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Role of cytokine gene polymorphisms on prognosis in hepatocellular carcinoma after radical surgery resection

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ABSTRACT

This study aimed to determine whether SNPs of cytokine genes influence survival of hepatocellular carcinoma (HCC) patients after radical surgery resection. We evaluated 14 SNPs of eight cytokine genes in 263 patients treated with radical surgery resection of HCC. Categorical variables were compared by the χ^2 test and Fisher's exact test. The Kaplan–Meier methods with log-rank test and Cox regression models were used to compare survival of resected HCC patients according to the genotype. Among the 14 studied SNPs of cytokine genes, only the TNF-α-863 (CA + CC) genotypes were revealed to be significant independent predictors of prolonged overall survival (OS) after HCC radical surgery resection (HR: 0.586, 95% CI: 0.355–0.968), considering for other clinical factors in a Cox proportional hazard model. Meanwhile, no significant association was found between the 14 SNPs and relapse-free survival (RFS) of resected HCC patients. In addition, combination analysis with the Th1 cytokine (IFN-γ, IL-2, IL-12B, TGF-β1) or Th2 cytokine (IL-6, IL-10) genetic polymorphisms by the Kaplan–Meier method and Cox multivariate analysis did not reveal any significant association between OS and RFS of resected HCC patients.

1. Introduction

Radical surgery resection is one of the principal treatment modalities for hepatocellular carcinoma (HCC). The 5-year survival rate of resected small hepatocellular carcinoma was 50% to 60%, about the resected large hepatocellular carcinoma was approximately 30% and the reduction of unresectable hepatocellular carcinoma than resection was 40% to 60% in nearly last 20 years (Zhao-you, 2001). However, there was recurrence and/or metastasis within 5 years in half of the patients in China regardless of very early tumor removal (Zhao-you, 2006). HCC prognosis is still poor and there is a need to improve post-resection long-term outcomes.

There is increasing evidence that HCC is inherently associated with the inflammatory process and the up-regulation of cytokines (Li et al., 2010). Cytokines are central in determining whether immune responses in the tumour microenvironment promote or inhibit cancer (Yu et al., 2009), or participate in tumor growth, invasion, and remote metastasis (Okamoto et al., 2010). In humans, main cytokines are included interleukin (IL), interferon (IFN), tumor necrosis factor superfamily (TNFSF), growth factor, chemokines and colony-stimulating factor (CSF). Genetic variations in different individuals may alter the function of cytokine proteins, influencing the risk of development and clinical outcomes of HCC.

Recently, some reports have revealed functional gene polymorphisms in cytokines associated with the prognosis of various cancers (DeMichele et al., 2003; Du et al., 2010; Lech-Maranda et al., 2013; Ling-ling et al., 2011; Motoyama et al., 2011; Sharma et al., 2008), the TNF-α-308, IL-10-592/1082 and IL-2-330 polymorphisms have also been reported to be a prognostic predictor of chronic lymphocytic leukemia, colorectal cancer and cell cancer, respectively (Lech-Maranda et al., 2013; Ling-ling et al., 2011; Sharma et al., 2008). However, few studies have reported on the prognostic role of cytokine gene polymorphisms in HCC patients treated for radical surgery resection. In this study, we investigated the potential prognostic roles of selective SNPs of cytokine genes, and evaluated the significance of the T helper (Th)1 cytokine or T helper (Th)2 cytokine genetic variants with combined SNPs on patient prognosis.

Abbreviations: CI, confidence interval; CSF, colony-stimulating factor; HBsAg, hepatitis B virus surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HR, Hazard Ratio; IL, Interleukin; IL-1B b, Interleukin-1 beta; IL-2, Interleukin-2; IL-4, Interleukin-4; IL-5, Interleukin-5; IL-6, Interleukin-6; IL-10, Interleukin-10; IL-13, Interleukin-13; IL-12B, Interleukin-12 beta; IGHV, immunoglobulin variable heavy-chain; IFN, Interferon; IFN-γ, Interferon-gamma; K-M, Kaplan–Meier-method; Log-rank, Log-rank test; MAF, Minor Allele Frequency; MMP-3, matrix metalloproteinase-3; NFAT, nuclear factor of activated T cells; OS, Overall survival; RFS, Relapse-free survival; TGF-β, Transforming Growth Factor-β; TNFSF, tumor necrosis factor superfamily; Th, T helper cell; TNF-α, tumor necrosis factor alpha.

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Table 1
SNPs of the cytokines genes evaluated in this study.

