Kondo Y, Akanuma M, Yoshida H, Koike K.	MICA by microRNAs.				
Liu Y, Higashitsuji H, Higashitsuji H, Itoh K, Sakurai T, Koike K, Hirota K, Fukumoto M, Fujita J.	Overexpression of gankyrin in mouse hepatocytes induces hemangioma by suppressing factor inhibiting hypoxia-inducible factor-1 (FIH-1) and activating hypoxia-inducible factor-1.	**Biochem Biophys Res Commun**	432(1)	22-27	2013
Koike K.	The oncogenic role of hepatitis C virus.	**Recent Results Cancer Res**	193	97-111	2014
Uchino K, Tateishi R, Nakagawa H, Shindoh J, Sugawara Y, Akahane M, Shibahara J, Yoshida H, Koike K.	Uninodular combined hepatocellular and cholangiocarcinoma with multiple non-neoplastic hypervascular lesions appearing in the liver of a patient with HIV and HCV coinfection.	**J Clin Virol**	57(2)	173-177	2013
Ohno M, Shibata C, Kishikawa T, Yoshikawa T, Takata A, Kojima K, Akanuma M, Kang YJ, Yoshida H, Otsuka M, Koike K.	The flavonoid apigenin improves glucose tolerance through inhibition of microRNA maturation in miRNA103 transgenic mice.	**Sci Rep**	3	2553	2013
Ikeda K, Izumi N, Tanaka E, Yotsuyanagi H, Takahashi Y, Fukushima	Fibrosis score consisting of four serum markers successfully predicts	**Hepatol Res**	43(6)	596-604	2013

J, Kondo F, Fukusato T, Koike K, Hayashi N, Kumada H.	pathological fibrotic stages of chronic hepatitis B.				
Urabe Y, Ochi H, Kato N, Kumar V, Takahashi A, Muroyama R, Hosono N, Otsuka M, Tateishi R, Lo PH, Tanikawa C, Omata M, Koike K, Miki D, Abe H, Kamatani N, Toyota J, Kumada H, Kubo M, Chayama K, Nakamura Y, Matsuda K.	A genome-wide association study of HCV induced liver cirrhosis in the Japanese population identifies novel susceptibility loci at MHC region.	**J Hepatol**	58(5)	875-882	2013
Hikita H, Nakagawa H, Tateishi R, Masuzaki R, Enooku K, Yoshida H, Omata M,Soroida Y, Sato M, Gotoh H, Suzuki A, Iwai T, Yokota H, Koike K, Yatomi Y, IkedaH.	Perihepatic lymph node enlargement is a negative predictor of liver cancerdevelopment in chronic hepatitis C patients.	**J Gastroenterol**	48(3)	366-373	2013
Lo PH, Urabe Y, Kumar V, Tanikawa C, Koike K, Kato N, Miki D, Chayama K, Kubo M, Nakamura Y, Matsuda K.	Identification of a functional variant in the mica promoter which regulates mica expression and increases HCV-related hepatocellular carcinoma risk.	**PLoS One**	8(4)	e61279	2013
Minami T, Kishikawa T, Sato M, Tateishi R, Yoshida H, Koike K.	Meta-analysis: mortality and serious adverse events of peginterferon plus ribavirin therapy for chronic hepatitis C.	**J Gastroenterol**	48(2)	254-268	2013

Ikeda H, Enooku K, Ohkawa R, Koike K, Yatomi Y.	Plasma lysophosphatidic acid levels and hepatocellular carcinoma.	**Hepatology**	57	417-418	2013
Takata A, Otsuka M, Yoshikawa T, Kishikawa T, Hikiba Y, Obi S, Goto T, KangYJ, Maeda S, Yoshida H, Omata M, Asahara H, Koike K.	MiRNA-140 acts as a livertumor suppressor by controlling NF-κB activity via directly targeting Dnmt1expression.	**Hepatology**	57	162-170	2013
Nishimura T, Yamaguchi K, Fujii H, Okada Y, Yokomizo C, Niimi T, Sumida Y, Yasui K, Mitsuyoshi H, Minami M, Umemura A, Shima T, Okanoue T, Itoh Y	Prediction of favorable clinical course in hepatitis C virus carriers with persistently normal serum alanine aminotransferase levels: A long-term follow-up study	Hepatol Res	43	557-562	2013
Okada Y, Yamaguchi K, Nakajima T, Nishikawa T, Jo M, Mitsumoto Y, Kimura H, Nishimura T, Tochiki N, Yasui K, Mitsuyoshi H, Minami M, Kagawa K, Okanoue T, Itoh Y	Rosuvastatin ameliorates high-fat and high-cholesterol diet-induced nonalcoholic steatohepatitis in rats	Liver Int	33	301-311	2013
Yoneda M, Imajo K, Eguchi Y, Fujii H, Sumida Y, Hyogo H, Ono M, Suzuki Y, Kawaguchi T, Aoki N, Sata M, Kanemasa K, Kohgo Y, Saibara T, Chayama K, Itoh Y, Yoshikawa T, Anza I K, Fujimoto K, Okanoue T, Nakajima A	Noninvasive scoring systems in patients with nonalcoholic fatty liver disease with normal alanine aminotransferase levels	J Gastroenterol	48	1051-1060	2013

