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Experimental study

TLR4 gene polymorphisms rs11536889 is associated with intracranial aneurysm susceptibility

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ABSTRACT

Intracranial aneurysm (IA) is a common lesion which often present asymptomatic until the time of rupture and result in subarachnoid hemorrhage (SAH). The pathogenesis of IA formation is complex and is influenced by both genetic and environmental risk factors. For exploring the detailed molecular and cellular mechanisms involved in the pathogenesis of IA, recent studies indicated inflammatory pathways and their genetic variants may as potential biomarkers. In this study, functionally relevant polymorphisms in the toll-like receptor 4 (TLR4) were screened in 330 IA patients and 313 controls from a Han Chinese population. Eight single nucleotide gene polymorphisms (SNPs) genotyped by the Improved Multiple Ligase Detection Reaction (iMLDR) method. Our results indicated that the presence of the minor allele (C) of the TLR4 SNP rs11536889 was associated with a decreased risk of IA (C vs. G, OR = 0.731; 95% CI 0.567–0.943; $P = 0.017$). This association was also present at the genotype level in a codominant model (GC vs. GG, OR = 0.447; 95% CI 0.226–0.884; $P = 0.020$) and a recessive model (CC vs. GG + GC, OR = 0.489; 95% CI 0.250–0.955; $P = 0.035$). In summary, we firstly found that the TLR4 SNP rs11536889 was significantly associated with the susceptibility of IA. Our results indicated TLR4 SNP rs11536889 may be a marker for IA risk, though the exact functional roles of TLR4 SNP rs11536889 in IA formation are still not very clear.

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1. Introduction

Intracranial aneurysm (IA) is a common lesion, and about 2–5% of the population with harbor IAs. IA often present asymptomatic until the time of rupture and result in subarachnoid hemorrhage (SAH) [1]. Ruptured IA lead to 85% of SAHs and contribute to 5–15% of strokes [2]. More importantly, ruptured IA often occur at a considerably young age, leading to high incidences of mortality and morbidity. Although the rate of IA is high and ruptured IA pateints' outcomes are catastrophic, the pathological mechanism of this disorder is still poorly understand. There are many environmental risk factors and genetic factors involved in IA developing. Hypertension and smoking are common risk factors that increase the susceptibility of developing IA through modifying the effects of genetic factors [3]. Beside, female gender, alcoholism and aging, also involved in the pathogenesis of IA [4,5]. Recently, some epidemiological studies have confirmed that about 10% of IA patients have a family history, and compared to patients with only second-degree relatives with IA, the risk of rupture in IA patients with a first degree relative with IA increased 3–7-fold [6,7]. Indeed, the details mechanism of how inherited and acquired risk factors cause aneurysm formation still poorly understand, but many assumptions have been proposed, one of which is hypothesized to be secondary to inflammatory effects on the vasculature and the immune response also involved in aneurysm formation [8,9]. Taken together, these findings indicate that inflammation may play an essential role in the pathogenesis of IA.

Toll-like receptors (TLRs) are type I transmembrane proteins, which are responsible for the detection of characteristic molecules of pathogens and to stimulate the innate immune response [10]. Among them, recent studies have found that TLR4 is involved in the pathogenesis of many inflammatory diseases [11–13]. As our previous studies found, TLR4 play a key role in cerebrovascular disease [14,15]. Importantly, accumulating evidences show that TLR4 contribute to the pathogenesis of abdominal aortic aneurysms. Besides, a study found modulating TLR4 by antagonism could attenuates the formation and progression of abdominal aortic aneurysms [16,17]. Indeed, during the pathophysiological formation of cerebral aneurysms, TLR4 is expressed in cerebral aneurysm walls and activates the NF-κB pathway in endothelial cells [18–20]. Thus, the genetic variability in TLR4 is essential for the pathogenesis of cerebral aneurysms. The present study explores the genetic role of TLR4 in cerebral aneurysms.

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2. Results

A total of 330 IA patients and 313 control subjects were included in this study. The demographic characteristics of the patients and controls are presented in Table 1. There were no significant differences between the IA patients and controls subjects for age, sex, and medical history number (including hypertension, diabetes, arrhythmia, coronary artery disease, smoking and alcohol use) ($P > 0.05$). As shown in Table 2, the most common site of aneurysm was the internal carotid artery (62.28%). Several aneurysms (≥2) were present in 56 (16.97%) patients.

Total eight SNPs were analyzed in this study. The characteristics of the TLR4 gene polymorphisms are presented in Table 3.

Using a case-control design, we observed novel associations with polymorphisms of TLR4 as well as the IA frequency (Table 4 and Table 5). We found that the presence of the minor allele (C) of the TLR4 SNP rs11536889 was associated with a decreased risk of IA (C vs. G, OR = 0.731; 95% CI 0.567–0.943; $P = 0.017$, Table 5). This association was also present at the genotype level in a codominant model (GC vs. GG, OR = 0.447; 95% CI 0.226–0.884; $P = 0.020$, Table 4) and a recessive model (CC vs. GG + GC, OR = 0.489; 95% CI 0.250–0.955; $P = 0.035$, Table 4), but not in a dominant model (GG vs. GC + CC, OR = 0.734; 95% CI 0.537–1.004; $P = 0.056$, Table 4). Besides, we did not find any other significant associations with other TLR 4 SNPs.

