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The Relationship between *IL-1β* Gene Polymorphisms and Coronary Artery Disease in Elderly Population

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Abstract

Coronary Artery Disease (CAD) is the leading cause of morbidity and death in people around the world. In recent years, many studies have shown that cytokine gene polymorphism can change protein expression and protein function, thereby affecting their role in CAD. Interleukin (IL)-1β is a classical inflammatory factor, and the gene mutation of *IL-1β* plays a very important role in the occurrence and development of CAD. In this paper, the relationship between *IL-1β* gene polymorphism and CAD reported in the past will be collected and briefly summarized. It is expected that these results can provide a reference for the early diagnosis and treatment of CAD.

Keywords: Coronary artery disease; Interleukin-1β; Gene polymorphism; Single nucleotide polymorphism

Abbreviations: CAD: Coronary Artery Disease; IL: Interleukin; CYP17A1: Cytochrome P450, Family 17: Subfamily A, polypeptide 1; MT2A: Metallothionein2A; RBP4: Retinal Binding Protein 4; MMP-1: Matrix Metallo Proteinase-1; SNP: Single Nucleotide Polymorphism; CRP: C-reactive Protein

Introduction

Cardiovascular disease is a complex disease, which is the leading cause of morbidity and mortality in people around the world, including China [1,2]. Coronary artery disease (CAD) is the most common heart disease associated with atherosclerosis. It is a complex, multi-step, multi-factor (including genetic and environmental factors) process [1,3]. Hypertension, hyperlipidemia, diabetes and smoking have been reported to play a vital role in the development of CAD [4]. However, environmental factors are not the best predictors of CAD risk. A large number of studies have shown that genetic variation may greatly affect the development of CAD, and many genetic polymorphisms may play an important role in the development of CAD, such as Cytochrome P450, Family 17, Subfamily A, polypeptide 1 (CYP17A1), Toll-like receptors, Metallothionein-2A (MT2A), Retinal Binding Protein 4 (RBP4), and Matrix metalloproteinase-1 (MMP-1) [5-10].

Inflammation has been reported to affect the progression of atherosclerosis, and cytokines are involved in the migration of neutrophils, lymphocytes and antigen-presenting cells (dendritic cells and monocyte/macrophage lineages) [10]. The polymorphisms of cytokine gene can change the expression and the function of protein, thereby affecting their role in the process of CAD. Specifically, previous studies have shown that genetic variation in the genes of interleukin, such as IL-1β, IL-1α, IL-6, IL-10, IL-16, IL-18 and IL-23A, may affect the development of CAD [11-16]. As such, genetic variations can help assess and identify the risks of CAD to intervene in the occurrence and development of CAD in advance.

The gene variation of *IL-1β* plays a very important role in the occurrence and development of CAD. In this paper, the relationship between *IL-1β* gene polymorphism and CAD reported in the past will be collected and briefly summarized. It is expected that these results can provide a reference for the early diagnosis and treatment of CAD.

IL-1β-511 and CAD

It has been reported that the -511 C/T (rs16944) polymorphism on the *IL-1β* promoter is associated with several inflammatory-related diseases, such as chronic hypochlorite reaction induced by *Helicobacter pylori*, gastric cancer, Alzheimer's disease and Alzheimer's disease meningococcal disease [17-20]. Other studies have shown that the polymorphism of IL-1β-511 C/T is associated with atherosclerosis in some populations [21-26].

Zhang et al. reported in 2006 that the polymorphism of -511 C/T locus in the promoter region of *IL-1β* was associated with the severity of CAD. It is also suggested that they may play a role in the secretion of IL-1β, the aggravation of inflammation and dyslipidemia [27]. In another study, Oda et al. also reported that the-511 T allele is a risk factor for atherosclerosis in the Japanese population [28]. Japanese and Italian populations with the CC genotype were also associated with the prevalence of CAD [19,22]. It has been shown that the T allele at -511 locus increases the production of *IL-1β* induced by serum lipase [16,29]. Lacovielloet et al. found that IL-1β-511 CC genotype was positively correlated with age in patients with myocardial infarction [21]. The results were consistent with what Chen et al. have found; age-based subgroup tests showed that the IL-1β-511 T allele was an independent risk factor for CAD in young people [30]. In addition, Rios et al. included 667 patients (253 Afro-Brazilians and 414 Brazilian Caucasians) who underwent coronary angiography and found a more common CC genotype at-511s in the African-Brazilian population. After adjusting for other CAD risk factors by multivariate Logistic

regression, it was found that IL-1β-511 CC genotype was an independent risk predictor of CAD in Africa-Brazil population, and the risk of CAD in Brazilian CC genotype population tripled [31].