Sumida Y, Naito Y, Tanaka S, Sakai K, Inada Y, Taketani H, Kanemasa K, Yasui K, Itoh Y, Okanoue T, Yoshikawa T	Long-term (>2 Yr) efficacy of vitamin E for non-alcoholic steatohepatitis	Hepato-Gastroenterology	60	1445-1450	2013
Nakahara T, Hyogo H, Yoneda M, Sumida Y, Eguchi Y, Fujii H, Ono M, Kawaguchi T, Imajo K, Aikata H, Tanaka S, Kanemasa K, Fujimoto K, Anzai K, Saibara T, Sata M, Nakajima A, Itoh Y, Chayama K, Okanoue T	Type 2 diabetes mellitus is associated with the fibrosis severity in patients with nonalcoholic fatty liver disease in a large retrospective cohort of Japanese patients	J Gastrienterol	online 26 November		2013
Kondo Y, Hasegawa G, Okada H, Senmaru T, Fukui M, Nakamura N, Sawada M, Kitawaki J, Okanoue T, Kishimoto Y, Amano A, Maruyama N, Obayashi H, Ishigami A	*Lepr*db/db mice with senescence marker protein-30 knockout (*Lepr*db/db *Smp*30Y/-) exhibit increase in small dense –LDL severe fatty liver despite being fed a standard diet	PLoS One	8(6)	e65698	2013
Shima T, Uto H, Ueki K, Takamura T, Kohgo Y, Kawata S, Yasui K, Park H, Nakamura N, Nakatou T, Tanaka N, Umemura A, Mizuno M, Tanaka J, Okanoue T	Clinicopathological features of liver injury in patients with type 2 diabetes mellitus and comparative study of histologically proven nonalcoholic fatty liver disease with or without type 2 diabetes mellitus	J Gastroenterol	48	515-525	2013
Ue M, Ikebe N, Munekage K, Ochi T, Ono M, Saibara T.	Hepatocyte destruction with enhanced collagen synthesis in the liver of	J Viral Hepat	20	350-357	2013

	chronic hepatitis C patients on hemodialysis.				
Osawa Y, Hoshi M, Yasuda I, Saibara T, Moriwaki H, Kozawa O.	Tumor necrosis factor-αpromotes cholestasis-induced liver fibrosis in the mouse through tissue inhibitor of metalloproteinase-1 production in hepatic stellate cells.	PLoS ONE	8	e65251	2013
Yoneda M, Imajo K, Eguchi Y, Fujii H, Sumida Y, Hyogo H, Ono M, Suzuki Y, Kawaguchi T, Aoki N, Sata M, Kanemasa K, Kohgo Y, Saibara T, Chayama K, Itoh Y, Yoshikawa T, Anzai K, Fujimoto K, Okanoue T, Nakajima A; Japan Study Group of Nonalcoholic Fatty Liver Disease.	Noninvasive scoring systems in patients with nonalcoholic fatty liver disease with normal alanine aminotransferase levels.	J Gastroenterol	48	1051-1060.	2013
Saibara T, Enomoto N, Kaneko S, Chayama K, Sata M, Imawari M, Onishi S, Okita K.	Clinical efficacy of combination therapy with ME3738 and pegylated interferon alpha-2a in patients with hepatitis C virus genotype 1.	Hepatol Res		doi: 10.1111/hepr.12139.	2013
Ono M, Ogasawara M, Hirose A, Mogami S, Ootake N, Aritake K, Higuchi T, Okamoto N,	Bofutsushosan, a Japanese herbal (Kampo) medicine, attenuates progression of	J Gastroenterol		DOI 10.1007/s00535-013-0852-8	

Sakamoto S, Yamamoto M, Urade Y, Saibara T, Oben JA.	nonalcoholic steatohepatitis in mice.				
Taketani H, Sumida Y, Tanaka S, Imajo K, Yoneda M, Hyogo H, Ono M, Fujii H, Eguchi Y, Kanemasa K, Chayama K, Itoh Y, Yoshikawa T, Saibara T, Fujimoto K, Nakajima A; Japan Study Group of NAFLD	The association of insomnia with gastroesophageal reflux symptoms in biopsy-proven nonalcoholic fatty liver disease.	J Gastroenterol.		Aug 22	2013
Hashiba M, Ono M, Hyogo H, Ikeda Y, Masuda K, Yoshioka R, Ishikawa Y, Nagata Y, Munekage K, Ochi T, Hirose A, Nozaki-Fujimura Y, Noguchi S, Okamoto N, Chayama K, Suganuma N, Saibara T.	Glycemic variability is an independent predictive factor for development of hepatic fibrosis in nonalcoholic Fatty liver disease.	PLoS One.	8	e76161	2013
Toda K, Hayashi Y, Yamashita A, Okabe M, Ono M, Saibara T.	Aromatase-null mice expressing enhanced green fluorescent protein in germ cells provide a model system to assess estrogen-dependent ovulatory responses.	Transgenic Res		Nov 22.	2013
Nakahara T, Hyogo H, Yoneda M, Sumida Y, Eguchi Y, Fujii H, Ono M, Kawaguchi T, Imajo K, Aikata H, Tanaka S,	Type 2 diabetes mellitus is associated with the fibrosis severity in patients with nonalcoholic fatty liver disease in a	J Gastroenterol.		Nov 26.	2013

