011. (査読あり)
40. **Kudo M\***: Diagnostic imaging of hepatocellular carcinoma: Recent progress. **Oncology** 81: 73-85, 2011. (査読あり)
41. Minami Y, **Kudo M\***: Review of dynamic contrast-enhanced ultrasound guidance in ablation therapy for hepatocellular carcinoma. **World J Gastroenterol** 17: 4952-4959, 2011. (査読あり)

## 6. 研究組織

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