Moreover, we have analyzed the relationship between polymorphisms of TLR4 and the risk of rupture among IA patients. Interestingly, we found the TLR4 SNP rs2149356 may associated with the risk of rupture among IA patients, although only 26 IA patients with presence of ruptured (Table 6 and Table 7).

Table 1
Demographic characteristics of TA patients and controls.

Variables	IA patients	Control patients	*P*
Demographic characteristics	*N* = 330	*N* = 313	
Age, mean (SD)	61.57 (12.41)	61.75 (12.93)	0.859
Male, number (%)	163 (49.39)	160 (51.11)	0.662
Medical history number (%)			
Hypertension	182 (55.15)	158 (50.48)	0.235
Diabetes	52 (15.76)	67 (21.41)	0.065
Arrhythmia	27 (8.18)	31 (9.90)	0.446
Coronary artery disease	76 (23.03)	87 (27.80)	0.165
Smoking	65 (19.70)	80 (25.56)	0.075
Alcohol use	42 (12.73)	38 (12.14)	0.822

Table 2
Clinical characteristics of aneurysms.

Characteristic	Number of IA, (%)
Site of aneurysm	
Internal carotid artery	246 (62.28)
Middle cerebral artery	35 (8.86)
Anterior cerebral artery	7 (1.77)
Anterior communicating artery	24 (6.08)
Posterior cerebral artery	24 (6.08)
Posterior communicating artery	33 (8.35)
Basilar artery	10 (2.53)
Vertebral artery	7 (1.77)
IA type	
Single aneurysm	260 (78.79)
Multiple aneurysms	56 (16.97)
Rupture IA patients	26 (7.88)

3. Discussion

In the present study, we first investigated the associations of common SNPs of the TLR4 gene with IA risk. The results of our study support the hypothesis of a significant genetic association between TLR4 gene and the development of IA. We found the TLR4 SNP rs11536889 is associated with the process of IA pathogenesis, as the presence of the minor allele (C) of rs11536889 was associated with a decreased risk of IA.

As a member of the TLRs family, TLR4 play crucial roles in innate and adaptive immunity processes. Which links infection to auto-inflammatory and autoimmune disease [21]. Usually, TLRs are receptors for exogenous stimuli. Recent studies have found that some endogenous molecules, including heat-shock proteins (HSPs), hyaluronic acid, β-defensin-2, oxidized-LDL (ox-LDL), fibronectin, and amyloid peptide, can directly or indirectly interact with the TLRs pathway [22–24]. For example, in human, HSP60 could stimulates vascular smooth muscle cell proliferation through TLR2 and TLR4 [25]. These findings suggest that TLR4 may play crucial roles in the pathophysiology of IA. TLRs could regulate inflammatory cascades (including NF-κB or MyD88 activation) and inflammatory cytokine release. Those processes also contribute to the pathogenesis of various inflammation-related diseases, including atherosclerosis and aneurysm [16,26–28]. To our knowledge, the process involved in aneurysm formation mainly including chronic inflammatory response, endothelial malfunction, the phenotype of vascular smooth muscle cell changed, extracellular matrix remodeling, vessel wall degeneration and subsequent cell death. Importantly, cerebral aneurysm formation is thought to be the result of chronic inflammation in arterial walls by hemodynamic stress [29].

However, how TLR4 promote pathogenesis of IA is still unknown. Previous studies have found that SNPs of genes that encode many inflammatory cytokines are involved in the pathogenesis of IA, examples of cytokines associated with IAs and with known genetic SNPs are TNF-α, IL-10, TGF-β, and IL-6 [30–33]. Interestingly, as those inflammatory cytokine upstream, TLR4 rs11536889 SNPs were also found to have associations with the risk of IA in our study. Thus, we hypothesize that TLR4 signaling mediated inflammatory cytokine release, contributing to the pathogenesis of IA by controlling the balance of vasoconstriction and vasodilation in response to hemodynamic stress. Monitoring the TLR4 rs11536889 SNPs may be of interest in IA pathogenesis. Thus, we would predict an individual's response to a given

Table 3
Characteristics of the TLR4 gene polymorphisms investigated in this study.

Genes	SNPs	Chromosome	Position	SNP Property	Length	Alleles	MAF(CHB_1000g)
TLR4	rs7869402	9	120478032	3′UTR	326	C>T	0.05
	rs11536889	9	120478131	3′UTR	326	G>C	0.22
	rs11536891	9	120479337	3′UTR	197	T>C	0.07
	rs11536878	9	120471553	intron3	316	C>A	0.10
	rs10759932	9	120465144	5′_flanking	423	T>C	0.31
	rs2149356	9	120474199	intron3	312	G>T	0.42
	rs7873784	9	120478936	3′UTR	227	G>C	0.07
	rs11536896	9	120479734	3′UTR	263	T>C	0.07

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