Kanemasa K, Fujimoto K, Anzai K, Saibara T, Sata M, Nakajima A, Itoh Y, Chayama K, Okanoue T; Japan Study Group of Nonalcoholic Fatty Liver Disease.	large retrospective cohort of Japanese patients.				
Tanaka K, Hyogo H, Ono M, Takahashi H, Kitajima Y, Ono N, Eguchi T, Fujimoto K, Chayama K, Saibara T, Anzai K, Eguchi Y, Japan Study Group of Nonalcoholic Fatty Liver Disease.	The upper limit of normal serum alanine aminotransferase levels in Japanese subjects.	Hepatology Research		DOI: 10.1111/hepr.12293	2013
Hashimoto E, Taniai M, Tokushige K.	Characteristics and diagnosis of NAFLD/NASH.	J Gastroenterol Hepatol	28 Suppl 4	64-70	2013
TokushigeK, HashimotoE, Kodama K.	Hepatocarcinogenesis in non-alcoholic fatty liver disease in Japan.	J Gastroenterol Hepatol	28 Suppl 4	88-92	2013
Sato K, Tanaka S, Mitsunori Y, Mogushi K, Yasen M, Aihara A, Ban D, Ochiai T, Irie T, Kudo A, Nakamura N, Tanaka H, Arii S.	Contrast-enhanced intraoperative ultrasonography for vascular imaging of hepatocellular carcinoma; clinical and biological significance.	Hepatology	57(4)	1436-1447	2013
Muramatsu S, Tanaka S, Mogushi K, Adikrisna R, Aihara A, Ban D, Ochiai T, Irie T, Kudo A, Nakamura N, Tanaka H, Nakayama K, Tanaka H,	Visualization of stem cell features in human hepatocellular carcinoma enlightened in vivo significance of tumor-host interaction and clinical	Hepatology	58(1)	218-228	2013

Yamaoka S, Arii S.	implication.				
Furuta M, Kozaki KI, Tanimoto K, Tanaka S, Arii S, Shimamura T, Niida A, Miyano S, Inazawa J.	The Tumor-suppressive mir-497-195 cluster targets multiple cell-cycle regulators in hepatocellular carcinoma.	PLoS One	8(3)	e60155	2013
Katsuta E, Tanaka S, Mogushi K, Matsumura S, Ban D, Ochiai T, Irie T, Kudo A, Nakamura N, Tanaka H, Tanabe M, Arii S.	Age-related clinicopathological and molecular features of patients received curative hepatectomy for hepatocellular carcinoma.	American Journal of Surgery			in press
Kudo A, Tanaka S, Ban D, Matsumura S, Irie T, Ochiai T, Nakamura N, Arii S, Tanabe M.	Alcohol consumption and recurrence of non-B or non-C hepatocellular carcinoma after hepatectomy: a propensity score analysis.	Journal of Gastroenterology			in press
Ogawa K, Tanaka S, Matsumura S, Murakata A, Ban D, Ochiai T, Irie T, Kudo A, Nakamura N, Tanabe M, Arii S.	EpCAM-Targeted therapy for human hepatocellular carcinoma.	Annals of Surgical Oncology			in press
Kudo A, Mogushi K, Takayama T, Matsumura S, Ban D, Irie T, Ochiai T, Tanaka H, Anzai N, Sakamoto M, Tanaka S, Arii S.	Mitochondrial metabolism in the Noncancerous Liver Determine the Occurrence of Hepatocellular Carcinoma: A Prospective Study.	Journal of Gastroenterology			in press

Okada-Iwabu M, Yamauchi T, Iwabu M, Honma T, Hamagami K, Matsuda K, Yamaguchi M, Tanabe H, Kimura-Someya T, Shirouzu M, Ogata H, Tokuyama K, Ueki K, Nagano T, Tanaka A, Yokoyama S, Kadowaki T.	A small-molecule AdipoR agonist for type 2 diabetes and short life in obesity.	Nature	503	493-499	2013
Moller JB, Pedersen M, Tanaka H, Ohsugi M, Overgaard RV, Lynge J, Almind K, Vasconcelos NM, Poulsen P, Keller C, Ueki K, Ingwersen SH, Pedersen BK, Kadowaki T	Body Composition is Main Determinant for the Difference in Type 2 Diabetes Pathophysiology between Japanese and Caucasians.	Diabetes Care		Oct 15 (Epub ahead of print)	2013
Nakaya K, Kubota N, Takamoto I, Kubota T, Katsuyama H, Sato H, Tokuyama K, Hashimoto S, Goto M, Jomori T, Ueki K, Kadowaki T.	Dipeptidyl peptidase-4 inhibitor anagliptin ameliorates diabetes in mice with haploinsufficiency of glucokinase on a high-fat diet.	Metabolism	62	933-951	2013
Akuta N, Suzuki F, Kawamura Y, Sezaki H,Hosaka T, Kobayashi M,Hara T, Kobayashi M, Saitoh S, Arase Y, Ikeda K, Kumada H	Utility of telaprevir-resistant variant detection for prediction of treatment efficacy in HCV genotype 1.	J Clin Microbiol.	52	193-200	2014
Arase Y, Kobayashi M, Kawamura Y, Suzuki F,Suzuki Y, Akuta N, Kobayashi M, Sezaki H,Saito S, Hosaka T, Ikeda K, Kumada H,	Impact of virus clearance for the developmentof hemorrhogic stroke in chronic hepatitis C.	J Med Virol.	86	169-175	2014

