

Manganese superoxide dismutase gene polymorphisms in psoriatic arthritis

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Abstract. The purpose of the present study is to investigate the role of manganese superoxide dismutase (MnSOD) gene polymorphisms in the susceptibility to psoriatic arthritis. MnSOD gene polymorphisms were determined by polymerase chain reaction/restriction fragment length polymorphisms method in fifty-two patients with psoriatic arthritis and 90 healthy controls. The genotype frequency of MnSOD 1183C/T was significantly higher in patients with psoriatic arthritis than in controls. In contrast, the frequency of MnSOD 1183T/T was significantly decreased in patients with psoriatic arthritis. The phenotype frequency of MnSOD 1183C was significantly increased in patients with psoriatic arthritis in comparison to healthy controls. Therefore, MnSOD 1183C polymorphisms may be a precipitating factor for the development of psoriatic arthritis.

1. Introduction

Psoriatic arthritis is a chronic inflammatory disease characterized by psoriatic skin lesion and axial and/or peripheral joints inflammation. Patients with psoriatic arthritis usually combine manifestations of seronegative spondyloarthropathy and/or rheumatoid arthritis. It may also have extra-articular involvement [1]. Psoriatic arthritis is more common in Caucasian, but relatively uncommon in Asians.

The etiology of psoriatic arthritis is still unknown. Genetic, environmental and immunologic factors may contribute to the susceptibility and clinical manifestations of this disease. Population and twin studies suggest polygenetic bases of this disease. Associations of psoriatic arthritis with some HLA have been found, but they are not conclusive [2,3].

Superoxide products levels are increased in patients with psoriatic arthritis [4]. Miyachi et al. showed

that the psoriatic sera increased generation of superoxide anion from normal polymorphonuclear leukocyte [5]. Increased superoxide production was also found in dermal fibroblast of psoriatic patients [6]. Superoxide dismutase (SOD), a primary antioxidant, accelerates the dismutation of the toxic superoxide radical produced during the oxidative processes into the less toxic molecules. There are 3 isoenzymes of SOD including manganese SOD (MnSOD), copper and Zinc SOD (CuZnSOD), and iron SOD (FeSOD). Lontz et al showed increased mRNA expression of MnSOD in psoriatic skin lesions [7]. MnSOD is an antioxidant enzyme, which is a scavenger of free radical oxygen, and protect from the damage of superoxide anion. There are 2 polymorphic sites in MnSOD gene including C1183T (Ala → Val) and T577C (Ile 58 Thr). These polymorphisms may influence the activity and stability of MnSOD. Therefore, MnSOD may be related to the pathogenesis of psoriatic arthritis. A report about the association of MnSOD gene polymorphisms with psoriatic arthritis is still unavailable. The purpose of the present study is to investigate the role of MnSOD gene polymorphisms in the susceptibility to psoriatic arthritis.

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Table 1
Frequencies of MnSOD gene polymorphisms in patients with psoriatic arthritis and controls

MnSOD C1183T (Ala -9 Val)	Psoriatic A <i>n</i> = 52(%)	Controls <i>n</i> = 90(%)	OR (95% CI)	p
<i>Genotype frequencies</i>				
C/C	2 (3.8)	3 (3.3)	1.2 (0.2–7.2)	NS
C/T	28 (53.8)	29 (32.2)	2.5 (1.2–4.9)	0.009
T/T	22 (42.3)	58 (64.4)	0.4 (0.2–0.8)	0.009
<i>Allele frequencies</i>				
C	32 (30.8)	35 (19.4)	1.8 (1.1–3.2)	0.04
T	72 (69.2)	145 (80.5)	0.5 (0.3–0.9)	0.04
<i>Phenotype frequencies</i>				
C	30 (57.7)	32 (35.6)	2.5 (1.2–4.9)	0.009
T	50 (96.2)	87 (96.7)	0.9 (0.1–5.3)	NS

Psoriatic A: psoriatic arthritis; OR: odds ratio; CI: confidence interval;
NS: not significant.