Pathway	Gene	Chromosome	Function region	Base change	SNP ID	Position	MAF
Th1	IL2	4q26-q27	nearGene-5	T/G	rs2069762	330	0.761
	IL12B	5q31.1-q33.1	UTR-3	A/C	rs3212227	1188	0.415
	TGF-β1	19q13.1	nearGene-5	C/T	rs1800469	509	0.500
	IFN-γ	12q14	nearGene-5	C/T	rs2069705	1615	0.195
		12q14	nearGene-3	A/G	rs2069727	5171	0.098
Th2	IL6	7p21	nearGene-5	G/C	rs1800796	572	0.233
	IL10	1q31-q32	nearGene-5	C/T	rs1800871	592	0.744
		1q31-q32	nearGene-5	C/A	rs1800872	819	0.262
	IL1B	2q14	nearGene-5	A/G	rs16944	511	0.537
		2q14	nearGene-5	G/C	rs1143623	1461	0.614
		2q14	nearGene-5	C/T	rs1143627	31	0.524
	TNFA	6p21.3	nearGene-3	C/T	rs1799964	1031	0.778
		6p21.3	nearGene-5	G/A	rs1800629	308	0.854
		6p21.3	nearGene-5	C/A	rs1800630	863	0.822

SNP, single nucleotide polymorphism; Th1, T helper (Th)1 cytokines; Th2, T helper (Th)2 cytokines; nearGene-5, 5′end promoter region; UTR-3, 3′end untranslated region; MAF, minor allele frequency.

Table 2
Clinicopathologic characteristics of 263 patients with resected HCC.

Clinicopathologic characteristics	n (%)	Clinicopathologic characteristics	n (%)
Gender (male:female)	250:13	Satellite nodule	21 (8.0)
Age(≦47 y:>47 y)	137:126	Portal vein tumor thrombus	55 (20.9)
Nationality (Han)	173 (65.9)	Envelope	95 (36.1)
HBsAg	222 (84.4)	Postoperative recurrence	129 (49.0)
General classification(bulky/nodules/widespread)	178:73:12	Distant metastasis	50 (19.0)
Tumor size(<5 cm/≧5 cm)	130:133	Death	111 (42.2)
Background cirrhosis	155 (41.1)	Follow-up period (mo, median with range)	50 (29–67)
Tumor number (single:multiple)	235:28		

2. Patients and methods

2.1. Study patients

Patients with newly diagnosed and pathologically confirmed HCC were recruited consecutively between February 2007 and September 2009 from two hospitals (First Affiliated Hospital of Guangxi Medical University and Tumor Hospital of Guangxi), both located in Nanning Guangxi China. All patients had undergone radical surgery resection and had similar background exposure from southern Guangxi. Excluded the patient who was diagnosed and treated in other hospitals or first discovered had distant metastasis. In total, we identified 280 patients, 263 (93.9%) of whom agreed to participate in this study and in the final analysis. Clinical information was collected from the medical records with patients' consent, and included in demographic, diagnosis time, imaging examination results and other clinical data; All of the patients were followed up to observe postoperative recurrence, distant metastasis and death condition by medical records or phone call. Clinical features such as general classification, tumor number, tumor size, background cirrhosis, satellite nodule, envelope, portal vein tumor thrombus and recurrence, and metastasis were confirmed by imaging examination. Overall survival (OS) was calculated in months from the date of tumor resection until death or until the date of the last follow-up. Relapse-free survival (RFS) was calculated in months from the date of tumor resection until relapse of disease or until the date of the last follow-up. The ethical committee of Guangxi Medical University approved the study and written informed consent was obtained from all the participants.

Table 3
Correlation between IL-1B-511/31, IL-6-572, IL-12B-1188 SNPs and clinical pathology of resected HCC.

Variables	Satellite nodule			Envelope		
	OR	95% CI	P value	OR	95% CI	P value
IL-1B-511 (AA/GA + GG)	0.33	0.131–0.828	0.024	1.594	0.838–3.030	0.153
IL-1B-31 (TT/TC + CC)	0.274	0.111–0.678	0.003	1.944	1.046–3.615	0.034
IL-6-572 (CC/CG + GG)	0.175	0.040–0.767	0.010	0.614	0.357–1.056	0.077
IL-12B-1188 (TT/TC + CC)	1.800	0.585–5.536	0.299	0.406	0.234–0.701	0.001

Table 4
Association between clinical characteristics and HCC prognosis.

Variables	OS				RFS			
	χ^2	P value	HR	95% CI	χ^2	P value	HR	95% CI
Tumor size	12.562	0.000	1.969	1.341–2.891	6.636	0.01	1.567	1.105–2.221
Tumor number	1.662	0.197	1.44	0.822–2.522	4.591	0.032	0.037	1.034–2.801
Satellite nodule	7.157	0.007	2.158	1.207–3.859	2.258	0.133	1.564	0.861–2.838
Portal vein tumor thrombus	19.502	0.000	2.39	1.600–3.571	7.467	0.006	1.716	1.153–2.552