Kobayashi T					
Akuta N, Suzuki F, Kobayashi M, Hara T, Sezaki H, Suzuki Y, Hosaka T, Kobayashi M,Saitoh S, Ikeda K, Kumada H	Correlation between hepatitis B virus surfaceantigen level and alpha-fetoprotein in patientsfree of hepatocellular carcinoma or severehepatitis	J Med Virol.	86	131-138	2014
Sezaki H, Suzuki F, Hosaka T, Akuta N, Fukushima T, Hara T, Kawamura Y, KobayashiM, Suzuki Y, Saitoh S, Arase Y, Ikreda K, Kumada H	Effectiveness and safety of reduced-dose telaprevir-based triple therapy in chronic hepatitis C patients	Hepatol Res.			Epub ahead of print
Tanaka M, Suzuki F, Seko Y, Hara T, Kawamura Y, Sezaki H, Hosaka T, Akuta N, Kobayashi M, Suzuki Y, Saitoh S, Arase Y, Ikeda K, Kobayashi M, Kumada H.	Renal dysfunction and hypophosphatemia during long-term lamivudine plus adefovir dipivoxil therapy in patients with chronic hepatitis B.	J Gastroenterol.			Epub ahead of print
Kobayashi M, Hosaka T,Suzuki F, Akuta N, Sezaki H, Suzuki Y, Kawamura Y, Kobayashi M, Saitoh S, Arase Y, Ikeda K, Miyakawa Y, Kumada H	Seroclearance rate of hepatitis B suerfaceantigen in 2,112 patients with chronichepatitis in Japan during long-term follow-up	J Gastroenterol.			Epub ahead of print
Kawamura Y, Ikeda K, Fukushima T, Hara T, Kobayashi M, Saitoh S, Sezaki H, Akuta N, Suzuki F, Suzuki Y, Arase Y, Kumada H	Potential of no-touch pincer ablation procedurefor small hepatocellular carcinoma	HepatolRes.			Epub ahead of print

	that uses amulitipolar radiofrequency ablation system: anexperrimental animal study.				
Suzuki F, Hosaka T, Suzuki Y, Akuta N, Sezaki H, Hara T, Kawamura Y, Kobayashi M, Saitoh S, Arase Y, Ikeda K, Kobayashi M, Watahiki S, Mineta R, Kumada H	Long-term efficacy and emergence of multidrugresistance in patients with lamivudine-refractory chronic hepatitis B treated bycombination therapy with adefovir pluslamivudine	J Gastroenterol.			Epub ahead of print
Arase Y, Kobayashi M, Suzuki F, Suzuki Y, Kawamura Y, Akuta N, Kobayashi M, Sezaki H, Saito S, Hosaka T, Ikeda K, Kumada H, Kobayashi T.	Effect of type 2 diabetes on risk formalignancies included hepatocellular carcinomain chronic hepatitis C	Hepatology.	3	964-973	2013
Hirakawa M, Ikeda K, Kobayashi M, Kawamura Y, Hosaka T,Sezaki H, Akuta N, Suzuki F, Suzuki Y, Saitoh S, Arase Y, Kumada H	Randomized controlled trial of a new procedureof radiofrequency ablation using an expandableneedle hepatocelluar carcinoma	Hepatol Res.	43	846-852	2013
Suzuki F, Suzuki Y, Sezaki H, Akuta N, Seko Y, Kawamura Y, Hosaka T, Kobayashi M,Saito S, Arase Y, Ikeda K, Mineta R, Watahiki S, Kobayashi M, Nakayasu Y, Tsuda H, Aoki K, Yamada I, Kumada H	Exploratory Study on telaprevir given every 8hat 500mg or 750mg with peginterferon-alpha-2ban d rivavirin in hepatitis C patients	Hepatol Res.	43	691-701	2013