However, there were also many studies indicating that there is no significant association between the -511 allele and *IL-1β* and CAD. Arman et al. found no association between IL-1β-511 C/T polymorphism and CAD risk in the Turkish population [32]. Chen et al. carried out a Meta-analysis and demonstrated that the results could not prove that IL-1β-511 T gene was the susceptible gene of CAD [33-34]. Zhou et al. from China also found that the polymorphism of IL-1 β-511 C/T was not associated with the risk of CAD [35]. Jabir et al. did not find any association between the polymorphism of this locus and CAD in the Saudi population [36], which is consistent with the results of previous studies in different ethnic groups [37-39].

IL-1β+3953 and CAD

Single Nucleotide Polymorphism (SNP) IL-1β+3953 is located at +3953 position in exon 5 of *IL-1β* gene and is thought to affect the expression of *IL-1β* [40]. Some studies have shown that IL-1 β+3953 polymorphism can increase the plasma levels IL-1 β [17]. However, there was no association between IL-1 β+3953 allele frequency or genotype distribution and CAD. Similarly, Arman et al. found that there was no relationship between CAD and IL-1 β+3953 polymorphism in the Turkish population [32].

However, Sreekanth et al. found that the T allele of IL-1β+3953 has a protective effect on the heart [41]. Their study found that the healthy Madalier population had the highest frequency of 54 per cent derived from the IL-1β+3953 T allele. The frequency of IL-1 β+3953 T allele varied from person to person, with 25 per cent of Caucasians and 35 per cent of Indians and only 3 per cent of Denmark, Turkey, the United States and China [19,42-44]. In Kashmir and other parts of India, the proportion is between 19 and 35 per cent [45-48]. The different distribution of this T allele raises questions about whether the protective effects of this allele against cardiovascular disease have developed in epidemiology in India. Their study also showed that populations with a high frequency of wild type allele IL-1β+3953 C were positively correlated with the prevalence of CAD. Sreekanth et al. have demonstrated that the T allele of IL-1β+3953 is a prognostic marker of CAD, especially in male patients with CAD and rheumatic heart disease.

IL-1β-31 and CAD

Early studies have shown that CAD may be associated with polymorphism at -31 locus in the *IL-1β* promoter region [27,28,31]. However, the position of SNPs in *IL-1β* promoter is not consistent in different ethnic and ethnic populations [49].

Jabir et al. did not find any significant association between polymorphism -31 C/T (rs114627) and CAD in the Saudi population [36].

However, Goracy et al. found that IL-1β-31 C/T allele was significantly associated with hypertension. Although no association was found between the polymorphism or haplotype of IL-1β-31 C/T and CAD, the data suggest that the IL-1β-31 C allele may be a risk factor for hypertension in the Polish population in Pomerania [38]. One study of patients who received treatment for coronary artery bypass grafting and percutaneous coronary intervention in another region of Poland have supported a positive correlation between IL-1β-31 T and restenosis in Mexican patients [21], it was clear that IL-1 β-31 TT mutations are associated with the risk of CAD requiring surgical treatment or percutaneous two-stage angioplasty.

IL-1β+3954 and CAD

The IL-1β+3954 T allele was associated with elevated levels of C-reactive protein (CRP) in all populations, such as patients with CAD, pancreatic cancer and rheumatoid arthritis [50-52]. One of the largest studies (n=454) specifically analyzed whether CRP levels were associated with common IL-1 gene cluster polymorphisms, confirmed that median CRP levels in patients with TT genotypes were twice as high as those in CC genotypes [50]. However, Zhou and Li et al. demonstrated that IL-1β+3954 C/T polymorphism was not associated with the risk of CAD [35,53].

Discussion

The pathogenesis of CAD involves a variety of genetic and inflammatory pathways, which play a role in regulating a variety of inflammatory cytokines, especially in different stages of atherosclerosis [54]. *IL-1β* is released by macrophages, platelets and damaged endothelial cells [55] and plays an important role in inflammatory response and related atherosclerosis. *IL-1β* has different biological functions, such as stimulating the proliferation of vascular smooth muscle cells and endothelial cells [56,57], increasing the expression of endothelial cell adhesion molecules [57], and changing endothelial cells. Promote coagulation and thrombosis [58], stimulate the synthesis of fatty acid carrier proteins through adipose tissue *in vitro* [59], and promote the secretion of other pro-inflammatory factors, such as IL-6, fibrinogen and CRP [60-62].

Conclusion

There is an imbalance between the polymorphism of *IL-1β* gene and other functional mutations in IL-1β, and the results are contradictory, which may be related to the different genes of race, the phenotype of the gene is strongly dependent on race and regional location. Another possibility is that differences in environmental factors have led to the absence of a certain association between these populations. In addition, it is well known that haplotype analysis may have a greater impact, however, most studies do not carry out haplotype analysis. Therefore, we need to conduct more in-depth research, investigate larger sample size and other ethnic groups, and consider gene-environment interaction and haplotype information, in order to further study the relationship between *IL-1β* gene polymorphism and CAD.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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