2. Materials and methods

Fifty-two patients with psoriatic arthritis and 90 healthy controls were enrolled in this study. All patients and controls are Taiwanese.

2.1. Polymorphisms of MnSOD gene

The C1183T (Ala-9Val) polymorphisms were determined by polymerase chain reaction (PCR)/restriction fragment length polymorphism (RFLP) method. The sequences of primers were 5' – AGCCCAGCCTGCGTAGAC –3' and 5' – TACTTCTC CTCGGTGACG –3'. After PCR, the PCR product was digested with BsaWI. A sequence with 1183T, valine at -9th amino acid, can be cleaved with BsaWI. The T5777C (Ile58Thr) polymorphisms were also determined by the PCR/RFLP method. A set of primers with mismatched nucleotide (underlined) was used. The sequences of primers were 5' – CGGATGTTATAGATAAGCTGG –3' and 5' – CAGTGCAGGCTGA AGAGAT –3'. After PCR, the PCR product was then digested with EcoRV. A sequence with 5777T, isoleucine at 58th amino acid, can be cleaved with EcoRV.

2.2. Statistical analysis

The chi-square test with Yate's correction or Fisher's exact test was used for statistical analysis. Odds ratio (OR) were calculated by the methods of Woolf [8] and by a modification of the method of Haldane [9].

3. Results

Table 1 shows the frequencies of MnSOD gene polymorphisms in patients with psoriatic arthritis and controls. The genotype frequencies of MnSOD 1183C/T was significantly higher in patients with psoriatic arthritis than in controls. In contrast, the frequency of MnSOD 1183T/T was significantly decreased in patients with psoriatic arthritis. The allele and phenotype frequencies of MnSOD 1183C was also significantly increased in patients with psoriatic arthritis. In contrast, the genotype frequency of MnSOD 1183T was significantly decreased.

4. Discussion

SOD defends cells against oxidative damage and plays an important role in controlling reactive oxygen and other radical species in cells [10]. MnSOD is tetrameric and inducible, which is located in human mitochondria [11]. MnSOD is the primary defense against reactive oxygen in mitochondria, and play an important role in preventing the development of late-onset diseases [12]. The defects of mitochondria are associated with the degenerative diseases of aging such as Parkinson's disease and Alzheimer's disease [13,14].

MnSOD gene is on the long arm of chromosome 6 (6q25). There are 2 polymorphic sites in MnSOD gene. The MnSOD gene with thymidine at nucleotide position 5777 encodes a native form of MnSOD, which has a stable tetrameric interface. However, MnSOD gene with nucleotide sequence 5777C encodes a mutant form, which has increased thermal instability and accelerated thermal inactivation [11,15]. The transport of MnSOD into mitochondria is mediated through

the interaction of the mitochondrial targeting sequence with receptors on the mitochondrial membrane. The Ala-9Val (C1183T) polymorphisms in the mitochondrial targeting sequence may influence the efficiency of MnSOD transport. The -9 Ala polymorphism results in the formation of α -helix and the -9 Val takes a β -sheet structure [16]. The α -helix structure is important for the effective transport of precursor proteins into mitochondria [17]. The amino acid substitution (Ala/Val) at position -9 of the mitochondrial targeting sequence may lead to misdirected trafficking, followed by the alteration of MnSOD activity in human mitochondria [18]. The polymorphisms of MnSOD gene were related to several diseases including Parkinson's disease, diabetes mellitus, and malignancies [16,19–22]. In this study, MnSOD 1183C/T is positively associated with the susceptibility to psoriatic arthritis. Psoriatic patients also have significantly increased allele and phenotype frequencies of MnSOD 1183C in comparison to controls. Therefore, MnSOD 1183C may be a precipitating factor for the development of psoriatic arthritis in Taiwan.

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