Hosaka T, Suzuki F, Kobayashi M, Seko Y, Kawamura Y, Sezaki H,Akuta N, Suzuki Y, Saitoh S, Arase Y, Ikeda K, Kobayashi M, Kumada H	Long-term entecavir treatment reduceshepatocellular carcinoma incidence in patientswith hepatitis B virus infection	Hepatology.	58	98-107	2013
Akuta N, Suzuki F, Seko Y, Kawamura Y, Sezaki H, Suzuki Y, Hosaka T, Kobayashi M,Hara T, Kobayashi M, Saitoh S, Arase Y, Ikeda K, Kumada H	Emergence of telaprevir-resistant variznts detected by ultra-deep sequencing after triple therapy in patients infected with HCV genotype 1	J MedVirol.	85	1028-1036	2013
Kawamura Y, Saitoh S, Arase Y, Ikeda K, Fukushima T, Hara T, Seko Y, Hosaka T, Kobayashi M, Sezaki H,Akuta N, Suzuki F, Suzuki Y, Fukuzawa K,Hamada Y, Takahashi J,Kobayashi M, Kumada H	Three-dimensional magnetic resonance imagingfor stringent diagnosis of advanced fibrosisassociated with nonalcoholic steatohepatitis	Hepatol Int.	7	850-858	2013
Seko Y, Ikeda K, Kawamura Y, Fukushima T, Hara T, Sezaki H, Hosaka T, Akuta N, Suzuki F, Kobayashi M, Suzuki Y,Saitoh S, Arase Y, Kumada H	Antiumor efficacy of transcatheter arterialchemoembolizatio n with warmed miriplatin inhepatocellular carcinoma	HepatolRes.	43	942-949	2013
Hosaka T, Suzuki F, Kobayashi M, Seko Y, kawamura Y, Sezaki H, Akuta N, Suzuki Y, Saitoh S, Arase Y, Ikeda K, Kobayashi M, Kumada H	Clearance of hepatitis B surface antigen duringlong-term nucleot(s)ide analog treatment inchronic hepatitis B: results from a nine-yearlongitudinal study	J Gastroenterol.	48	930-941	2013

Akuta N, Suzuki F, Fukushima T, Kawamura Y, Sezaki H,Suzuki Y, Hosaka T, Kobayashi M, Hara T, Kobayashi M, Saitoh S, Arase Y, Ikeda K, Kumada H	Prediction of treatment efficacy and telaprevir-resistant variants after triple therapy in patients infected with HCV genotype 1	J Clin Microbiol.	51	2862-2868	2013
Kawamura Y, Ikeda K, Fukushima T, Seko Y, Hara T, Sezaki H, Hosaka T, Akuta N, Kobayashi M, Saitoh S, Suzuki F, Suzuki Y, Arase Y, Kumada H	What Is the most effective drug delivery systemfor cisplatin during the treatment of hepatic tumors with single-session transcatheter chemotherapy? A pilot study.	Gut Liver.	5	576-584	2013
Hara T, Akuta N, Suzuki F, Sezaki H, Susuki Y, Hosaka, Kobayashi M, Saitoh, Kumada H	A pilot study of triple therapy with telaprevir,peginterferon and ribavirin for elderly patientswith genotype 1 chronic Hepatitis C.	J Med Virol.	85	1746-1753	2013
Imai N, Ikeda K, Seko Y, Kawamura Y, Sezaki H, Hosaka T, Akuta N, Kobayashi M,Saitoh S, Suzuki F, Suzuki Y, Arase Y, Kumada H	Transcatheter arterial chemotherapy withmiriplatin for hepatocellular carcinomapatients with chronic renal failure: report ofthree cases.	Gut Liver.	7	246-251	2013
Oze T, Hiramatsu N, Mita E, Akuta N, Sakamoto N, Nagano H, Itoh Y, Kaneko S, Izumi N, Nomura H, Hayashi N, Takehara T.	A multicenter survey of re-treatment with pegylated interferon plus ribavirin combination therapy for patients with	Hepatol Res	43	35-43	2013

	chronic hepatitis C in Japan.				
Ogura S, Saitoh S, Kawamura Y, Sezaki H,Hosaka T, Akuta N, Kobayashi M, Suzuki F,Suzuki Y, AraseY, Ikeda K, Kumada H	Magnetic resonance laparoscopy: A new non-invasive technique for the assessment ofchronic viral disease.	HepatolRes.	43	836-845	2013
Akuta N, Suzuki F, Seko Y, Kawamura Y, Sezaki H, Hosaka T, Kobayashi M, Kobayashi M, Saitoh S, Arase Y, Ikeda K, Kumada H	Efficacy and anticarcinogenic activity ofribavirin combination therapy for hepatitis Cvirus-related compensated cirrhosis	Intervirology.	56	37-45	2013
Seko Y, Akuta N, Suzuki F, Kawamura Y,Sezaki H, Sezaki H, Suzuki Y, Hosaka T, Kobayashi M, Kobayashi M, Saitoh S, Arase Y, Ikeda K. Kumada H	Amino acid substitutions in the hepatitis CVirus core region and lipid metabolosm areassociated with hepatocarcinogenesis innonresponders to interferon plus ribavirincombination therapy.	Intervirology.	56	13-21	2013
Yamada S, Kawaguchi A, Kawaguchi T, Fukushima N, Kuromatsu R, Sumie S, Takata A, Nakano M, Satani M, Tonan T, Fujimoto K, Shima H, Kakuma T, Torimura T, Charlton MR, Sata M	Serum albumin level is a notable profiling factor for non-B, non-C hepatitis virus-related hepatocellular carcinoma: A data-mining analysis	Hepatol Res.			in press
Kawaguchi T, Nagao Y, Sata M	Independent factors associated with altered plasma active ghrelin levels in HCV-infected patients	Liver Int.	33	1510-6	2013

Taniguchi E, Kawaguchi T, Sakata M, Itou M, Oriishi T, Sata M	Lipid profile is associated with the incidence of cognitive dysfunction in viral cirrhotic patients: A data-mining analysis	Hepatol Res.	43	418-24	2013
Sakata M, Kawahara A, Kawaguchi T, Akiba J, Taira T, Taniguchi E, Abe M, Koga H, Kage M, Sata M	Decreased expression of insulin and increased expression of pancreatic transcription factor PDX-1 in islets in patients with liver cirrhosis: a comparative investigation using human autopsy specimens	J Gastroenterol.	48	277-85	2013
Katoh H, Okamoto T, Fukuhara T, Kambara H, Morita E, Mori Y, Kamitani W, MatsuuraY.	Japanese Encephalitis Virus Core Protein Inhibits Stress Granule Formation through an Interaction with Caprin-1 and Facilitates Viral Propagation	J Virol	87	489-502	2013
Suzuki R, Matsuda M, Watashi K, Aizaki H, Matsuura Y, Wakita T, Suzuki T.	Signal peptidase complex subunit 1 participates in the assembly of hepatitis C virus through an interaction with E2 and NS2	PLoS Pathog		doi:10.1371/journal.ppat.1003589	2013
Lee H, Komano J, Saitoh Y, Yamaoka S, Kozaki T, Misawa T, Takahama M, Satoh T, Takeuchi O, Yamamoto N, Matsuura Y, Saitoh T, Akira S.	Zinc-finger antiviral protein mediates retinoic acid inducible gene I-like receptor-independent antiviral response to murine leukemia virus	Proc Natl Acad Sci U S A	110	12379-12384	2013

Yoshio S, Kanto T, Kuroda S, Matsubara T, Higashitani K, Kakita N, Ishida H, Hiramatsu N, Nagano H, Sugiyama M, Murata K, Fukuhara T, Matsuura Y, Hayashi N, Mizokami M, Takehara T.	Human BDCA3 (+) dendritic cells are a potent producer of IFN-λ in response to hepatitis C virus	Hepatology	57	1705-1715	2013
Kimura T, Katoh H, Kayama H, Saiga H, Okuyama M, Okamoto T, Umemoto E, Matsuura Y, Yamamoto M, Takeda K.	Ifit1 inhibits Japanese encephalitis virus replication through binding to 5' capped 2'-O unmethylated RNA	J Virol	87	9997-10003	2013
Tripathi LP, Kambara H, Chen YA, Nishimura Y, Moriishi K, Okamoto T, Morita E, Abe T, Mori Y, Matsuura Y, Mizuguchi K.	Understanding the biological context of NS5A-host interactions in HCV infection: a network-based approach	J Proteome Res	12	2537-2551	2013
Ratnoglik SL., Aoki C., Sudarmono P., Komoto M., Deng L., Shoji I., Fuchino H., Kawahara N., and Hotta H.	Antiviral activity of extracts from Morinda citrifolia leaves and chlorophyll catabolites pheophorbide a and pyropheophorbide a, against hepatitis C virus.	Microbiol. Immunol.		doi: 10.1111/1348-0421.12133	2014
Adianti M., Aoki C., Komoto M., Deng L., Shoji I., Wahyuni T., Lusida M., Soetjipto S., Fuchino H., Kawahara N., and Hotta H.	Anti-hepatitis C virus compounds obtained from Glycyrrhiza uralensis and other Glycyrrhiza species.	Microbiol. Immunol.		doi: 10.1111/1348-0421.12127	2014
Tao RR, Huang JY, Lu YM, Hong LJ, Wang H, Masood MA, Ye WF, Zhu DY, Huang Q, Fukunaga K, Lou YJ, Shoji I, Wilcox CS, Lai EY, Han F.	Nitrosative stress induces peroxiredoxin 1 ubiquitination during ischemic insult via E6AP activation in endothelial cells both in vitro and in vivo.	Antioxid & Redox Sign.		doi: 10.1089/ars.2013.5381	2013

Mawatari S., Uto H., Ido A., Nakashima K., Suzuki T., Kanmura S., Kumagai K., Oda K., Tabu K., Tamai T., Moriuchi A., Oketani M., Shimada Y., Sudoh M., Shoji I., and Tsubouchi H.	Hepatitis C virus NS3/4A protease inhibits complement activation by cleaving complement component 4.	PLoS One	8	e82094, 1-7	2013
Wahyuni TS., Tumewu L., Permanasari AA., Apriani E., Adianti M., Rahman A., Widyawaruyanti A., Lusida MI., Fuad A., Soetjipto, Nasronudin, Fuchino H., Kawahara N., Shoji I., Deng L., Aoki C., and Hotta H.	Antiviral activities of Indonesian medicinal plants in the East Java region against hepatitis C virus.	Virol. J.	10	259, 1-9	2013
Ichimura T, Taoka M, Shoji I, Kato H, Hatakeyama S, Isobe T, and Hachiya N.	14-3-3 Proteins sequester a pool of soluble TRIM32 ubiquitin ligase to repress autoubiquitination and cytoplasmic body formation.	J. Cell. Sci.	126	2014-2026	2013
El-Shamy A, Shindo M, Shoji I, Deng L, Okuno T, and Hotta H.	Polymorphisms of the Core, NS3 and NS5A proteins of hepatitis C virus genotype 1b associate with development of hepatocellular carcinoma.	Hepatology	58	555-563	2013
Horiuchi Y, Takagi A, Kobayashi N, Moriya O, Nagai T, Moriya K, Tsutsumi T, Koike K, Akatsuka T.	The effect of the infectious dose and the presence of HCV core gene on mouse intrahepatic CD8 T-cells.	**Hepatol Res**			[Epub ahead of print]
Uranbileg B, Enooku K, Soroida Y, Ohkawa R, Kudo Y, Nakagawa H, Tateishi R, Yoshida H, Shinzawa S, Moriya K, Ohtomo N, Nishikawa T,	High ubiquitous mitochondrial creatine kinase expression in hepatocellular carcinoma	Int J Cancer.	134	2189-98.	2014

Inoue Y, Tomiya T, Kojima S, Matsuura T, Koike K, Yatomi Y, Ikeda H.	denotes a poor prognosis with highly malignant potential.				
Yotsuyanagi H, Ito K, Yamada N, Takahashi H, Okuse C, Yasuda K, Suzuki M, Moriya K, Mizokami M, Miyakawa Y, Koike K	High levels of hepatitis B virus after the onset of disease lead to chronic infection in patients with acute hepatitis B.	Clin Infect Dis.	57(7)	935-42	2013
He G, Dhar D, Nakagawa H, Font-Burgada J, Ogata H, Jiang Y, Shalapour S, Seki E, Yost SE, Jepsen K, Frazer KA, Harismendy O, Hatziapostolou M, Iliopoulos D, Suetsugu A, Hoffman RM, Tateishi R, Koike K, Karin M.	Identification of Liver Cancer Progenitors Whose Malignant Progression Depends on Autocrine Il-6 Signaling	Cell	155(2)	284-96	2013
Sato M, Kato N, Tateishi R, Muroyama R, Kowatari N, Li W, Goto K, Otsuka M, Shiina S, Yoshida H, Omata M, Koike K.	The Impact of Pnpla3 Polymorphisms on the Development of Hepatocellular Carcinoma in Patients with Chronic Hepatitis C Virus Infection.	Hepatol Res			2014

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Increased serum mitochondrial creatine kinase activity as a risk for hepatocarcinogenesis in chronic hepatitis C patients

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Serum mitochondrial creatine kinase (MtCK) activity was reportedly increased in cirrhotic patients although less prominent than that in hepatocellular carcinoma (HCC) patients. To elucidate the clinical significance of serum MtCK activity in chronic liver disease, 171 chronic hepatitis C patients were enrolled. Serum MtCK activity in study subjects was correlated with serum albumin, platelet counts, liver stiffness values and serum aspartate and alanine aminotransferase. In mouse fibrotic liver induced by bile duct ligation, ubiquitous MtCK mRNA and protein expressions were significantly enhanced and its immunoreactivity was increased, predominantly in hepatocytes. During the mean follow-up period of 2.7 years, HCC developed in 21 patients, in whom serum MtCK activity was significantly higher than that in patients without HCC development. Multivariate Cox regression analysis revealed that higher serum MtCK activity was a risk for HCC development. A cutoff value of MtCK for the prediction of HCC development was determined as 9.0 U/L on receiver operating characteristics analysis, where area under receiver operating characteristics curve was 0.754, with a sensitivity of 61.9%, a specificity of 92.8% and a high negative predictive value of 94.2%. Cumulative incidence of HCC was significantly higher in patients with serum MtCK activity of >9.0 U/L compared to those with serum MtCK activity of ≤9.0 U/L even in patients with elevated liver stiffness value, >15 kPa. In conclusion, serum MtCK activity may be increased correlatively with the stage of liver fibrosis and hepatocellular damage. Increased serum MtCK activity is an independent risk for hepatocarcinogenesis in chronic hepatitis C patients.

Hepatocellular carcinoma (HCC) is one of the common malignancies worldwide,[1] and the number of patients suffering from HCC is currently increasing in many countries.[2,3] As HCC has a specific feature that it usually develops in the setting of chronic liver injury,[2] especially liver cirrhosis,[4] cancer surveillance, when performed intensively in patients with chronic liver injury, could lead to HCC detection in its early stage, where biomarkers for HCC may play an important role. Although novel therapies have been developed to prolong survival in patients with advanced HCC, their effects are rather limited,[5] suggesting that the effective way for early detection of HCC is urgently needed. To this end, many attempts have been made to explore a novel biomarker for HCC,[6,7] among which we have recently found that serum mitochondrial creatine kinase (MtCK) activity was increased in patients with HCC. Among two tissue-specific isozymes of MtCK, that is, ubiquitous MtCK (uMtCK) and sarcomeric MtCK (sMtCK), we have found that the increase in serum MtCK activity in HCC patients was mostly owing to uMtCK, not sMtCK.[8] We have further found high expression of uMtCK mRNA in human HCC cell lines compared to normal human liver tissue.[8] Recently, we have reported that high uMtCK expression in HCC denotes a poor prognosis with highly malignant potential.[9] It is worth noting the increased uMtCK expression occurred not only upon malignant changes in the liver, but also in several other malignant tumors such as gastric cancer, breast cancer and lung cancer.[10–13]

In our previous report, we have observed that serum MtCK activity was also increased in patients with liver cirrhosis compared to healthy control although less prominent than in HCC patients.[8] In fact, an elevated serum MtCK

Key words: ubiquitous mitochondrial creatine kinase, hepatocellular carcinoma, liver fibrosis

Abbreviations: AFP: alpha-fetoprotein; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CT: computed tomography; DCP: des-gamma-carboxy prothrombin; GGT: γ-glutamyltransferase; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; MtCK: mitochondrial isoenzyme of creatine kinase; sMtCK: sarcomeric mitochondrial creatine kinase; uMtCK: ubiquitous mitochondrial creatine kinase

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What's new?
Chronic liver injury such as viral hepatitis increases the risk to develop hepatocellular carcinoma (HCC). Here, the authors show that serum mitochondrial creatine kinase activity, a potential new biomarker for progressive liver damage, was increased in patients with chronic hepatitis C virus infection and correlated with the stage of liver fibrosis and hepatocellular damage. Similar results were reproduced in mice after liver damage via bile duct ligation. Notably, high serum mitochondrial creatine kinase activity was an independent risk factor for hepatocarcinogenesis in viral hepatitis patients, underscoring the promise of this new marker in the prediction and possibly pathogenesis of HCC.

activity was previously reported in patients with liver cirrhosis,[14] where MtCK was described as "Macro CK type 2."[14,15] However, the clinical significance of increased serum MtCK activity in cirrhotic patients has not been clarified yet. In our study, we wondered whether serum MtCK activity might be increased in patients with not only liver cirrhosis but also chronic liver disease, in general, with less fibrosis, and if so, what would be the clinical significance of increased serum MtCK activity in patients with chronic liver disease. To address these questions, we sought to analyze serum MtCK activity in patients with chronic hepatitis C without the presence and the history of HCC.

Material and Methods

Subjects

One-hundred seventy-one patients with chronic hepatitis C, who visited the Department of Gastroenterology, The University of Tokyo Hospital, Tokyo, Japan, between January 2010 and April 2011, were enrolled. Chronic hepatitis C was defined as serum anti-hepatitis C virus antibody positivity and a detectable HCV RNA level, having persistent liver damage for more than 6 months, where other causes of liver disease such as hepatitis B and alcohol abuse had been excluded. Patients with HCC at the time of enrollment or with past history of HCC were excluded from this analysis, where HCC was ruled out by ultrasonography, dynamic computed tomography (CT) and/or magnetic resonance imaging. To assess a potential relationship between serum MtCK activity and liver fibrosis, all the enrolled patients undertook liver stiffness measurement.

Our study was carried out in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Institutional Research Ethics Committees of the authors' institutions. In our study, informed consent was obtained for the use of the samples.

Measurement of MtCK activity

MtCK activity was measured with an immune-inhibition method using two types of anti-MtCK monoclonal antibodies, that is, an anti-uMtCK monoclonal antibody and an anti-sMtCK monoclonal antibody in addition to an anticreatine kinase-M antibody[16] as described previously.[8] JCA-BM8040 (JEOL, Tokyo, Japan) was used as an automatic analyzer. The regression line of this assay was linear up to at least 1,800 U/L. The minimum detection limit was 1.9 U/L. The within-run coefficient variations were 3.1 and 0.8% at the mean MtCK activities of 25.7 and 64.4 U/L, respectively. The between-run coefficient variations were 2.3% for both the mean MtCK activities of 24.0 and 59.5 U/L.

Measurements of other parameters

Ordinary serum chemistry parameters, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transpeptidase (GGT) and total bilirubin, were analyzed using JCA-BM8040 (JEOL, Tokyo, Japan). Complete blood count examination was performed using XE-5000 (Sysmex, Kobe, Japan). Prothrombin time was measured using ACL TOP (Mitsubishi Chemical Medience, Tokyo, Japan). Alpha-fetoprotein (AFP) and des-gamma-carboxy prothrombin (DCP) were analyzed by a two-site immunoenzymetric assay using ST AIA-PACK AFP (TOSOH, Tokyo, Japan) and Lumipulse Presto PIVKAII (EIDIA, Tokyo, Japan), in automatic analyzers, AIA 2000 (TOSOH) and Lumipulse® PrestoII (FUJIREBIO, Tokyo, Japan), respectively. Liver stiffness was measured using transient elastography (FibroScan 502; EchoSens, Paris, France) as described previously.[17]

Animals and induction of liver fibrosis

Liver fibrosis was induced in C57BL/6N mice (CLEA Japan, Japan) by bile duct ligation at 4 weeks after the operation as described previously.[18]

All animals received humane care and the experimental protocol was approved by Animal Research Committee of the University of Tokyo.

Quantitative real-time polymerase chain reaction

Total RNA of mouse livers was extracted using TRIZOL reagent (Invitrogen, Carlsbad, CA). One microgram of purified total RNA was transcribed using a Transcriptor First Strand cDNA Synthesis Kit (Roche Diagnostics, Mannheim, Germany). Quantitative real-time polymerase chain reaction (PCR) was performed with a TaqMan Universal Master Mix No AmpErase UNG (Applied Biosystems, Foster City, CA). Mouse uMtCK primers and probe were obtained from Applied Biosystems, TaqMan Gene Expression Assays (Mm00438221_m1). The samples were incubated for 10 min at 95°C, followed by 40 cycles at 95°C for 15 sec and 60°C for 60 sec. The target gene mRNA expression level was relatively quantified to 18S